Sustainability, Agri, Food and Environmental Research, (ISSN: 0719-3726), vol 13, 2025
http://dx.doi.org/

Tetronic Acid and Tetramic Acid derived pesticides and their toxicity: A Review.

Pesticidas derivados del ácido tetrónico y ácido tetrámico y su toxicidad: una revisión.

Shariq Hussain[1], Madhavi Gaur[2]

1- Department of Zoology, Barkatullah University, Bhopal, India-462001, India. email: catch2shariq@gmail.com

2- Department of Zoology, Saint Hirdaram Girls College, Bhopal, India-462001, India, email: gaur.madhavi@yahoo.com

ABSTRACT

Pesticides are a group of chemicals that have brought a remarkable change in agricultural deeds by refining quality and production of crops, but their toxic behavior towards organisms has always been a major worry. From past few years, global attention has increased many times in this context and several new insecticides have been introduced by different agencies to combat this issue. The damage caused by pests is always in focus so that new pesticides with improved action can be formed with least toxicity. Tetronic and Tetramic acid derived pesticides have arisen as new pesticides with a flexible mode of action by acting as acaricides, there by obstructing acetyl CoA carboxylase in lipid biosynthesis. These insecticides include tetronic acid derivatives like Spiromesifen, Spirodiclofen and tetramic acid derivatives like Spirotetramat and Spiropidion. Although these pesticides have arisen a new hope to deal with pests like whiteflies and mites but their toxic nature can't be ignored. So in this review we would like to highlight the main toxic targets of these newly introduced pesticides so as awareness can be generated for rational use of pesticides.

Key Words: Spirotetramat, Spiropiodion, Spirodiclofen, Spiromesifen, Pesticide toxicity. Acetyl Co-A Carboxylase enzyme

RESUMEN

Los pesticidas son un grupo de químicos que han traído un cambio notable en las prácticas agrícolas al mejorar la calidad y producción de los cultivos, pero su comportamiento tóxico hacia los organismos siempre ha sido una gran preocupación. En los últimos años, la atención mundial ha aumentado muchas veces en este contexto y diferentes agencias han introducido varios insecticidas nuevos para combatir este problema. El daño causado por las plagas siempre está enfocado para que se puedan formar nuevos pesticidas con acción mejorada con la menor toxicidad. Los pesticidas derivados del ácido tetrónico y tetrámico han surgido como nuevos

pesticidas con un modo de acción flexible al actuar como acaricidas, obstruyendo la acetil CoA carboxilasa en la biosíntesis de lípidos. Estos insecticidas incluyen derivados del ácido tetrónico como Spiromesifen, Spirodiclofen y derivados del ácido tetrámico como Spirotetramat y Spiropidion. Aunque estos pesticidas han surgido como una nueva esperanza para hacer frente a plagas como la mosca blanca y los ácaros, no se puede ignorar su naturaleza tóxica. Por lo tanto, en esta revisión nos gustaría resaltar los principales objetivos tóxicos de estos pesticidas recientemente introducidos para que se pueda generar conciencia sobre el uso racional de los pesticidas.

Palabras clave: Spirotetramat, Spiropiodion, Spirodiclofen, Spiromesifen, Toxicidad por plaguicidas. Enzima Acetil Co-A Carboxilasa.

INTRODUCTION

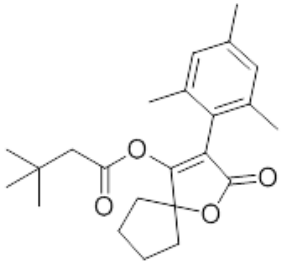
Insects have been found to be a drastic cause of decline in crop production by damaging it at various levels. To control this destruction by insects, different insecticides are used worldwide. However most of insects reveal a unique capability to develop resistance against these insecticides. So, very often new pesticides are introduced in market with new target sites. This ability of resistance against insecticides has forced the formation of new novel insecticides to expedite the development of management policies for Insect resistance (Gravalos et al., 2015). Among the families of insecticides, keto-enol insecticides are recently introduced chemicals which are tetronic/tetramic acid derivates also called cyclic ketonols belonging to 23rd group of insecticides in IRAC (Insecticide Resistance Action Committee) classification and hinder acetyl CoA carboxylase functions (Muehlebach et al.,2019). These insecticides commonly include Spirotetramat, Spiropiodion, Spiromesifen and Spirodiclofen (Sparks and Nauen, 2015). The inhibitory function of these insecticides mainly target Acetyl- CoA Carboxylase enzyme (EC-6.4.1.2) in fatty acid biosynthesis reactions with enol form being most active against ACC (Lummen et al., 2014). Although these pesticides are mostly used by farmers against whiteflies, thrips, aphids, psyllids etc. (Nauen et al., 2005 and Guillen et al., 2014), they have a satisfactory ecotoxicological outline being harmonious with pollinators (Bielza et al., 2005) and translocating via xylem and phloem (Bruck et al., 2009). These insecticides have been introduced in market since 2003 by Bayer with different trade names time to time. In spite of having almost a similar biological activity by interfering in lipid biosynthesis, Spirodiclofen has been found more effective against mites, Spiromesifen against mites and whiteflies, Spirotetramat against sucking pests and Spiropidion against aphids and red mites (Yamamoto, 2018). Besides controlling insect populations, unfortunately the increased use of these insecticides has affected a lot of flora and fauna coming in contact with them either directly or indirectly. Reproductive toxicity being a prime focus of concern, several species of animals including rats and humans has been found to develop damages in their reproductive systems by repetitive exposure to such chemicals.

A) Insecticides of Tetronic Acid derivatives:

1.1 Spiromesifen: (M.W=370.48 g/mol and Chemical Formula $C_{22}H_{30}O_4$)(Fig.1)

[3-mesityl-2-oxo-1-oxaspiro [4.4] non-3-en-4-yl- 3, 3-dimethylbutyrate (IUPAC)]

Spiromesifen is a type of spiro-cyclic tetronic acid derived insecticide that was developed by Bayer Crop Sciences in 2006 and is available in market by the name Oberon. It is active against mites and white flies. The insecticide has been already approved in countries like Mexico, Indonesia, United States, Israel, and Germany since 2013 (Directorate general for Health and Food Safety, 2016) but in India The Best Agrolife Limited (BAL) was legalized for manufacturing of Spiromesifen by CIBRC (Central Insecticides Board and Registration Committee) in 2018. European commission however introduced it in 2013 (European Food Safety Authority, 2012).



3-mesityl-2-oxo-1-oxaspiro [4.4] non-3-en-4-yl- 3,3-dimethylbutyrate (IUPAC)

Fig.1- Spiromesifen

1.2.1 Mode of Action:

Spiromesifen is a non-systemic enzyme inhibitor which works on lipid metabolism by suppressing Acetyl-CoA Carboxylase which causes dryness of insect and finally death (Nauen et al., 2005). It has also been reported to cause decline in different mite species (Bretschneider et al., 2003). A recently revealed mode of action with Insect Growth Regulator (IGR) like properties that obstruct with lipid biosynthesis by destruction of Acetyl-CoA Carboxylase, upset the developmental stages and fecundity in insects (Dekeyser, 2005). In the meantime no cross resistance to other mite populations has been found, it has emerged as a valuable tool for cross commodity resistance management program (Nauen et al., 2000).

1.3 Toxicity:

Spiromesifen has been found to be very toxic in both animals and plants and the

Toxicity has varied from species to species mostly dependent on routes of administration. Routes of administration may vary from Ingestion, inhalation, skin absorption to eye contact. It is harmful if contacted directly by skin, swallowed or inhaled. In rats an acute oral and inhalation toxicity was reported by exposing continuously for 4hrs with LD_{50} (male/female combined Rat) > 2,000 mg/kg and LC_{50} (male/female combined Rat) 1.8 mg/L respectively. However no death by acute dermal toxicity at LD_{50} (male/female combined Rat) > 2,000 mg/kg was observed.

With LC_{50} inhalation > 4873 mg/cum/4hr, LD_{50} dermal > 2000 mg/kg/24hr and LD_{50} oral > 2500 mg/kg was reported. A significant hepatotoxicity has also been reported in rats at 3mg/Kgbw however no record of acute, chronic and sub-chronic neurotoxicity in them (European Food Safety Authority, 2007).

Spiromesifen has been found to cause reproductive toxicity in rats. Reproductive toxicity has been reported as dose dependent and related with parental toxicity. However developmental toxicity was reported to be related with maternal toxicity (Safety Data Sheet By Bayer, 2017).

In Drosophila melanogaster it cause decrease in weight of ovaries and reduction in number of oocytes produced thereby decreasing overall fertility and fecundity (Kissoum et al., 2020).

In fishes LC_{50} of about 0.0155mg/L with exposure time of 96 hours was reported in Rainbow trout (Oncorhynchus mykiss). For aquatic invertebrates like Daphnia magna EC_{50} >0.09 mg/L has already been reported (Safety Data Sheet By Bayer, 2017).

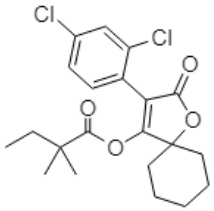
For mammals LD_{50} is about 2000mg/Kgbw if inhaled or orally ingested and 4000mg/Kgbw if absorbed by skin (Neun et al., 2005). It is also toxic for aquatic flora and fauna including fishes (Bayer, 2017). Although it was finalized that Spiromesifen has no genotoxic and carcinogenic behavior but the amount and route of administration may show a variable toxicity (European Food Safety Authority, 2007). In rabbit skin corrosion with slight irritation, respiratory sensation was reported. In Guinea no specific organ toxicity has been reported so far. By assessing mutagenicity or genotoxicity, no such reports have been published so far (Safety Data Sheet By Bayer, 2017). In laboratory animals acute exposure of Spiromesifen has caused inhibitive lipid biosynthesis with loss of weight, adrenal atropy, hormonal changes, spleen atropy, increased level of liver enzymes and decrease in triglycerides (United States Environmental protection Agency, 2007).

2.1 Spirodiclofen:

(M.W = 411.30 g/mol and Chemical Formula $C_{21}H_{24}Cl_2O_4$) Fig.2.

[3-(2, 4 dichlorophenyl)-2-oxo-1-oxaspiro [4.5] dec-3-en-4-yl 2, 2-dimethyl-butanoate (IUPAC)]

Spirodiclofen is a type of keto-enol acaricide pesticide which belongs to tetronic acid class, used to control mites and San Jose scale on fruits like nut, grapes and pome by inhibiting lipid bio-synthesis (De Maeyer and Geerinck, 2009). It was developed by Bayer Crop Science and marketed under trade names Envidor and Brinka.



3-(2, 4 dichlorophenyl)-2-oxo-1-oxaspiro [4.5]dec-3-en-4-yl 2,2-dimethylbutanoate (IUPAC)

Fig.2- Spirodiclofen

2.2 Mode of action:

Spirodiclofen is a selective and non-systemic insecticide which inhibits acetyl CoA carboxylase by interfering lipid biosynthesis and interrupt basic development in insects. It is important enzyme in lipid biosynthesis with a crucial role in carboxylation of Acetyl CoA (Harwood, 1988). The metabolic pathway involves breaking of ester linkage and formation of free enol metabolites followed by hydroxylation of ring (Freyberger, 2002).

2.3 Toxicity:

Spirodiclofen has been reported to cause different stages of toxicity in different living forms. Technically it produces a less amount of acute toxicity when administrated via oral, dermal or nasal routes. However it causes no irritation but may act as skin sanitizer (Wirnitizer and Romeike, 1998; Wirnitizer and Hartmann, 2002; MacBean, 2010). Spirodiclofen has also been found to disrupt endocrine system with endogenous mediated toxicological responses.

Spirodiclofen has been found to act against developmental stages of mites. It has been found to decrease fecundity of females and decrease in egg lying with decreased lipid content in Tetranychus urticae (Schobert and Schlenk, 2008).

For reproductive toxicity; in dogs, leydig cell were found to be get vacuolated with hypertrophy when treated with Spirodiclofen. In rats with chronic exposure to Spirodiclofen, hypertrophy was also reported with hyperplasia leading to adenomas has been reported. In chronic study of female rats, they were found to produce adenocarcinomas with uterine nodules (Eiben, 1997).

In adrenal cortex, cytoplasmic vocuolation with increased adrenal weight were found in both sexes of mice, rats and dogs.

In male rabbits and rats a delayed sexual maturation, decreased sperm count, atropy of testes has been reported so far by treating with Spirodiclofen. In females a sever ovarian luteal cell vocuolation and degeneration has been found (Eiben, 2000).

Spirodiclofen has been reported to cause mutagenicity and carcinogenicity in male and female rats by developing uterine adenocarcinoma and Leydig cell adenoma. Liver tumors have also been found to be caused by administration of Spirodiclofen in rats and can be carcinogenic to humans also (Whale, 2000).

No sub chronic and acute neurotoxicity has been reported so far (Sheets and Gilmore, 2001)

In Mammalian Chinese Hamster Lung Fibroblasts V79 Cells gene mutation and chromosomal aberrations have been found with a reported cytotoxicity in later stages (Herbold, 1996).

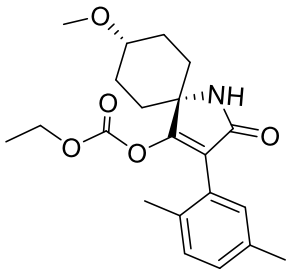
Spirodiclofen has also been found to have a limited effect on human cell line MCF7 breast cancer cell line for estrogen receptors and prostrate Pc-3 cell line for androgen receptors (California Environmental Protection Agency, 2006).

B) Insecticides of Tetramic Acid derivatives:

3.1 Spirotetramat: (M.W= 374.44 g/mole Chemical formula: $C_{21}H_{27}NO_5$) Fig.3

[cis-4-(ethoxycarbonyloxy) -8- methoxy -3- (2, 5-xylyl)-azaspiro- [4, 5] dec-3-en-2-one) (IUPAC)]

Spirotetramat is an insecticide which belongs to keto-enol class of pesticides with sub class tetramic acid derivatives. The name was proposed by International Standard organization (ISO) for cis-4-(ethoxycarbonyloxy)-8-methoxy-3-(2,5-xylyl)-azaspiro[4,5]dec-3-en-2-one) (IUPAC). It is also famous by its other names like Movento® and Ultor®. Chemically it is an azospiro compound (methoxycyclohexane) fused at 4th and 5th positions of 1-5-dihydro-2H-pyrrol-2-one substituted at 3rd and 4th position by dimethylphenyl and ethoxycarbonyl(oxy) groups in cis-isomer respectively.



cis-4-(ethoxycarbonylyoxy)-8-methoxy-3-(2,5-xylyl)-azaspiro
[4,5]dec-3-en-2-one)

Fig. 3- Spirotetramat

3.2 Mode of Action:

Spirotetramat is extensively used insecticide to control damage caused by aphids, whiteflies, mites and other sucking insects to different crops. It acts as an inhibitor of lipid biosynthesis in insects. Being ambimobile in nature, it is transported in both directions in vascular bundles of plants (Bruck et al.,2009). Commercially it was first introduced by Bayer Crop Science under the name Movento®.

3.3Toxicity:

Spirotetramat produces a low to moderate level of toxicity by dermal and oral routes with LD_{50} in rats > 2000mg/kgbw and inhalation LC_{50} > 4.18 mg/L of air. It can cause skin and eye irritation (European Food Safety Authority, 2013).

In rats treated with Spirotetramat for about a week, a significant loss in weight with damage to the genitals and liver has been reported (Liu et al., 2011). The metabolites of Spirotetramat in rats are readily absorbable with a variable concentration in different tissues and organs (Wu et al., 2012). In soil it acts as a contaminant by possessing potential genetic and biochemical toxicity to earth worms (Zhang et al., 2015). Remarkably, various adversarial effects of Spirotetramat on marine and fresh water organisms have also been reported in previous studies including Ceriodaphnia and Dhapnia (Chen and Stark, 2010), Chen et al., 2018),

catfishes like Clarias gariepinus (Agbohessi et al., 2013), Chinese bufo (Bufo bufo gargarizans) and tadpole larvas (Yin et al., 2009).

It has also been reported for causing various types of skin irritations (Ye, 2011). In larval instars susceptibility and effect of exposure may considerably differ, resulting in a sub-lethal effect (Wang et al., 2009). So there may be a level of possible sub-lethal effects of Spirotetramat.

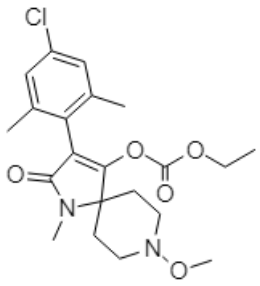
In spider mite Tetranychus urticae (Chen et al., 2011), the western flower thrips Frankliniella occidentalis (Guillen et al., 2014), and the citrus red mite Panonychus citri, Spirotetramat shows a robust toxicity with least reproduction by exposed females (Hu et al., 2010; Ouyang et al., 2012).

The toxicity of Spirotetramat on developmental stages of Tatranychus urticae with effects on fertility and viability has also been reported (Marcic et al., 2012).

4.1 Spiropidion: (M.W=422.9 g/mol and Chemical Formula $C_{21}H_{27}ClN_2O_5$) Fig.4

[3-(4-chloro-2, 6-dimethylphenyl)-8-methoxy-1-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-en-4-yl ethyl carbonate (IUPAC)]

Spiropidion is another tetramic acid derived insecticide that acts on sucking pests. It was developed by Syngenta Crop Protection under the brand name Elestal in 2020 currently available in Guatemala and Iran for control of pests. It is a proinsecticide (Casida, 2017) with enol ethyl group cleaved in vivo to release active component that binds at target site in mites (Jeschke, 2016). Being an azaspiro compound it acts on wide range on insects including whiteflies, aphids, scales and mites by disrupting Acetyl CoA carboxylase enzyme necessary for lipid biosynthesis (Muehlebach et al., 2020). The insecticide is used in wide range of crops like melons, oranges, tomatoes, cotton and soya to protect them from pests.



3-(4-chloro-2, 6-dimethylphenyl)-8-methoxy-1-methyl-2-oxo-1,8-diazaspiro[4.5]dec-3-en-4-yl ethyl carbonate (IUPAC)

Fig. 4- Spiropidion

4.2 Mode of Action:

Spiropidion acts on Acetyl Co-A carboxylase there by inhibiting lipid biosynthesis and a decrease production of lipids is achieved and inhibiting bio membrane production in insects. It is a proinsectcide which become active in-vivo and is favorable for pollinators and non-target pests.

4.3 Toxicity:

Spiropidion is found to be very toxic in organisms their by causing different levels of toxicity which are dose dependent. However it is non-irritant to skin. In rats the acute median lethal dose LD_{50} was found to be greater than 2000mg/kgbw and dermal LD_{50} more than 5000mg/kg bw. The toxicity leads to reduction in concentration of cholesterol and triglycerides with systemic neurotoxicity.

In mouse carcinogenicity was reported on 80 week study at 65.4mg/kgbw per day while as in rat at 2.4 mg/kg bw. In two generation reproductive toxicity reproduction and fertility was greatly inhibited at 23mg/kgbw with parental toxicity at 7.8mg/kgbw and offspring toxicity at similar dose as for fertility causing weight reduction overall. The developmental toxicity revealed maternal toxicity caused at 30mg/kgbw and fetal toxicity was reported at 100mg/kgbw. Neurotoxicity was reported at higher doses at 150 mg/kgbw. In mammals e.g. rabbit developmental toxicity was found at 10-30mg/kgbw. Thyroid follicular hypertrophy was reported in female rats has also been reported. Due to lack of genotoxicity, Spiropiodion is unlike to cause any carcinogenic risk to humans. Spiropidion was also found to be non-teratogenic and non-immunotoxic. It was also found to be inducer of hepatic activity (FOA and WHO, 2022).

DISCUSSION

Although the use of pesticides is increasing day by day, there is an immediate need of awareness and restriction procedures that must be followed to minimize the ill effects of pesticides. The available toxicity information of tetramic and tetronic acid derives pesticides suggests their rational use by following prescribed procedures (Zyoud et al., 2010). The toxicity at different levels like neurotoxicity, reproductive toxicity, carcinogenicity, hepatotoxicity and cell toxicity in general caused by pesticides by acting as acetyl CoA carboxylase enzyme inhibitors (Clemens and Jurgen, 2012) is of major concern because at any stages of development they can directly or indirectly inhibit lipid biosynthesis.

Declaration of Interest:

The present review and conclusions drawn reflect only the professional work product of authors and there is no conflict of interest related to the content of this review.

REFERENCES

Bielza P., Contreras J., Quinto V., Izquierdo J., Mansanet V. and Elbert A. (2005). Effects of Oberon 240 SC on bumble bees pollinating greenhouse tomatoes. Pflanzenschutz- Nachrichten Bayer (58): 469–484.

Bretschneider T., Buchhol B.J., Fisher R. and Nauen R. (2003). Spirodiclofen and Spiromesifen, novel acaricidal and insecticidal tetronic acid derivatives with a new mode of action. Crop Protection Research (57):697-701.

Bruck E., Elbert A., Fischer R., Krueger S., Kuhnhold J., Klueken A.M., Nauen R., Niebes J.F., Reckmann U., Schnorbach H.J., Steffens R. and Van. (2009). Waetermeulen X. Movento®, an innovative ambimobile insecticide for sucking insect pest control in agriculture: biological profile and field performance. Crop Protection (10): 838–844.

California environmental protection agency. (2011). Toxicology data review summary for Spirodiclofen. Department of Pesticide Regulation Calfornia, p11.

Casida J.E.(2017). Why pro-drugs and pro-pesticides succeed. Chemical Research Toxicology (30):1117–1126.

Chen X.D. and Stark J.D. (2010). Individual and population level toxicity of the insecticide, Spirotetramat and the agricultural adjuvant, destiny to the Cladoceran, Ceriodaphnia dubia. Ecotoxicology (6): 1124–1129.

Chen X., Zhang C. and Zhao M. (2011). Melatonin alleviates lipo-polysaccharide induced hepatic SREBP-1c activation and lipid accumulation in mice. Journal of Pineal Research (51): 416–425.

Chen Y., Tao FY., Liu X.Y., Wang M.C., Rao Q., Gu D.L. and Wu H.M. (2018). Acute and chronic toxicities of Spirotetramat to Daphnia magna. Chin. Journal of Pesticide Science (1): 118–123.

Clemens L. and Jurgen D. (2012). Tetronic Acid Insecticides and Acaricides Inhibiting Acetyl-CoA Carboxylase. , Bioactive Heterocyclic Compound Classes: Agrochemicals (10): 265–278.

De Maeyer L. and Geerinck R. (2009). The multiple target use of Spirodiclofen (Envidor 240 SC) in IPM pomefruit in Belgium. Communications in Agricultural and Applied Biological Sciences (1): 225–232.

Dekeyser M.A. (2005). Acaricide mode of action. Pest Management Science (61):103-110.

Directorate general for Health and Food Safety (DGHF). (2016). Entry on Spiromesifen in the EU pesticide database and entry in the national registers of plant protection products in Switzerland, Austria and Germany. European pesticide Commission p112-116.

Eiben R. (1997). BAJ 2740: One-Generation Study in Wistar Rats. Bayer Agriculture. (1): 164-165.

Eiben R. (2000). Two-Generation Study in Wistar Rats. Bayer Agriculture (1): 1002.

European Food Safety Authority (EFSA). (2007). Conclusion on the peer review of the pesticide risk assessment of the active substance Spiromesifen. European Food Safety Authority Journal (7):1–69.

European Food Safety Authority (EFSA). (2012). Conclusion on the peer review of the pesticide risk assessment of the active substance Spiromesifen. European Food Safety Authority Journal (10): 56.

Food and Agricultural Organisation and World Health Organisation (2022). Report 2021-Pesticide residues in food-Joint FOA/WHO meeting on pesticide residues Rome. FAO and WHO. (1):232-236

Freyberger A. (2002). Effects on Rat Testicular Mitochondrial NADH (Reduced Nicotinamide Adenine Dinucleotide) and NADPH (Reduced Nicotinamide Adenine Dinucleotide Phosphate) Levels. Bayer Agriculture (1):44.

Gravalos C., Fernandez E., Belando A., Moreno I., Ros C. and Bielza P.(2015). Cross-resistance and baseline susceptibility of Mediterranean strains of Bemisia tabaci to Cyantraniliprole. Pest Management Science (71): 1030–1036.

Guillen J., Navarro M. and Bielza P. (2014). Cross-resistance and baseline susceptibility of Spirotetramat in Frankliniella occidentalis (Thysanoptera: Thripidae). Journal of Economic Entomology (107): 1239–1244.

Harwood J.L. (1988). Fatty acid metabolism. Annual Review of Plant Physiology (31): 101–138.

Herbold. B. (1996). In Vitro Mammalian Chromosome Aberration Test with Chinese Hamster V79 Cells. Bayer Agriculture(1): 37-38.

Jeschke P. (2016). Propesticides and their use as agrochemicals. Pest Management Science (72):210–225.

Kissoum N., Bensafi-Gheraibia H., Hamida Z.C. and Soltani N. (2020). Evaluation of the pesticide Oberon on a model organism Drosophila melanogaster via topical toxicity test on biochemical and reproductive parameters in Comparative Biochemistry and Physiology Part C. Toxicology & Pharmacology (228):108666

Liu K.C., Lin S.W. and Ge W. (2011). Differential regulation of gonadotropin receptors by estradiol in the zebra fish ovary involves nuclear estrogen receptors that are likely located on the plasma membrane. Endocrinology (11): 4418–4430.

Lummen P., Khajehali J., Luther K. and Van Leeuwen T. (2014). The cyclic keto-enol insecticide spirotetramat inhibits insect and spider mite acetyl-CoA carboxylases by interfering with the carboxyltransferase partial reaction. Insect Biochemestry and Molecular Biology (55): 1–8.

MacBean C.(2010).Spirodiclofen.The ePesticide Manual, 15th Edition, Version 5.0.1 British Crop Protection Council. Surrey UK.

Marcic D., Petronijevic S., Drobnjakovic T., Prijovic M., Peric P. and Milenkovic S. (2012). The effects of Spirotetramat on life history traits and population growth of Tetranychus. Experimental and Applied Acarology (56):113–122.

Muehlebach M., Buchholz A., Zambach W., Schaetzer J., Daniels M., Hueter O., Kloer D.P.,Lind R., Maienfisch P. and Pierce A. (2020). Spiro N-methoxy piperidine ring containing aryldiones for the control of sucking insects and mites: Discovery of Spiropidion. Pest Management Science (76): 3440–3450.

Muehlebach M., Schaetzer J., Buchholz A., Flemming A.J., Godfrey C.R., Godineau E., Hamer M., Hatt F., Hueter O., Kloer D., Maienfisch P., Oliver S., Perruccio F., Pitterna T., Popp C., Senn R., Slater R., Smejkal T., Stafford D., Wenger J., Wildsmith L., ZambachW. (2019).Abstr IUPAC2019 Ghent Crop Protection Chemistry 3.1.9.

Nauen R., Schnorbach H.J. and Elbert A. (2005). The biological profile of Spiromesifen (Oberon®) – A new tetronic acid insecticide / acaricide. Pflanzenschutz Nachrichten Bayer (58): 417–440.

Nauen R.,Stumpf N. and Elbert A.(2000). Efficacy of BAJ 2740, a new acaricidal tetronic acid derivative, against tetranychid spider mite species resistant to conventional acaricides. Proceedings of Brighton Crop Protection Pests & Diseases (1): 453–458.

Ouyang Y., Montez G.H., Liu L. and Grafton-Cardwell E.E. (2012). Spirodiclofen and Spirotetramat bioassays for monitoring resistance in citrus red mite, Panonychus citri. Pest Management. Science (68): 781–787.

Safety data sheet suspension concentrate (SDS) (2022). Safety data sheet of oberon insecticide. Crop Protection Pests and Diseases, Bayer Crop Science (3): 453–458

Schobert, R. and Schlenk A. (2008). Tetramic and tetronic acids: An update on new derivatives and biological aspects. Bioorganic and Medicinal Chemistry (8): 4203–4221

Sheets L. and Gilmore R. (2001). A Subchronic Neurotoxicity Screening Study with Technical Grade BAJ 2740 in Wistar Rats. Bayer Corporation and Pathology Associates International (14): 524-525.

Sparks T.C. and Nauen R. (2015). Mode of action classification and insecticide resistance management. Pesticide Biochemistry and Physiology (121):122–128.

Spiropidion discovery, Broad spectrum control of sucking insects and mites for multicrop utility (2021). Recent Highlights in the Discovery and Optimization of Crop Protection Products (1):241-260.

Stuart B, Sheets L. and Gilmore R. (2000). An Acute Oral Neurotoxicity Screening Study with Technical Grade BAJ 2740 in Wistar Rats. Bayer Corporation and Pathology Associates International (870):432-433.

United States Environmental protection Agency (USEP) (2007). Spiromesifen Human Health Risk Assessment. (331): 16.

Wang D., Gong P., Li M., Qiu X. and Wang K. (2009). Sublethal effects of spinosad on survival, growth and reproduction of Helicoverpa armigera . Pest Management Science, (65): 223–227.

Whale B. (2000). Technical Grade BAJ 2740 240: An Oncogenicity Testing Study in the Mouse. Bayer Corporation (1): 2467.

Wirnitzer U. and Hartmann E. (2002). BAJ 2740 Study on Subchronic Toxicity in Wistar Rats Bayer Agriculture (1):117.

Wirnitzer U. and Romeike A. (1998). BAJ 2740 Study on Subchronic Toxicity in Wistar Rats. Bayer Agriculture (1): 647.

Wu H.M., Wei F.L., Zhu G.N. and Lou Y.G. (2012). Study on distribution and metabolism of Spirotetramat in rat. Chinese Journal of Pesticide Science (4): 417–422.

Yamamoto A. (2018). Trends in Acaricide and nematicide development. Trends in Pesticide Discovery Research (1) 212.

Ye X. (2011). A novel mechanism of action Insecticide: Spirotetramat. World Pesticide (5): 54–55.

Yin X.H., Zhu G.N., Li X.B. and Liu S.Y. (2009). Genotoxicity evaluation of Chloropyrifos to amphibian Chinese toad by comet assay and micronucleus test. Mutation Research (680): 2–6.

Zhang Q.M., Zhang G.L., Yin P.J., Lv Y.Z., Yuan S., Chen J.Q., Wei B.B. and Wang C.X.(2015). Toxicological effects of soil contaminated to the earthworm Eisenia fetida. Chemosphere (139): 138–145.

Zyoud S.H., Sawalha A.F., Sweileh W.M., Awang R., Al-Khalil S.I., Al-Jabi S.W., and Bsharat N.M. (2010) Knowledge and practices of pesticide use among farm workers in the West Bank, Palestine: Safety implications. Environ. Health Prev. Med. (15): 252-261.

Received: 04th February 2023; Accepted: 15th February 2023; First distribution: 07th May 2023