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

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

An Overview on Toxic Effects of Acetamiprid

Amira Hilal Hilal Ibrahem Ghoneim[1], Marwa A Abass[1], Dalia Ibrahim Ahmed Mesallam[1], Samah M Ahmed[2], Alshaimaa Morsi[1]*

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

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

Abstract

Pesticides are a major class of pollutants of concern for the health of life and ecosystems. For instance, acetamiprid is a new-generation chloronicotinyl insecticide widely used as an alternative to organophosphates and carbamates to control insect pests. Acetamiprid is designed to target nicotinic acetylcholine receptors in insects, but its extensive use has led to adverse effects in non-targeted organisms including mammals. Traces of acetamiprid have been detected in various food products, water and soil. Moreover, the metabolism of acetamiprid generates toxic metabolites detected in the brain, liver, plasma and urine of rodents. Prolonged environmental or accidental exposure to acetamiprid alters hematological, biochemical and structural profiles, leading to neurological, hepatorenal, immunological, genotoxic and reproductive effects. Here we review acetamiprid metabolism and toxicity studies in mammals. Therapeutic use of plant extracts and antioxidants against acetamiprid-generated oxidative stress are also summarized. Genetic damage, chromosomal aberrations and depletion of antioxidants suggest that oxidative stress is the main mechanism for acetamiprid-induced toxicity.

Keywords: Toxic Effects of Acetamiprid, pesticide.

Mini review article **Corresponding Author*, e-mail: *emy.viva2013@gmail.com*

1. Introduction

Acetamiprid, (E)-N′-[(6-Chloro-3-pyridyl) methyl]-N2-Cyano N′methylacetamidine, is the new-generation chloronicotinyl insecticide with structural similarity to nicotine [1]. It was first synthesized in the year 1984, whereas the first commercial product containing acetamiprid was registered in 2002 for crops and livestock. Since the last decade, acetamiprid is broadly used in agricultural, domestic, and public health activities as a replacement of more hazardous pesticides like organophosphates, carbamates and pyrethroids [2]. Long-term and unplanned use of organophosphate and organochlorine pesticides in agriculture and domestic field has caused pesticide resistance in several insect pests [3]. Acetamiprid has overcome this resistant limitation effectively and is known to act significantly against insect pests [4].

1.1. Uses

In agriculture, acetamiprid has been used globally to control sucking insects, aphids, leafhoppers, moths, beetles, hemipterans, lepidopteron and pests of commercial crops along with fruits, flowers and ornamental plants [5]. In domestic and public health activities, acetamiprid is used to control flies, cockroaches, mosquitoes, ticks, and mites and is found to be equally effective at various stages of their growth [6]. It has been used commercially in cherry farming also, due to its great effectiveness against cherry fruit fly larvae [1].

1.1.1. Products

Acetamiprid-based products are sold throughout the world under various trade names like Pristine, Assail, Mospilan, Epik and Chipko [7].

1.1.2. Physical &chemical properties

Acetamiprid is odorless, white crystalline solid and its chemical formula is (C10H11ClN4), it has physical half-life: <1 to 8.2 day in aerobic soil conditions and with melting point: 98.9 °C [9].

1.2. Environmental Residuals

Traces of acetamiprid has been detected in soil (2µg/kg) [10], water (2.50 ng/L, 0.2–7.7 µg/L) [11], food [2] and in crops including mustard (0.01–0.91 µg/g) [12], gram (0.010–0.394 µg/g) [13], chilly (0.0207–0.1039 µg/g) [14] and watermelon (0.002–0.085) [15].

1.3. Absorption and Metabolism of Acetamiprid

Acetamiprid is readily soluble in water and can easily contaminate the food resources in the environment [16]. Direct and indirect exposure to acetamiprid is closely associated with its accumulation in various tissues [10]. Mice orally exposed to acetamiprid (30 mg/kg b.wt) showed a

higher amount of acetamiprid residues in liver tissue than kidney, suggesting organ-specific accumulation of acetamiprid inside the body [17]. Other studies also reported higher acetamiprid concentration in liver tissue than testis in rodents [18]. An in vitro study by Brunet et al. [19] investigated the role of temperature and concentration on acetamiprid absorption in human colon carcinoma cells (CaCo-2-14). At 37 °C, 100% absorption of acetamiprid was detected that reduced to 33% at 4 °C suggesting a significant role of temperature in acetamiprid absorption. In CaCo-2-14 cells, acetamiprid was absorbed through both apical to basal and basal to apical pathways [19]. In fact, studies have reported significant levels of acetamiprid and its metabolites in the liver, kidney and other tissues of mice [20]. Acetamiprid is known to metabolize readily inside the living tissues through demethylation, deacetylation and hydrolysis of cyano-imine linkage. Kolanczyk et al. [21] reported that acetamiprid is mainly converted to N-desmethyl-acetamiprid ($C_9H_9ClN_4$) in microsomes of rats. Some other studies also detected acetamiprid metabolites in various tissues and fluids and found N-desmethyl-acetamiprid as common and the most detectable metabolite [22]. These findings suggested N-desmethyl-acetamiprid as a major metabolite of acetamiprid [23] that might be associated with toxicity symptoms of acetamiprid exposure.

1.4. Mechanism of Action

Acetamiprid is an agonist at nicotinic acetylcholine receptors which make it highly efficient for controlling insect pests. In insects, acetamiprid exposure interrupts nerve transmission, alters membrane potential so it results in neuronal hyper excitation, paralysis and death [24]. Although acetamiprid is highly toxic to insects [25], various studies have shown that acetamiprid has significant affinities for mammalian nicotinic acetylcholine receptors that is responsible for its toxicity to mammalian tissues [26]. Some studies have reported inhibition of mRNA expression of α3, α4 and α7 nicotinic acetylcholine receptor subunits in rats'cerebellar cells [27], different brain regions [28] and testis of mice [29] following acetamiprid exposure. In mammals, nicotinic acetylcholine receptors are majorly located in the neuromuscular [30] and reproductive system [31].

1.4.1. Acetamiprid induced Toxicity

Wide and continuous use of acetamiprid has presented it as an environmental toxicant and its exposure imposes organ system toxicity adversely affecting immune physiology, ion balance and behavior. Easy solubility and rapid biological interaction of acetamiprid make the living tissues more susceptible to its exposure [32]. The residue of acetamiprid has been reported in urine [33], digestive tract [22] and brain [20] and acetamiprid has been shown to accumulate in liver and testis tissue of mice [34]. Various animal studies have shown the dose-dependent acetamiprid toxicity and suggested the generation of oxidative stress in various tissues. Sub-chronic oral exposure of acetamiprid was observed to induce oxidative stress mediated structural alterations in liver and kidney [35], hematological and biochemical alterations in hepatic tissue of rats [25] in dose-dependent manner. Acetamiprid is known to cause impaired locomotors activity, tremors and nervous system-associated disorders in mice. The down regulation in efferent nerve transmission and abnormal generation of afferent transmission at neuromuscular synapse might be associated with its neurotoxic symptoms [36]. Acetamiprid exposure is shown to affect the synaptic strength of neurons, desensitize ionic receptors [37] and neural degeneration [26] in the hippocampus of rats. Acetamiprid exposure is known to alter socio-sexual and anxiety behavior [38], memory loss, impaired learning ability and also decline the activity latency time in rats [37].

Various case studies have reported toxicity and physical symptoms of acetamiprid exposure in humans. In humans, physical symptoms consist of nausea, vomiting, weakness, convulsions, tachycardia, increased heart rate, increased urine flow, hypotension, hypoxia and thirst [39] followed by lactic acidosis [40] suggesting that physical symptoms of acute acetamiprid poisoning in mammals coincide with symptoms of organophosphate poisoning. Acute ingestion of acetamiprid pesticides in humans is reported to cause death. A case study has reported causality of 7-year-old girl who was intentionally subjected to the unknown acute high dose of acetamiprid by her sibling [22].Additionally, Kushwaha et al. [41] also reported the symptoms similar to organophosphate poisoning in 2.5-year-old buffalo who swallowed 100 g of acetamiprid. Non-lethal exposure of acetamiprid to living animals led to the rise of its metabolites in the body [42] and the concentration of acetamiprid and its metabolites has shown a relationship with toxicity of various vital organs. These evidences confirm that acetamiprid is highly toxic to the mammalian system also and may generate system specific detrimental effects.

1.5. In vitro studies

Acetamiprid has been shown to cause degenerative changes in various in vitro studies. Rats pheochromocytoma adrenal medulla cells (PC12) treated with acetamiprid (100–700 μM) resulted in a significant increase in MDA levels, reactive oxygen species generation and loss of mitochondrial membrane potential which altered oxygen uptake and metabolism inside PC12 cells [4]. Mehtap et al. [43] observed that pancreatic cell line (AR42J) treated with acetamiprid (1–6 mM) caused non-significant reactive oxygen species production but significantly reduced glutathione levels at higher concentrations. It suggested that inner mitochondrial membrane damage observed in these cells might be associated with acetamiprid mediated glutathione depletion.

1.6. In vivo studies

Exposure of acetamiprid to living tissues leads to production of free radicals inside tissues. The interaction of free radicals with cells causes a cascade of reactions leading to tissue damage through oxidation of structural molecules and depletion of antioxidants capacity. These free radicals are associated with oxidative stress generation. It has been shown that chronic exposure to acetamiprid significantly increased malondialdehyde levels, injury biomarkers and decreased superoxide dismutase and catalase activities along with histopathological degeneration in dose-dependent manner in liver and kidney tissues of rats suggesting generation of oxidative stress as a root cause of toxicity [44]. In addition, acetamiprid has been shown to act as a mutagen, alter gene expression, and interfere with cell apoptosis. Apoptosis is a process that results in the controlled death of cells, regulated by pro- and anti-apoptotic proteins.

The main inducers of intrinsic apoptosis include oxidative stress, DNA damage, and altered gene expression [45]. In one study, Annabi et al. [4] discovered a significantly negative impact on cell viability, increasing DNA damage and apoptosis (caspase-dependent) in PC12 cells treated with ACE (100–700 M). In another study, Senyildiz et al. [46] observed DNA damage in human neuroblastoma cells (SHSY-5Y) and human hepatocellular carcinoma cells (HepG2) after ACE treatment in a dose-dependent manner. Administration of ACE to pregnant rats during organogenesis phase caused a developmental toxic impact in way of morphological, soft tissue, and skeletal abnormalities [47] Moreover, Babel'ová et al. [48] discovered that when prokaryotic-stage mouse embryos were treated with NEOs (acetamiprid, thiacloprid, thiamethoxam, and clothianidin) and associated product solutions, all NEO insecticides at 100 µmol/L had a negative impact on mouse embryo development. At a concentration of 10 µmol/L, ACE and thiamethoxam both lowered blastocyst quality.

References

[1] R.K. Shakthi Devan, P.C. Prabu, S. Panchapakesan. (2015). Immunotoxicity assessment of sub-chronic oral administration of acetamiprid in Wistar rats. Drug and Chemical Toxicology. 38(3): 328-336.

[2] H.A. Craddock, D. Huang, P.C. Turner, L. Quirós-Alcalá, D.C. Payne-Sturges. (2019). Trends in neonicotinoid pesticide residues in food and water in the United States. 1999–2015. Environmental Health. 18: 1-16.

[3] R. Mosbah, Z. Djerrou, A. Mantovani. (2018). Protective effect of Nigella sativa oil against acetamiprid induced reproductive toxicity in male rats. Drug and Chemical Toxicology. 41(2): 206-212.

[4] E. Annabi, I. Ben Salem, S. Abid-Essefi. (2019). Acetamiprid, a neonicotinoid insecticide, induced cytotoxicity and genotoxicity in PC12 cells. Toxicology Mechanisms and Methods. 29(8): 580-586.

[5] P. Bagri, S.K. Jain. (2019). Assessment of acetamiprid-induced genotoxic effects in bone marrow cells of Swiss albino male mice. Drug and Chemical Toxicology. 42(4): 357-363.

[6] T. Çavaş, N. Çinkılıç, O. Vatan, D. Yılmaz, M. Coşkun. (2012). In vitro genotoxicity evaluation of acetamiprid in CaCo-2 cells using the micronucleus, comet and γH2AX foci assays. Pesticide Biochemistry and Physiology. 104(3): 212-217.

[7] M. Renaud, T. Akeju, T. Natal-da-Luz, S. Leston, J. Rosa, F. Ramos, H.M. Azevedo-Pereira. (2018). Effects of the neonicotinoids acetamiprid and thiacloprid in their commercial formulations on soil fauna. Chemosphere. 194: 85-93.

[8] H. Takahashi, J. Mitsui, N. Takakusa, M. Matsuda, H. Yoneda, J. Suzuki, T. Kishimoto. (1992). NI-25. a new type of systemic and broad spectrum insecticide.

[9] T. Yamada, H. Takahashi, R. Hatano. (1999). A novel insecticide, acetamiprid. In Nicotinoid insecticides and the nicotinic acetylcholine receptor (pp. 149-176). Tokyo: Springer Japan.

[10] J.M. Bonmatin, E.A. Mitchell, G. Glauser, E. Lumawig-Heitzman, F. Claveria, M.B. van Lexmond, F. Sánchez-Bayo. (2021). Residues of neonicotinoids in soil, water and people's hair: A case study from three agricultural regions of the Philippines. Science of the Total Environment. 757: 143-822.

[11] B.S.G. Zoumenou, M.P. Aïna, I. Imorou Toko, A. Igout, C. Douny, F. Brose, M.L. Scippo. (2019). Occurrence of acetamiprid residues in water reservoirs in the cotton basin of Northern Benin. Bulletin of Environmental Contamination and Toxicology. 102: 7-12.

[12] S.K. Pramanik, J. Bhattacharyya, S. Dutta, P.K. Dey, A. Bhattacharyya. (2006). Persistence of Acetamiprid in/on Mustard (Brassica juncea L.). Bulletin of Environmental Contamination & Toxicology. 76(2).

[13] R.K. Gupta, S. Gupta, V.T. Gajbhiye, H.C. Wiener, G. Singh. (2005). Residues of imidacloprid, acetamiprid and thiamethoxam in gram. Pesticide Research Journal. 17(1): 46-50.

[14] D. Sanyal, D. Chakma, S. Alam. (2008). Persistence of a neonicotinoid insecticide, acetamiprid on chili (Capsicum annum L.). Bulletin of Environmental Contamination and Toxicology. 81: 365-368.

[15] J. Wu, K. Wang, H. Zhang. (2012). Dissipation and residue of acetamiprid in watermelon and soil in the open field. Bulletin of Environmental Contamination and Toxicology. 89: 644-648.

[16] M. Gaweł, T. Kiljanek, A. Niewiadowska, S. Semeniuk, M. Goliszek, O. Burek, A. Posyniak. (2019). Determination of neonicotinoids and 199 other pesticide residues in honey by liquid and gas chromatography coupled with tandem mass spectrometry. Food Chemistry. 282: 36-47.

[17] J.J.Z. Yi-Wang, H.Y. Xiang, Z. Jia-Hua, X.Z. Wang. (2012). Acetamiprid residues in male mice and its effect on liver function. Journal of Animal and Veterinary Advances. 11(15): 2706-2710.

[18] R.S. Devan, A. Mishra, P.C. Prabu, T.K. Mandal, S. Panchapakesan. (2015). Sub-chronic oral toxicity of acetamiprid in Wistar rats. Toxicological & Environmental Chemistry. 97(9): 1236-1252.

[19] J.L. Brunet, M. Maresca, J. Fantini, L.P. Belzunces. (2008). Intestinal absorption of the acetamiprid neonicotinoid by Caco-2 cells: transepithelial transport, cellular uptake and efflux. Journal of Environmental Science and Health Part B. 43(3): 261-270.

[20] K.A. Ford, J.E. Casida. (2006). Chloropyridinyl neonicotinoid insecticides: diverse molecular substituents contribute to facile metabolism in mice. Chemical Research in Toxicology. 19(7): 944-951.

[21] R.C. Kolanczyk, M.A. Tapper, B.R. Sheedy, J.A. Serrano. (2020). In vitro metabolism of imidacloprid and acetamiprid in rainbow trout and rat. Xenobiotica. 50(7): 805-814.

[22] O. Yeter, A. Aydın. (2014). Determination of Acetamiprid and IM-1-2 in P ost M ortem Human Blood, Liver, Stomach Contents by HPLC-DAD. Journal of Forensic Sciences. 59(1): 287-292.

[23] J.T. Marfo, K. Fujioka, Y. Ikenaka, S.M. Nakayama, H. Mizukawa, Y. Aoyama, K. Taira. (2015). Relationship between urinary N-desmethyl-acetamiprid and typical symptoms including neurological findings: a prevalence case-control study. PloS one. 10(11): e0142172.

[24] S. Gasmi, R. Rouabhi, M. Kebieche, A. Salmi, S. Boussekine, N. Toualbia, B. Djabri. (2016). Neurotoxicity of acetamiprid in male albino rats and the opposite effect of quercetin. Biotechnology Indian Journal. 12(7): 113.

[25] S. Chakroun, L. Ezzi, I. Grissa, E. Kerkeni, F. Neffati, R. Bhouri, H. Ben Cheikh. (2016). Hematological, biochemical, and toxicopathic effects of subchronic acetamiprid toxicity in Wistar rats. Environmental Science and Pollution Research. 23: 25191-25199.

[26] M. Shamsi, M. Soodi, S. Shahbazi, A. Omidi. (2021). Effect of Acetamiprid on spatial memory and hippocampal glutamatergic system. Environmental Science and Pollution Research. 28: 27933-27941.

[27] J. Kimura-Kuroda, Y. Komuta, Y. Kuroda, M. Hayashi, H. Kawano. (2012). Nicotine-like effects of the neonicotinoid insecticides acetamiprid and imidacloprid on cerebellar neurons from neonatal rats. PloS one. 7(2): e32432.

[28] H. Terayama, H. Endo, H. Tsukamoto, K. Matsumoto, M. Umezu, T. Kanazawa, K. Sakabe. (2016). Acetamiprid accumulates in different amounts in murine brain regions. International Journal of Environmental Research and Public Health. 13(10): 937.

[29] H. Terayama, N. Qu, H. Endo, M. Ito, H. Tsukamoto, K. Umemoto, K. Sakabe. (2018). Effect of acetamiprid on the immature murine testes. International Journal of Environmental Health Research. 28(6): 683-696.

[30] I.M.P. Valenzuela, M. Akaaboune. (2021). The metabolic stability of the nicotinic acetylcholine receptor at the neuromuscular junction. Cells. 10(2).

[31] P. Kumar, S. Meizel. (2005). Nicotinic acetylcholine receptor subunits and associated proteins inhuman sperm. Journal of Biological Chemistry. 280(27): 25928-25935.

[32] A. Phogat, J. Singh, V. Kumar, V. Malik. (2022). Toxicity of the acetamiprid insecticide for mammals: A review. Environmental Chemistry Letters: 1-26.

[33] G. Ichikawa, R. Kuribayashi, Y. Ikenaka, T. Ichise, S. M. Nakayama, M. Ishizuka, S. Yoshihara. (2019). LC-ESI/MS/MS analysis of neonicotinoids in urine of very low birth weight infants at birth. PLoS One. 14(7): e0219208.

[34] J.J. Zhang, W.A.N.G. Yi, H.Y. Xiang, M.X. LI, W.H. LI, X.Z. WANG, J.H. ZHANG. (2011). Oxidative stress: role in acetamiprid-induced impairment of the male mice reproductive system. Agricultural Sciences in China. 10(5): 786-796.

[35] B.U. Karaca, Y.E. Arican, T. Boran, S. Binay, A. Okyar, E. Kaptan, G. Özhan. (2019). Toxic effects of subchronic oral acetamiprid exposure in rats. Toxicology and Industrial Health. 35(11-12): 679-687.

[36] V. Dukhnytskyi, V. Sokolyuk, P. Boiko, I. Ligomina, V. Goncharenko. (2020). The acute toxicity assesment of Mospilan RP and Actara 25 WG for White Mice.

[37] P.S. Mandal, S. Mondal, S.S. Karnam, K. Purohit. (2015). A behavioral study on learning and memory in adult Sprague dawley rat in induced Acetamiprid toxicity.

[38] K. Sano, T. Isobe, T.T. Win-Shwe, S.F. Nakayama, T. Kawashima, C. Tohyama, F. Maekawa. (2016). In utero and lactational exposure to acetamiprid induces abnormalities in socio-sexual and anxiety-related behaviors of male mice. Frontiers in Neuroscience. 10: 185-797.

[39] T. Imamura, Y. Yanagawa, K. Nishikawa, N. Matsumoto, T. Sakamoto. (2010). Two cases of acute poisoning with acetamiprid in humans. Clinical Toxicology. 48(8): 851-853.

[40] S. Pirasath, R. Senthuran, C. Athirayan, M. Gevakaran, M. Guruparan, A. Gnanathasan. (2021). Acute poisoning with acetamiprid: a case report. Journal of Medical Case Reports. 15: 1-5.

[41] N. Kushwaha, A. Mohan, A.U. Bhikane. (2018). Accidental acetamiprid poisoning in a buffalo. Iranian Journal of Veterinary Research. 19(4): 318.

[42] T. Ogawa, J. Ueyama, T. Suzuki, M. Iwai, X.P. Lee, T. Kumazawa, H. Seno. (2018). In vivo metabolic profiling for acetamiprid in rat plasma by liquid chromatography quadrupole time-of-flight mass spectrometry. Medical Mass Spectrometry. 2(1): 34-40.

[43] K.A.R.A. Mehtap, E. ÖztaŞ, G. Özhan. (2020). Acetamiprid-induced Cyto-and genotoxicity in the AR42J pancreatic cell line. Turkish Journal of Pharmaceutical Sciences. 17(5): 474.

[44] B.S. El-Bialy, M.A. Abd Eldaim, A. Hassan, M.M. Abdel-Daim. (2020). Ginseng aqueous extract ameliorate lambda-cyhalothrin-acetamiprid insecticide mixture for hepatorenal toxicity in rats: role of oxidative stress-mediated proinflammatory and proapoptotic protein expressions. Environmental Toxicology. 35(2): 124-135.

[45] L. Zuščíková, D. Bažány, H. Greifová, N. Knížatová, A. Kováčik, N. Lukáč, T. Jambor. (2023). Screening of toxic effects of neonicotinoid insecticides with a focus on acetamiprid: A review. Toxics. 11(7): 598.

[46] M. Şenyildiz, A. Kilinc, S. Ozden. (2018). Investigation of the genotoxic and cytotoxic effects of widely used neonicotinoid insecticides in HepG2 and SH-SY5Y cells. Toxicology and Industrial Health. 34(6): 375-383.

[47] S.M. Abou Zeid. (2018). Developmental toxicity of acetamiprid in rats. World Journal of Pharmaceutical Sciences. 7: 113-126.

[48] J. Babeľová, Z. Šefčíková, S. Čikoš, A. Špirková, V. Kovaříková, J. Koppel, D. Fabian. (2017). Exposure to neonicotinoid insecticides induces embryotoxicity in mice and rabbits. Toxicology. 392: 71-80.