DEVELOPMENT AND HYGIENIC SUBSTANTIATION OF CALCULATING MODELS FOR PROGNOSIS OF PYRAZOLECARBOXAMIDES, CARBOXAMIDES, TRIAZOLES, CARBAMATES CLASSES OF FUNGICIDES TOXICITY DEPEND ON THEIR PHYSICAL AND CHEMICAL PROPERTIES

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Abstract: Methods for determining the toxicological parameters of pesticides are long-term, labor-intensive and require significant financial and resource costs, which is why laboratories do not always cope with the increasing flow of chemical plant protection products. In solving this problem, the important role is played by methods of mathematical modeling and prediction of xenobiotics toxicity.
The **aim** of the research is the scientific substantiation of the possibility of creating and using of calculation models for predicting the toxicity of various classes of fungicides.
Materials and methods. Toxicometry indices and physico-chemical parameters of widely used in the world agriculture fungicides were used for analysis. Statistical processing of the results was carried out using IBM SPSS StatisticsBase v.22 and MS Excel statistical program packages.
Results. Significant correlation dependences between the toxic properties of fungicides of the class of pyrazole-carboxamides, carboxamides, triazoles, imidazoles, carbamates, dithiocarbamates, methoxyacrylates and their physico-chemical properties were found.
Discussion. In most of cases, the calculated values correlated with experimentally established. For all valid pairs of resultant and factorial variables, a reliable correlation relationship was established.
Conclusion. It was proved that the proposed calculation models for forecasting the hazard of studied fungicides are adequate and significant. The developed algorithm makes it possible to substantially simplify the conduction of toxicological experiments provided that there are data on the physical and chemical properties of the studied compounds and to accelerate the procedure for registration of new fungicides of the studied classes.
Keywords: fungicides, toxicology, calculation models, regression equations, toxicometric parameters, physical and chemical properties.

1. Introduction

Methods for determining the toxicological parameters of pesticides are long-term, labor-intensive and require significant financial and resource costs, which is why laboratories do not always cope with the increasing flow of chemical plant protection products [1]. In solving this problem, the important role is played by methods of mathematical modeling and prediction of xenobiotics toxicity, the results of which can be used both for substantiation of toxicological parameters, and at the stage of experiment planning, which will reduce the errors probability and study duration [2].

Foreign laboratories and institutes have for some time used calculation models of the toxicometric parameters dependence on the physico-chemical properties of xenobiotics [3, 4].

In Ukraine and a lot of other countries, such models for fungicides and herbicides do not exist today, and there are no legal grounds for using the conclusions and threshold values obtained by European experts.

The actuality of the search for alternative approaches to toxicological assessment of pesticides is confirmed by the fact that on May 2, 2017, Ukraine joined the European Convention for the Protection of Vertebrate Animals used for experiments and other scientific purposes of March 18, 1986 [5].

The aim of the research is the scientific substantiation of the possibility of creating and using of calculation models for predicting the toxicity of various classes of fungicides.

2. Materials and methods

Studies were conducted at the Hygiene and ecology institute of Bogomolets National medical university during 2015–2017 years.

In order to develop and substantiate calculation methods in the hygienic assessment of the studied group of pesticides hazards, an array of experimentally established values of LD_{50} (median death dose) with oral and percutaneous admission, LC_{50} (median death concentration) with inhalation admission and NO(A)EL (threshold doses) has been used [6].

For analysis fungicides, which belong to the most widely used in the world agriculture of next chemical classes [7] have been selected: 18 active ingredients (a. i.) of *carboxamide, pyrazole-carboxamide class*; 26 a. i. of *triazole class*; 5 a. i. of *imidazole class*; 21 a. i. of *carbamate class*.

In the initial stages of the study, Pearson's correlation between the toxicological parameters of fungicides and their physical and chemical properties (molecular weight, water solubility, vapor pressure, melting point, distribution coefficient in the octanol-water system (log $P_{o/w}$), surface tension) was analyzed. Data on the physico-chemical properties of fungicides are derived from the IUPAC PPDB [6].

Statistical processing of the results was carried out using IBM SPSS StatisticsBase v.22 and MS Excel statistical program packages (methods of descriptive statistics, correlation and regression analysis of data).

3. Results

Initially Pearson's correlation dependences between the toxic properties of fungicides of the class of pyrazole-carboxamides, carboxamides, triazoles, imidazoles, carbamates, dithiocarbamates, methoxyacrylates and their physico-chemical properties was analyzed.

The results of the correlation analysis on the array of 18 active substances of the class of pyrazole-carboxamides and carboxamides showed that there is a definite positive relationship between dermal LD_{50}, oral LD_{50} and vapor pressure (r=0.53 and 0.70, respectively, p<0, 05). With the determination coefficient (R^2), the proportion of the effect of the investigated factor on the parameters of toxicometry was determined and it was established that the effect fraction of the vapor pressure is 28.5 and 48.3 %, respectively. Also, a positive correlation between NO(A)EL value and water solubility was found (r=0,62; p<0,05). The fraction of this index impact is 39 %.

An analysis of the 26 active substances of the triazole class revealed a negative correlation between NO(A)EL and molecular weight (r=−0.42; p<0.05), the fraction of this index influence

is 17.9 %. There is a significant relationship between NO(A)EL and water solubility (r=0.52; p<0.05) with fraction 27.3 %.

In the analyzed array of carbamates, a positive correlation between LD_{50} per cut and surface tension was detected (r=0.89; p<0.05); negative correlation between LC_{50} inhal. and the surface tension (r=–0.97; p<0.05) and correlation between NO(A)EL and water solubility (r=0.47; p<0.05). Fraction of surface tension effect on LD_{50} per cut and LC_{50} inhal. amounted to 80.1 and 93.5 %, respectively; the water solubility of the studied compounds on NO(A)EL value – 22.5%.

Also an estimation using regression analysis was carried out and on the basis of it, taking into account the determination coefficient, the regression equations, which most closely approximated the connection between the selected physical and chemical properties and the parameters of toxicometry, were selected (**Table 1**). The significance of the obtained regression equations was checked by Fischer's F-criterion, and the individual coefficients in the regression equation (a, b) – by Student's t-criterion.

Assessment of the «a» and «b» coefficients adequacy has shown that in all regression equations they are significant for Student's t-criterion (p<0.05), except for the equation # 6. In this equation, the free coefficient «a» was not reliable, since the absolute value of the criterion t_a was less than $t_{cr.}$, which indicates the impossibility of using this regression equation to predict the risk of fungicides of the carbamates group.

4. Discussion

It can be assumed that as lower the vapor pressure, the lower volatility of the substance and its greater amount remains in the stern or on the skin surface and penetrates into the body of warm-blooded animals and humans, causing more damage [8], which leads to LD_{50} decrease. A positive correlation between NO(A)EL value and water solubility can be explained by the fact that water-soluble compounds are rapidly metabolized and excreted from the body without a tendency to accumulate [9], which reduces toxic manifestations and causes increasing of NO(A)EL.

The revealed dependence between NO(A)EL and molecular weight is due to the fact that compounds with very high molecular weight form isomers that significantly increase the specificity of their action and toxicity, in contrast to substances with a low molecular weight that are badly penetrated into the body, and low molecular weight compounds that can penetrate into the blood with inhalation, oral or percutaneous admission, easily passing through histohemic barriers [10].

It is known that as higher the surface tension, the faster substance will evaporate from the application surface, and the worse it will penetrate through it. Therefore, probably, with increasing surface tension, the inhalation toxicity of the substance increases (LC_{50} decreases) and dermal decreases (LD_{50} increases) [11].

It is proved that the proposed calculation models for forecasting the hazard of pyrazolecarboxamides, carboxamides, triazoles, carbamates fungicides classes are adequate and significant according to the Fisher test (p<0.05). The developed algorithm makes it possible to substantially simplify the conduction of toxicological experiments provided that there are data on the physical and chemical properties of the studied compounds and to accelerate the procedure for registration of new fungicides of the studied classes.

Conclusions:

1. It has been established that there is a significant positive correlation between fungicides of pyrazolecarboxamides, carboxamides class toxicological parameters (LD_{50} per os, LD_{50} per cut, NO(A)EL) and vapor pressure, water solubility (r=0.53; 0.70 and 0.62, respectively, at p<0.05).

2. A significant negative correlation was found between the NO(A)EL values of triazole fungicides and molecular weight; and the positive correlation with water solubility.

3. There is a significant correlation between LD_{50} per cut and surface tension, a negative correlation between LC_{50} inhal. and surface tension, between the NO(A)EL value of carbamates class fungicides and water solubility (r=0.89; –0.97 and 0.47, respectively, at p<0.05.

Table 1

Models of toxicological parameters of different classes of fungicides prediction (linear regression equations)

Chemical class	Observations number (n)	No. of equation	Regression equation	Indices of model adequacy			Coefficients certainty indices		
				F-criterion		approximation reliability (R^2)	a	b	$t_{cr.}$**
				F	$F_{cr.}$ **		t	t	
Carboxx amides, pyrazole-carboxamides	17	1	LD_{50} per os=−2×10^{+06}X_1^2+25046X_1+3355	6,39*	4,49	0,285	4,47*	2,53*	2,12
	17	2	LD_{50} per cut=11515X_1 + 2888	14,03*	4,54	0,483	6,39*	3,75*	2,13
	15	3	NO(A)EL=3×10^{-05}X_2^2−0,030X_2+4,753	8,31*	4,67	0,390	4,51*	2,88*	2,16
Triazoles	23	4	NO(A)EL=−6,11ln(X_3)+37,40	4,58*	4,32	0,179	2,84*	2,14*	2,08
	23	5	NO(A)EL=0,552ln(X_2)+0,102	7,89*	4,32	0,273	3,49*	2,81*	2,08
Carbamates	7	6	LD_{50} per cut=24327ln(X_4)−99022	12,07*	10,13	0,801	2,93	3,47*	3,18
	7	7	LC_{50} inhal.=−29,3ln(X_4)+126,1	42,9*	10,13	0,942	6,97*	6,55*	3,18
	19	8	NO(A)EL=2×10^{-05}X_2+6,775	4,93*	4,45	0,225	2,95*	2,22*	2,11

*Note: * – significant results; ** – (at p=0,05 and number of freedom degrees k_1=1, k_2=n-2); X_1 – vapor pressure, mPa; X_2 – water solubility, mg/l; X_3 – molecular weight; 6. X_4 – surface tension, mN/m*

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