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COMPARATIVE TOXICOLOGICAL AND HYGIENIC ASSESSMENT AND COMBINED ACTION OF MODERN FUNGICIDES BASED ON AZOXYSTROBIN, PYDIFLUMETOFEN, PROPICONAZOLE

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Annotation. *The creation of combined pesticide formulations for the purpose of more effective protection of agricultural crops is a significant factor in the importance of assessing their synergistic effects. Substances that produce a similar pesticidal effect, in combination with each other, can enhance the toxic effect and, therefore, show dose additivity. The aim is toxicological and hygienic evaluation and determination of the type of combined action of pydiflumetofen, azoxystrobin and propiconazole - the active substances of the mixed formulations "Miravis Ace 275 SE" and "Miravis Neo 300 SE" according to toxicity indicators. Analytical review of scientific publications was carried out using data from EFSA, FAO, ECHA, PPDB, Internet sites. According to the literature, a comparative toxicological-hygienic evaluation of fungicidal preparations and their active substances was carried out. The general mechanism of fungicidal action was evaluated according to the classification developed by the Fungicide Resistance Action Committee (FRAC). The hazard class according to the toxic metric parameters of the substances under study was determined in accordance with the Hygienic classification of pesticides according to the degree of hazard (DSanPiN 8.8.1.002-98). The nature and type of combined action was carried out according to the Finney method with evaluation according to the criteria of acute toxicity. Systematization of data, their structuring for the purpose of further toxicological assessment of substances at the level of their inactive and threshold doses was carried out in the table editor Microsoft Excel 2019 (Microsoft Office 2019, Microsoft). As a result of the conducted research, the most toxic mixed fungicide "Miravis Neo 300 SE" based on three active substances was determined (the average lethal dose (LD50) is 550 mg/kg). It has been established that in cases of combinations of active substances to obtain a lethal effect, a dose of substances that does not exceed 100% in total is required, which indicates the strengthening (potentiation) of toxicity. It was pointed out that the share of propiconazole in the potentiation of the toxic effect in both mixed preparations is the highest compared to other active substances and is 0.87 for "Miravis Neo 300 SE" and 0.88 for "Miravis Ace 275 SE". It was observed that the adverse effects of simultaneous exposure to several pesticides may change during the transition from acute to chronic exposure. Therefore, it is important to continue the research of the active substances of pesticides with the determination of limiting criteria for harmfulness, taking into account the remote effects of exposure. Thus, the toxicological and hygienic assessment made it possible to establish that the combined fungicides "Miravis Neo 300 SE" and "Miravis Ace 275 SE" are more toxic in the mode of single oral exposure in comparison with the single-component fungicide "Miravis 200 SC". Increased toxicity (potentiation) can be considered as a consequence of the simultaneous exposure of several active substances. The active substance propiconazole poses the main danger of adverse effects on the body at the level of lethal doses. The obtained values of the potentiation coefficients will be taken into account in further studies of the risk assessment of complex and combined effects of pesticides on workers and their potential danger when entering the human body with food products.*

Keywords: *fungicides, azoxystrobin, pydiflumetofen, propiconazole, acute toxicity, danger, combined action.*

Introduction

Progress in the development of the chemical method of plant protection is based on the fundamental achievements of modern genomics, which make it possible to create active substances of pesticides with new sites of action, to study the mechanisms of cross-resistance and to identify compounds that are able to interact with these sites, complementing each other in terms of the spectrum of pesticide action.

The Ukrainian agro-industrial complex in the sector of crop protection technologies is replenished with new fungicides "Miravis 200 SC", "Miravis Ace 275 SE" and "Miravis Neo 300 SE", created by Syngenta Crop Protection AG (Switzerland) according to modern innovative technologies for combating a complex of diseases of grain, fruit, and vegetable crops.

The composition of the formulation "Miravis 200 SC" as an active substance includes pydiflumetofen; the "Miravis Ace 275 SE" is a combined fungicide, which includes pydiflumetofen and propiconazole; the combined product "Miravis Neo 300 SE" contains three active substances: pydiflumetofen, azoxystrobin and propiconazole.

The combination of these substances in pesticide formulations provides a long-term protective and therapeutic effect and makes it possible to significantly expand the range of controlled diseases.

Determination of the mechanism aimed at pesticide activity against target organisms is of great importance in understanding the general mode/mechanism of toxic action on warm-blooded animals, including humans. Compounds that produce a similar pesticide effect, in combination with each other, can increase the toxic effect and, therefore, show dose additivity [1].

The aim - toxicological and hygienic evaluation and determination of the type of combined effect of pydiflumetofen, azoxystrobin and propiconazole - active substances of the mixed preparations "Miravis Ace 275 SE" and "Miravis Neo 300 SE" according to toxicity indicators.

Materials and methods

The object of the research is the fungicidal formulations "Miravis 200 SC", "Miravis Ace 275 SE", "Miravis Neo 300 SE" and their active substances pydiflumetofen, azoxystrobin and propiconazole. Research materials were scientific publications, including reports of the European Food Safety Agency (EFSA), the Food and Agriculture Organization (FAO), the European Chemicals Agency (ECA), the database of pesticide properties (PPDB), electronic resources related to the toxicological properties of the studied substances. The general mechanism of fungicidal action was evaluated according to the classification developed by the Fungicide Resistance Action Committee (FRAC) [7]. The assessment of the toxicity of drugs and their active substances for laboratory animals and their danger to humans was carried out in accordance with the Hygienic Classification of Pesticides by Degree of Hazard (DSanPiN 8.8.1.002-98) [8].

Determination of the nature and type of combined action was carried out according to the method of Finney (1952), using the toxic metric data of combined drugs and their active substances (estimation according to the criteria of "lethal effect", Yu. S. Kagan, 1981). This method allows determine the nature and type of combined action (summation, antagonism, potentiation) from the simultaneous exposure to the body of two or more chemical substances for which the average lethal doses (LD50) and the percentage content of the substance included in the LD50 of the mixture are known. Summation occurs when the sum of percentages is equal to 100, the sum of percentages less than 100 indicates a potentiation effect, more than 100 - antagonism. In the case of detection of increased toxicity, the potentiation coefficient was determined. Systematization of data, their structuring for the purpose of further toxicological evaluation of substances at the level of their inactive and threshold doses was carried out in the spreadsheet editor Microsoft Excel 2019 (Microsoft Office 2019, Microsoft).

The research was carried out as part of the Scientific Research Work Prevention of the negative impact of pesticides on human health when they are ingested with plant products (State registration number: 0120U100806).

Results. Discussion

In order to assess the relationship between fungicidal activity and potential risks of the combined effect of the investigated mixed preparations based on pydiflumetofen, azoxystrobin and propiconazole, their classification was carried out according to the mechanism of action on the target harmful factors (Table 1).

Pydiflumetofen is a broad-spectrum fungicide from a relatively new class of SDHIs - succinate dehydrogenase (SDH) inhibitors of the 2nd generation, a chemical class of carboxamides, a new subgroup of N-methoxy-pyrazole-carboxamides. SDH is a functional part of the tricarboxylic acid cycle and is associated with mitochondrial respiration (complex II in the mitochondrial respiration chain) [14].

Azoxystrobin from the group methoxyacrylates of class of strobilurins is an analogue of natural metabolites of the fungus Strobilurins Oudemansins, belongs to the group of QoI-fungicides, the mechanism of action of which is associated with the disruption of electron transfer in the chain of cytochromes b and c1 of complex III (ubiquinone-cytochrome c-oxidoreductase or bc1-complex), which leads to inhibition of mitochondrial respiration and energy deficit of the target organism [12].

Propiconazole belongs to the chemical class of triazoles, the mechanism of action is a demethylation inhibitor (DMI-fungicide) [13]. The fungicidal effect is the result of direct inhibition of the activity of lanosterol-14-alpha-demethylase CYP51 - an important enzyme in the biosynthesis of ergosterol, which ensures the integrity of cell walls. The CYP51 gene is the only member of the CYP family and its catalytic properties are identical in plants, fungi, prokaryotes and higher species. It is therefore likely that the mechanism by which triazoles exert their fungicidal activity is responsible for some of the toxic effects in mammals.

In this manner, according to the classification [7], pydiflumetofen and azoxystrobin by the type of biochemical action on the organism of the pathogen belong to the common group of inhibitors of cellular respiration (group C), propiconazole - to inhibitors of sterol synthesis in cell membranes (group G). The combination of these substances in pesticide formulations contributes to their biological effectiveness and, at the same time, increases the potential danger of synergistic effects from the simultaneous exposure of substances characterized by

Table 1. Classification of studied fungicides by mechanism of action.

Common name (ISO); [CAS RN]; chemical group	Biochemical mechanism of action / Target site and code	Group name
Pydiflumetofen; [1228284-64-7]; N-methoxy-(phenyl--ethyl)-pyrazole-carb-oxamides	C. Respiration / C2 complex II: succinate dehydrogenase	SDHI (Succinate dehydrogenase inhibitors) (SDHI-fungicides)
Azoxystrobin; [131860-33-8]; methoxyacrylates	C. Respiration / C3 complex III: cytochrome bc1 (ubiquinol oxidase) at Qo site *(cyt b gene)*	Quinone outside Inhibitors (QoI-fungicides)
Propiconazole; [60207-90-1]; triazoles	G. Sterol biosynthesis in membranes / G1 C14-demethylase in sterol biosynthesis *(erg11/cyp51)*	Demethylation Inhibitors (DMI-fungicides)

Table 2. Toxicometric parameters of pesticide formulations and active substances and their hygienic classification according to the degree of hazard.

Hazard criteria	Toxicity parameters (animal species)					
	"Miravis 200 SC"	"Miravis Ace 275 SE"	"Miravis Neo 300 SE"	Pydiflumetofen	Azoxystrobin	Propiconazole
Acute oral toxicity, LD_{50}, mg/kg	2958 rat, ♀	> 2000 rat, ♀	550 rat, ♀	> 5000 rat, ♀	> 5000 rat, mouse (♂,♀)	550 (rat, ♀), 1490 (mouse, ♂,♀)
Acute dermal toxicity, LD_{50}, mg/kg	> 5000 rat (♂, ♀)	> 5000 rat (♂,♀)	> 5000 rat (♂, ♀)	> 5000 rat (♂,♀)	> 2000 rat (♂,♀)	> 5000 rat (♂,♀)
Acute inhalation toxicity, LC_{50}, mg/m³	3500 rat (♂, ♀)	> 2130 rat (♂,♀)	> 2080 rat (♂, ♀)	> 5110 rat (♂,♀)	698 (rat,♀) 962 (rat,♂)	> 5800 rat (♂,♀)
Skin irritation	absent (rabbit)	absent (rabbit)	mild (rabbit)	absent (rabbit)	mild (rabbit)	absent (rabbit)
Eye irritation	mild (rabbit)	moderate (rabbit)	moderate (rabbit)	mild (rabbit)	mild (rabbit)	absent (rabbit)
Skin sensitization	absent (mouse)	absent (mouse)	absent (mouse)	absent (mouse)	absent (guinea pigs)	absent (guinea pigs)
Hazard class	II	II	II	III	II	III

Note: ♂ - males, ♀ - females

Table 3. The content (%) active substances (a.s.) in the composition of the studied preparations and acute oral toxicity with their combined effect on rats.

Name of the preparation	The content (%) a.s. in the preparation			LD_{50}, mg/kg *
	Pydiflumetofen	Azoxystrobin	Propiconazole	
"Miravis Neo 300 SE"	7,5	10,0	12,5	550 / 165
"Miravis Ace 275 SE"	15,0	- **	12,5	2000 / 550

Notes: * - in the numerator the LD50 of the preparation based on the entire component composition, in the denominator - the LD_{50} of the preparation taking into account only the active substances; ** - the active ingredient in the composition of the preparation is absent.

common mechanisms of action.

Using the toxic metric parameters, established for formulations and their active substances by different routes of entry into the body, their comparative toxicological and hygienic evaluation was carried out (Table 2) [2, 5, 6, 9, 10, 11].

In accordance with the Hygienic Classification of Pesticides by Degree of Hazard (DSanPiN 8.8.1.002-98), an integral hazard class - II (hazardous) was determined for all the studied preparations according to the limiting criterion - inhalation toxicity.

Inhalation toxicity is also the limiting criterion of hazard for Pydiflumetofen and azoxystrobin, according to which Pidiflumetofen belongs to the III class of hazard (moderately hazardous), azoxystrobin - to the II class of hazard (hazardous). The integral hazard class of propiconazole is III (moderately hazardous), the limiting criterion is oral and inhalation toxicity.

The obtained results of comparative assessment of toxicometric parameters of active substances and preparative forms based on them made it possible to make the following conclusion. The three-component formulation Miravis Neo 300 SE, which includes pydiflumetofen, azoxystrobin and propiconazole (LD_{50} of the formulation is 550 mg/kg), was the most toxic when administered orally to rats. The two-component formulation "Miravis Ace 275 SE" containing pydiflumetofen and propiconazole (LD_{50} slightly exceeds 2000 mg/kg) is less toxic for this route of administration. The least toxic is the formulation "Miravis 200 SC" based on a single substance of pydiflumetofen (LD50 - 2958 mg/kg).

To take into account the combined effect of the active substances in the composition of the mixed preparations "Miravis Neo 300 SE" and "Miravis Ace 275 SE", the contribution of each substance to the average lethal dose of the mixtures was studied (Table 3).

The data in Table 3 show that the amount of pydiflumetofen in "Miravis Neo 300 SE" and "Miravis Ace 275 SE" is in a ratio of 1:2, the content of propiconazole is the same, and azoxystrobin is only in preparation "Miravis Neo 300 SE".

When pydiflumetofen, azoxystrobin and propiconazole were administered orally to rats at the level of lethal doses, the sum of percentages of their LD_{50} was 14.43%, with a combination of pydiflumetofen and propiconazole, the sum of percentages of LD_{50} was 51.45% (Table 4).

Thus, in both cases of combinations of active substances in the mixed preparations "Miravis Neo 300 SE" and "Miravis Ace 275 SE" to obtain a lethal effect, a dose of substances that does not exceed 100% in the sum

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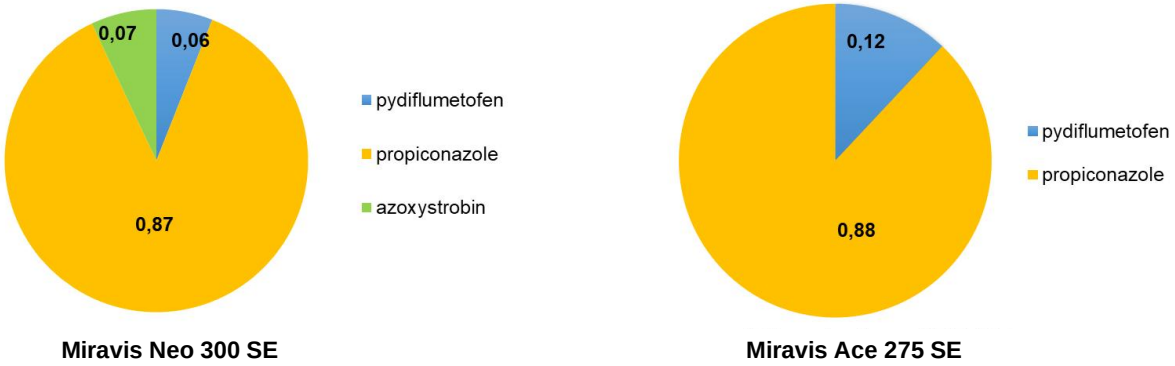
Table 4. The content (mg/kg) of a.s. in the LD50 composition of the preparation and the percentage of this amount from the LD50 of each substance.

Name of the active substance	The content (mg/kg) of a.s. in the LD50 composition*		% of the LD50 of the active substance	
	"Miravis Neo 300 SE"	"Miravis Ace 275 SE"	"Miravis Neo 300 SE"	"Miravis Ace 275 SE"
Pydiflumetofen	41,25	300,00	0,83	6,00
Azoxystrobin	55,00	- **	1,10	-
Propiconazole	68,75	250,00	12,50	45,45
The amount of percentage from LD50 a.s.			**14,43**	**51,45**

Notes: * - LD_{50} of the preparation taking into account only active substances (165 mg/kg for "Miravis Neo 300 SE" and 550 mg/kg - for "Miravis Ace 275 SE"; ** - the active substance in the composition of the preparation is absent.



Miravis Neo 300 SE **Miravis Ace 275 SE**

Fig. 1. The contribution of active substances in the potentiation of toxicity.

is required, which indicates the potentiation of toxicity.

The degree of potentiation was determined by the potentiation coefficient, which shows how many times the toxicity increased. It was established that for the combined preparation "Miravis Neo 300 SE" (pydiflumethofen, 75 g/l + azoxystrobin, 100 g/l + propiconazole, 125 g/l) potentiation coefficient is 6.9 (100% : 14.43%). For the preparation "Miravis Ace 275 SE" (pydiflumethofen, 150 g/l + propiconazole, 125 g/l), the potentiation effect is weaker, potentiation coefficient is 1.9 (100% : 51.45%).

It is worth mentioning that the content of propiconazole in the studied combined drugs is the same and amounts to 12.5% (Table 3). However, the content of this substance in the total dose of active substances that leads to a lethal effect is different and amounts to 68.75 mg/kg and 250 mg/kg for "Miravis Neo 300 SE" and "Miravis Ace 275 SE", accordingly (Table 4). And the share of propiconazole in the potentiation of the toxic effect in both mixed preparations is the highest compared to other active substances and is 0.87 for "Miravis Neo 300 SE" and 0.88 for "Miravis Ace 275 SE" (Fig. 1).

It is known that at the level of lethal doses and concentrations, manifestations of all types of combined action (summation, potentiation, antagonism) are possible, which has a certain theoretical basis, since one of the ingredients of the mixture can affect enzymes that metabolize another ingredient of the mixture.

Research conducted in the 1990s by domestic scientists established cases of potentiation of the action of preparative forms of pesticides containing organophosphorus compounds and pyrethroids through their toxicokinetic interaction with organic solvents as components of the mixture, as well as by increasing the period of detoxification of pyrethroids by some organophosphorus compounds.

Establishing the "dose-time-effect" dependence is of great importance for determining the nature of the simultaneous exposure of the active substances of pesticides, since the adverse effects of such exposure may change during the transition from acute to chronic exposure.

A characteristic feature of the toxicological properties of the modern action substances of pesticide substances is their potential hazard of remote effects of action at the level of doses significantly lower than their LD_{50}. In this case, the criteria for evaluating combined effects at the level of threshold and ineffective doses are physiological and biochemical indicators that reproduce the mechanism of action of the substances under study. The interactions of such substances are determined by both toxicokinetic and toxicodynamic mechanisms, and it is difficult to predict them.

Therefore, the risk assessment for humans from the simultaneous exposure of several substances must be carried out in each specific case and based on the data from the test of the respective mixtures. The premise of such an assessment is the grouping of active substances of pesticides into cumulative assessed groups (CAG) according to the general mechanism of toxic action. For this, it is necessary to carry out a thorough study of each individual substance that is part of the mixture, with the

establishment of the method/mechanism of action, dose dependences for individual effects for different durations of exposure, and determination of the limiting criterion of harmfulness, of which primarily depends on the manifestation of the toxicological effect.

Therefore, the obtained research results made it possible to establish the main active substance of mixed pesticides, which poses a significant risk of adverse effects on the body at the level of lethal doses. This substance turned out to be propiconazole.

From the analysis of literature data, it is known that propiconazole, as one of the substances of the class of triazoles, was studied in the assessment of the cumulative effects of pesticides and was included in two CAG groups: the group of substances that cause craniofacial malformations for the assessment of acute dietary risk and the group of substances for chronic assessment, for which are characterized by hepatotoxicity [3].

In the European Union (EU), after a second review, propiconazole was classified by experts of the risk assessment committee as a reproductive toxicant of category 1B H360D (may cause harm to the unborn child) [4].

The above allows to predict the possible negative impact of mixed pesticide preparations on human health and determines the need for their further toxicological assessment and determination of limiting criteria for harmfulness, taking into account remote effects of exposure.

Conclusions and prospects for further development

1. The comparative toxicological and hygienic assessment made it possible to establish that the combined fungicides "Miravis Neo 300 SE" and "Miravis Ace 275 SE" are more toxic in the mode of single oral exposure in comparison with the single-component fungicide "Miravis 200 SC".

2. Intensification of toxicity (potentiation) can be regarded as a consequence of the simultaneous effect on the body of several active substances. Propiconazole contributes the most to potentiation of toxicity.

3. The obtained values of the potentiation coefficients will be taken into account in further studies of the risk assessment of the complex and combined effect of pesticides on workers and their potential danger when entering the human body with food products.

Toxicological evaluation and determination of the limiting criteria for the harmfulness of pydiflumetofen, azoxystrobin and propiconazole, taking into account the remote effects of exposure in order to study their combined effect on workers and when they enter the human body with food products.

References

[1] Antonenko, A. M., Vavrinevych, O. P., Korshun M. M., & Omelchuk S. T. (2019). Особливості механізмів дії сучасних пестицидів на функціонування щитоподібної залози (огляд літератури) [Peculiarities of the mechanisms of action of modern pesticides on the functioning of the thyroid gland (literature review)]. *Довкілля та здоров'я - Environment and health,* 2(91), 60-64. DOI: https://doi.org/10.32402/dovkil2019.02.060

[2] ECHA (European Chemicals Agency). (2016). Committee for Risk Assessment (RAC). (2016). Opinion proposing harmonized classification and labelling at EU level of propiconazole. CLH-O-0000001412-86-139/F. Adopted 9 December 2016. URL: https://echa.europa.eu/documents/10162/723fe08d-2ec7-105b-51aa-05064bd91ac3

[3] EFSA (European Food Safety Authority). (2009). Scientific Opinion on risk assessment for a selected group of pesticides from the triazole group to test possible methodologies to assess cumulative effects from exposure throughout food from these pesticides on human health. *EFSA Journal,* 7(9), 1167, 187. DOI: https://doi.org/10.2903/j.efsa.2009.1167

[4] EFSA (European Food Safety Authority). (2017). Conclusion on the peer review of the pesticide risk assessment of the active substance propiconazole. *EFSA Journal* 15(7), 4887, 28. https://doi.org/10.2903/j.efsa.2017.4887

[5] European Commission. (2019). Combined Draft Assessment Report prepared according to Regulation (EC) №1107/2009 and Proposal for Harmonised Classification and Labelling (CLH Report) according to Regulation (EC) №1272/2008. Pydiflumetofen. (1, p. 280). URL: https://echa.europa.eu/documents/10162/da5eb3c8-0089-60e5-44e5-68936d4f26e6

[6] Food and Agriculture Organization of the United Nations (FAO). (2022). Specifications and evaluations for agricultural pesticides. Azoxystrobin. URL: https://www.fao.org/3/ca2760en/ca2760en.pdf

[7] Fungicide Resistance Action Committee (2022). FRAC Code List©*2022: Fungal control agents sorted by cross-resistance pattern and mode of action (including coding for FRAC Groups on product labels). URL: https://www.frac.info/docs/default-source/publications/frac-code-list/frac-code-list-2022--final.pdf?sfvrsn=b6024e9a_2

[8] Ministry of Health of Ukraine (1998). Пестициди. Гігієнічна класифікація пестицидів за ступенем небезпечності: DSanPiN 8.8.1.002-98. (затверджено МОЗ України 28.08.98 №2) [Pesticides. Hygienic classification of pesticides by degree of danger: DSanPiN 8.8.1.002-98. (approved by the Ministry of Health of Ukraine on August 28, 1998 №2)]. *Збірник важливих офіційних матеріалів з санітарних та протиепідемічних питань - A collection of important official materials on sanitary and anti-epidemic issues*, 9(1), 249-266. Київ - Kyiv, 2000.

[9] Miravis ACE (2019). Фунгіцид (A21573C). Syngenta Crop Protection, LLC https://www.syngenta-us.com/sds-label/miravis_ace

[10] Miravis® 200 SC, k.s. (2022). *Фунгіциди. Засоби захисту рослин [Fungicides. Plants protecting tools].* ТОВ "Сингента" - Syngenta LLC. URL: https://www.syngenta.ua/product/crop-protection/miravisr-200-sc-k-s

[11] Miravis® Neo 300 SE, SE. (2022). *Фунгіциди. Засоби захисту рослин [Fungicides. Plants protecting tools].* ТОВ "Сингента" - Syngenta LLC. URL: https://www.syngenta.ua/product/crop-protection/miravisr-neo-300-se-se

[12] Pesticide Properties Data Base (PPDB). Azoxystrobin (Ref: ICI 5504). URL: http://sitem.herts.ac.uk/aeru/ppdb/en/Reports/54.htm

[13] Pesticide Properties Data Base (PPDB). Propiconazole (Ref: CGA 64250). URL: http://sitem.herts.ac.uk/aeru/ppdb/en/Reports/551.htm

[14] Pesticide Properties Data Base (PPDB). Pydiflumetofen (Ref: SYN 545794). URL: http://sitem.herts.ac.uk/aeru/ppdb/en/Reports/3086.htm

ПОРІВНЯЛЬНА ТОКСИКОЛОГО-ГІГІЄНІЧНА ОЦІНКА ТА КОМБІНОВАНА ДІЯ СУЧАСНИХ ФУНГІЦИДІВ НА ОСНОВІ АЗОКСИСТРОБІНУ, ПІДІФЛУМЕТОФЕНУ, ПРОПІКОНАЗОЛУ

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Анотація. *Створення комбінованих пестицидних формуляцій з метою більш ефективного захисту сільськогосподарських культур є визначним фактором важливості оцінки їх синергічних ефектів. Речовини, які виробляють подібний пестицидний ефект, у комбінації одна з одною можуть підсилювати токсичний ефект і, отже, проявляти адитивність дози. Мета дослідження - токсиколого-гігієнічна оцінка та визначення типу комбінованої дії підіфлуметофену, азоксистробіну та пропіконазолу - діючих речовин сумішевих препаратів "Міравіс Ейс 275 SE, CE" та "Міравіс Нео 300 SE, CE" за показниками токсичності. Аналітичний огляд наукових публікацій проведений з використанням даних EFSA, FAO, ECHA, PPDB, інтернет-сайтів. За даними літератури проведена порівняльна токсиколого-гігієнічна оцінка фунгіцидних препаратів та їх діючих речовин. Загальний механізм фунгіцидної дії оцінювали відповідно до класифікації, розробленої Комітетом із дій щодо резистентності фунгіцидів (FRAC). Клас небезпечності за параметрами токсикометрії досліджуваних речовин визначали згідно з Гігієнічною класифікацією пестицидів за ступенем небезпечності (ДСанПіН 8.8.1.002-98). Характер та тип комбінованої дії проводили за методом Фінні з оцінкою за критеріями гострої токсичності. Систематизацію даних, їх структурування з метою подальшої токсикологічної оцінки речовин на рівні їх недіючих і порогових доз проводили у табличному редакторі Microsoft Excel 2019 (Microsoft Office 2019, Microsoft).*

У результаті проведених досліджень визначений найбільш токсичний сумішевий фунгіцид "Міравіс Нео 300 SE, CE" на основі трьох діючих речовин (середньосмертельна доза (ЛД50) становить 550 мг/кг). Встановлено, що у випадках комбінацій діючих речовин для отримання смертельного ефекту потрібна доза речовин, яка у сумі не перевищує 100%, що вказує на підсилення (потенціювання) токсичності. Відмічено, що частка пропіконазолу у потенціюванні токсичного ефекту в обох сумішевих препаратах є найвищою у порівнянні з іншими діючими речовинами та становить 0,87 для "Міравіс Нео 300 SE, CE" та 0,88 - для "Міравіс Ейс 275 SE, CE". Зазначено, що несприятливі ефекти від одночасного впливу кількох пестицидів можуть змінюватися при переході від гострого досліду до хронічного. Тому важливо продовжити дослідження діючих речовин пестицидів з визначенням лімітуючих критеріїв шкідливості з урахуванням віддалених ефектів впливу. Таким чином, проведена токсиколого-гігієнічна оцінка дозволила встановити, що більш токсичними в режимі однократного перорального впливу є комбіновані фунгіциди "Міравіс Нео 300 SE, CE" та "Міравіс Ейс 275 SE, CE" у порівнянні з однокомпонентним фунгіцидом "Міравіс 200 SC, KC". Підсилення токсичності (потенціювання) можна розцінювати як наслідок одночасного впливу кількох діючих речовин. Діюча речовина пропіконазол становить основну небезпеку несприятливого впливу на організм на рівні смертельних доз. Отримані значення коефіцієнтів потенціювання будуть враховані у подальших дослідженнях оцінки ризику комплексного та комбінованого впливу пестицидів на працюючих та їх потенційної небезпеки при надходженні до організму людини з харчовими продуктами.

Ключові слова: *фунгіциди, азоксистробін, підіфлуметофен, пропіконазол, гостра токсичність, небезпечність, комбінована дія.*