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HYGIENIC SUBSTANTIATION OF CALCULATION MODELS FOR TOXICITY PROGNOSIS OF DIFFERENT HERBICIDES CLASSES

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Abstract. Significant positive correlation between the toxicometry parameters of the studied herbicides (LD_{50} per os, LD_{50} per cut, LC_{50} inhal., NO(A)EL) and molecular weight, water solubility, vapor pressure, solubility in fats ($r = 0.40–1.00$ at $p \leq 0.05$) were established. There was a significant negative correlation between NO(A)EL and molecular weights ($r = -0.70$ at $p<0.05$), LD_{50} per os, LD_{50} per cut and melting point ($r = -0.77$ and -0.76 respectively at $p<0.05$). LC_{50} inhal. and fat solubility and vapor pressure ($r = -0.92$ and -0.70, respectively, at $p<0.05$). A significant positive correlation between LD_{50} per cut and LC50 inhal. and the solubility of sulphonylcarbonyl-triazolinone herbicides in water ($r = 1.0$ at $p<0.05$) were established. The calculation models for predicting the toxicity of herbicides of pyrazole and trikcton, sulfonylurea, urea, sulfonyl-carbonyl-triazolnion, imidazolinone classes were created, their reliability was statistically approved.

Keywords: herbisides, toxicology, calculation models, regression equations.

Introduction. In world practice, calculation models that are used to determine toxicometrics parameters, depending on the physical and chemical properties of substances contained in computer programs, the so-called calculation in silico already exist [1, 2].

Estimation methods complement *in vitro* experiments to minimize the needs in experimental animal, reduce cost and time for toxicological tests. In addition, the calculation methods have a unique advantage in their ability to assess the toxicity of chemicals before they are synthesized [2, 3].

In many countries of the world no such models for herbicides exist today.

On the market of many countries of the world more and more pesticide formulations of Chinese production are getting out [4–6]. Conducting a full range of toxicological studies for each of their active substances is not appropriate, both from the standpoint of bioethics and economics. That is why today it is relevant to search for alternative approaches to the toxicological evaluation of xenobiotics, including pesticides.

The **purpose** of the work was to provide a hygienic substantiation for calculation models of herbicides of different classes toxicity prediction.

Materials and methods. The Hygiene and ecology institute of O. O. Bogomolets National Medical University was cooperating with Chinese manufacturers of pesticides for many years. As a result of such a long-term cooperation, models of prediction of herbicides toxicity was developed.

For the analysis and development of mathematical models of toxicity assessment, we selected herbicides of the following chemical classes most widely used in Ukraine and in the world [7–11]: pyrazoles and triketones ($n = 11$); sulfonylureas ($n = 34$); ureas ($n = 9$); sulfonylcarbonyl-triazolinones ($n = 3$); imidazolinones ($n = 6$). For calculation models substantiation we used an array of toxicometry parameters, experimentally established in the acute — LD_{50} (median lethal dose) with oral and percutaneous admission, LC50 (median lethal concentration) with inhalation admission and chronic experiments — NO(A)EL (threshold doses) [12].

Statistical processing of the results was carried out using a package of statistical programs IBM SPSS "Statistics v.22" and MS Excel. The justification of the calculation models for predicting the hazard of herbicides of the studied classes is based on correlation and regression analysis, taking into account the determination coefficient, which most closely approximates the connection between the selected toxicological parameters and physicochemical properties. The significance of the obtained regression equations was checked by the Fisher's F-criterion, the individual coefficients in the regression equation (a, b) — according to the Student's t-criterion.

Results and discussions. At the first stage, within each of the five studied classes of pesticides, we analyzed Pearson correlation relationships between the toxicometry parameters of substances (LD_{50} at oral and percutaneous intake by laboratory animals, LC_{50} with inhalation intake and NO(A)EL) and their physical and chemical properties (molecular mass, water solubility, vapor pressure, melting point, distribution coefficient in the octanol-water system (log Po/w)). Statistically significant results of correlation analysis are given in Table 1.

Between the water solubility and LC_{50} and LD_{50} with the percutaneous intake values of sulfanylcarbonyl-triazolinones, as well as imidazolinones NO(A)EL, a positive relationship indices for inactive ingredients (a.i.) increases, and, accordingly, their toxicity decreases. This happens due to the fact that water-soluble compounds do not tend to accumulate in the body and are rapidly derived from it [13, 14].

Similarly, a direct correlation was found between the log Po/w and oral LD_{50} indices for pyrazoles and triketones, sulfonylureas; pyrazoles and triketones, imidazolinones NO(A)EL, ureas dermal LD_{50}.

This dependence (with increasing solubility in fats, the value of the index increases and the toxicity of the substance reduces) is not quite typical, since log Po/w is an indicator of the bioavailability of toxic substances, but mainly with a large molecular weight [13, 14].

Table 1. — Relationship between toxicological parameters of herbicides and their physical and chemical properties

Compound class	Resulting variable	Factorial variable	Statistical parameters*		
			correlation coefficient	determination coefficient, %	number of observations (n)
Pyrazoles and triketones	LD_{50} per os, mg/kg	melting temperature, °C	-0.77	60	11
		log $P_{o/w}$	0.71	51	
	LD_{50} per cut, mg/kg	melting temperature, °C	-0.76	58	
	LC_{50} inhal., мг/м^3	log $P_{o/w}$	-0.92	85	
		vapour pressure, mPa	-0.70	45	
	NO(A)EL, mg/kg	molecular mass	-0.70	45	
		log $P_{o/w}$	0.81	66	9
		vapour pressure, mPa	0.67	45	11
Sulfonylureas	LD_{50} per os, mg/kg	log $P_{o/w}$	0.40	16	31
	LD_{50} per cut, mg/kg	vapour pressure, mPa	0.45	18	33
	LC_{50} inhal., mg/m^3	vapour pressure, mPa	-0.58	33	29
Ureas	LD_{50} per cut, mg/kg	molecular mass	0.90	81	9
		log $P_{o/w}$	0.77	59	
	NO(A)EL, mg/kg	molecular mass	0.77	59	6
Sulfanylcarbo-nyl-triazolinones	LD_{50} per cut, mg/kg	molecular weight	1	100	3
		water solubility, mg/l	1	100	
	LC_{50} inhal., mg/m^3	water solubility, mg/l	1	100	
Imidazolinones	LD_{50} per cut, mg/kg	molecular mass	0.83	69	6
	NO(A)EL, mg/kg	water solubility, mg/l	0.94	88	
		log $P_{o/w}$	0.83	69	5
* — only significant results are given in table ($p<0.05$).					

This dependence (with increasing solubility in fats, the value of the index increases and the toxicity of the substance reduces) is not quite typical, since log Po/w is an indicator of the bioavailability of toxic substances, but mainly with a large molecular weight [13, 14].

However, it is known that for compounds with a small molecular weight, other mechanisms for penetration into the body, such as passage through the pores of biological membranes and others, can be realized [15]. In this case, it is likely that such a mechanism was implemented. The classical inverse relationship was found only between LC_{50} and solubility in organic compounds of herbicides from pyrazoles and triketones classes.

The inverse correlation between the vapor pressure and the LC_{50} value of pyrazoles and triketones and sulfonylureas was revealed: the higher the vapor pressure, the greater the volatility of the substance and the lower its median lethal concentration, that is, the higher toxicity [13, 14]. Between vapor pressure and sulfonylureas dermal LD_{50} and pyrazoles and triketones NO(A)EL a positive correlation was found: the lower the vapor pressure, the lower the volatility of the compound and more of the substance remains in the stern or on the surface of the skin and penetrates into the body of warm-blooded animals and humans, that is, the manifestations of toxicity are likely to be greater.

It is known that low-molecular substances in the form of gas or solution, as a rule, easily penetrate into the blood through the lungs, gastrointestinal tract, skin, quickly distributed in tissues, passing through histohemic barriers [14, 15]. This confirms the reliability of the positive correlation between molar mass and dermal LD_{50} of ureas, imidazolinones and sulfonylcarbonyl-triazolinones. The exception is the negative correlation between the molecular weight and the NO(A)EL value of pyrazoles and triketones (the higher the molecular weight, the lower threshold dose value and the higher toxicity). Such a pattern can be explained by the fact that compounds with very high molecular mass form isomers, which greatly increases the specificity of their action and toxicity [15].

The connection (negative) of the melting point with the parameters of toxicometry was found only in the pyrazoles and triketones chemical class: with increasing melting point, oral and dermal LD_{50} values decrease, that is, the toxicity of these compounds increases. This may be due to the fact that the degradation of such substance requires a higher temperature, and therefore it retains its initial physical and chemical properties for longer.

At the next stage, based on the obtained correlation dependences, formulas for calculating the relevant parameters of toxicity and threshold values of herbicides were developed, which are given in Table 2.

The adequacy of mathematical models was checked by Fisher's criterion and the index of approximation reliability; the reliability of the coefficients of the linear regression equations — according to the Student's reliability criterion (Table 2).

Also, exponential, logarithmic, polynomial and step functions were used to approximate the dependencies of the toxicometry parameters on the physical and chemical properties of the studied substances, except for the linear one. In table 3 the mathematical models with the greatest values of approximation accuracy (R2) are given.

Table 2. — Models of herbicides different classes hazard prediction (linear regression equations)

Compound class	Number of observa-tions (n)	№	Regression equation	Adequacy indices of*					
				models			coefficients		
				Fisher's criterion		R^2	a	b	T_{cr}**
				F	F_{cr}**				
Pyrazoles and triketones	11		LD_{50} per os = -47.06X_1 + 11862	13.41*	5.12	0.5984	6.30*	-3.66*	2.26
	11		LD_{50} per os = 1104.5X_2 + 4588.1	12.53*	5.12	0.5058	7.54*	-3.54*	2.26
	11		LD_{50} per cut = -18.368 X_1 + 5736.5	12.54*	5.12	0.5821	7.55*	-3.54*	2.26
	11		LC_{50} inhal. = -0.6665 X_2 + 4.2624	41.15*	5,12	0.8546	16.05*	-6.41*	2.26
	11		LC_{50} inhal. = -60.29X_3 + 4.3464	7.32*	5.12	0.4485	8.47*	-2.71*	2.26
	11		NO(A)EL = -0.0005X_4 + 1.2271	7.32*	5.12	0.0003	8.47*	-2.71*	2.26
	9		NO(A)EL = 0.5003 X_2 + 0.7521	13.36*	5.12	0.6561	2.46*	3.65*	2.26
	11		NO(A)EL = 43.313 X_3 + 0.4691	7.32*	5,12	0.4188	8.47*	-2.71*	2.26
Sulfonylureas	31		LD_{50} per os = -131.29 X_2 + 4838.9	6.11*	4.17	0.0853	25.59*	-2.47*	2.04
	33		LD_{50} per cut = 21243 X_3 + 2412.4	6.63*	4.15	0.1762	11.97*	2.57*	2.04
	29		LC_{50} inhal. = -25.803 X_3 + 5.3894	13.36*	4.18	0.331	29.43*	-3.65*	2.05
Ureas	9		LD_{50} per cut = 1.1525 X_4 + 1849.2	29.40*	5.12	0.8077	9.59*	5.42*	2.26
	9		LD_{50} per cut = 677.98 X_2 + 415.77	10.13*	5.12	0.5913	0.61	3.18*	2.26
	6		NO(A)EL =307.86 X_4 – 318.38	10.13*	5.12	0.6273	0.61	3.18*	2.26
Sulfanylcarbo-nyl-triazolinones	3		LD_{50} per cut = 103.45 X_4 – 38385	254.68*	161.45	0.9961	-14.44*	15.96*	12.71
	3		LD_{50} per cut = 0.0704X_5 + 1972.6	603.90*	161.45	0.9918	19.62*	24.57*	12.71
	3		JILC$_{50}$ inhal. = 0.1054 X_5 – 39.125	6508.27*	161.45	0.9998	63.50*	80.67*	12.71
Imidazolinones	6		LD_{50} per cut = 59.44 X_4 – 14314	8.82*	5.99	0.6881	-2.48*	2.97*	2.45
	6		NO(A)EL = 0.0013 X_5 + 55.627	28.08*	5.99	0.8753	0.87	5.30*	2.45
	5		NO(A)EL = 139.04 X_2 – 66.634	6.61*	6.61	0.6878	-0.43	2.57*	2.57

* — significant result;
** — p = 0.05 and degrees of freedom $k_1 = 1$, $k_2 = n-2$.
Notes:
1) X_1 — melting temperature, °C;
2) X_2 — log $P_{o/w}$;
3) X_3 — vapour pressure, mPa;
4) X_4 — molecular mass;
5) X_5 — water solubility, mg/l;
6) R^2 — reliability of approximation.

Table 3. — Models of different classes herbicides hazard prediction (nonlinear regression equations)

Compound class	Number of observations (n)	№	Regression equation	Model adequacy indices (R^2)
Pyrazoles and triketones	11	1	LD_{50} per os = -3016ln(X_1) + 19514	0.745
	11	2	LD_{50} per os = 380.96 X_2^2 + 194.51 X_2 + 3058.1	0.6205
	11	3	LD_{50} per cut = -0.0346 X_1^2 – 10.331X_1 + 5401.7	0.5932
	11	4	LC_{50} inhal. = 0.014 X_2^2 – 0.7037 X_2 + 4.2081	0.8552
	11	5	LC_{50} inhal. = 4612.1 X_3^2 – 308.62 X_3 + 5.1046	0.7748
	11	6	NO(A)EL = -0.0003 X_4^2 + 0.2104 X_4 – 39.54	0.0648
	9	7	NO(A)EL = 0.3156 X_2^2 – 0.031 X_2 – 0.5456	0.8159
	11	8	NO(A)EL = -439.52 X_3^2 + 66.978 X_3 + 0.3969	0.4242
Sulfonylureas	31	9	LD_{50} per os = 28.583 X_2^2 – 157.95 X_2 + 4798.6	0.0952
	33	10	LD_{50} per cut = 131000 X_3^2 + 8786.9X_3 + 2456.7	0.1833
	29	11	LC_{50} inhal. = 5.3411$e^{-6.779\ X3}$	0.3712
Ureas	9	12	LD_{50} per cut = 0.0006 X_4^2 – 0.2462 X_4 + 2113.5	0.8823
	9	13	LD_{50} per cut = 397.02 X_2^2 – 2237.3 X_2 + 5117.6	0.7787
	6	14	NO(A)EL = 113.66 X_4^2 – 515.41 X_4 + 501.3	0.9755
Sulfanylcarbonyl-triazolinones	3	15	LD_{50} per cut = -3.6004 X_4^2 + 3019.4X_4 – 628059	1.00
	3	16	LD_{50} per cut = -2 × 10^{-06} X_5^2 + 0.1425 X_5 + 1938.2	1.00
	3	17	LC_{50} inhal. = -5 × 10^{-10} X_5^2 + 9 × 10^{-05} X_5 + 1.977	1.00
Imidazolinones	6	18	LD_{50} per cut = 2.4821 X_4^2 – 1364.4X_4 + 189165	0.9801
	6	19	NO(A)EL = 3 × 10^{-09} X_5^2 – 0.0008 X_5 + 93.866	0.9173
	5	20	NO(A)EL = 38.639 X_2^2 – 32.202 X_2 – 45.853	0.9890

Notes:
1) X_1 — melting temperature, °C;
2) X_2 — log $P_{o/w}$;
3) X_3 — vapour pressure, mPa;
4) X_4 — molecular mass;
5) X_5 — water solubility, mg/l;
6) R^2 — reliability of approximation.

In order to verify toxicometry indices of adequacy values using proposed equations, we made the following calculations. and the results were compared with the actual values of oral and dermal LD_{50}, inhalation LC_{50} and NO(A)EL (Figure 1).

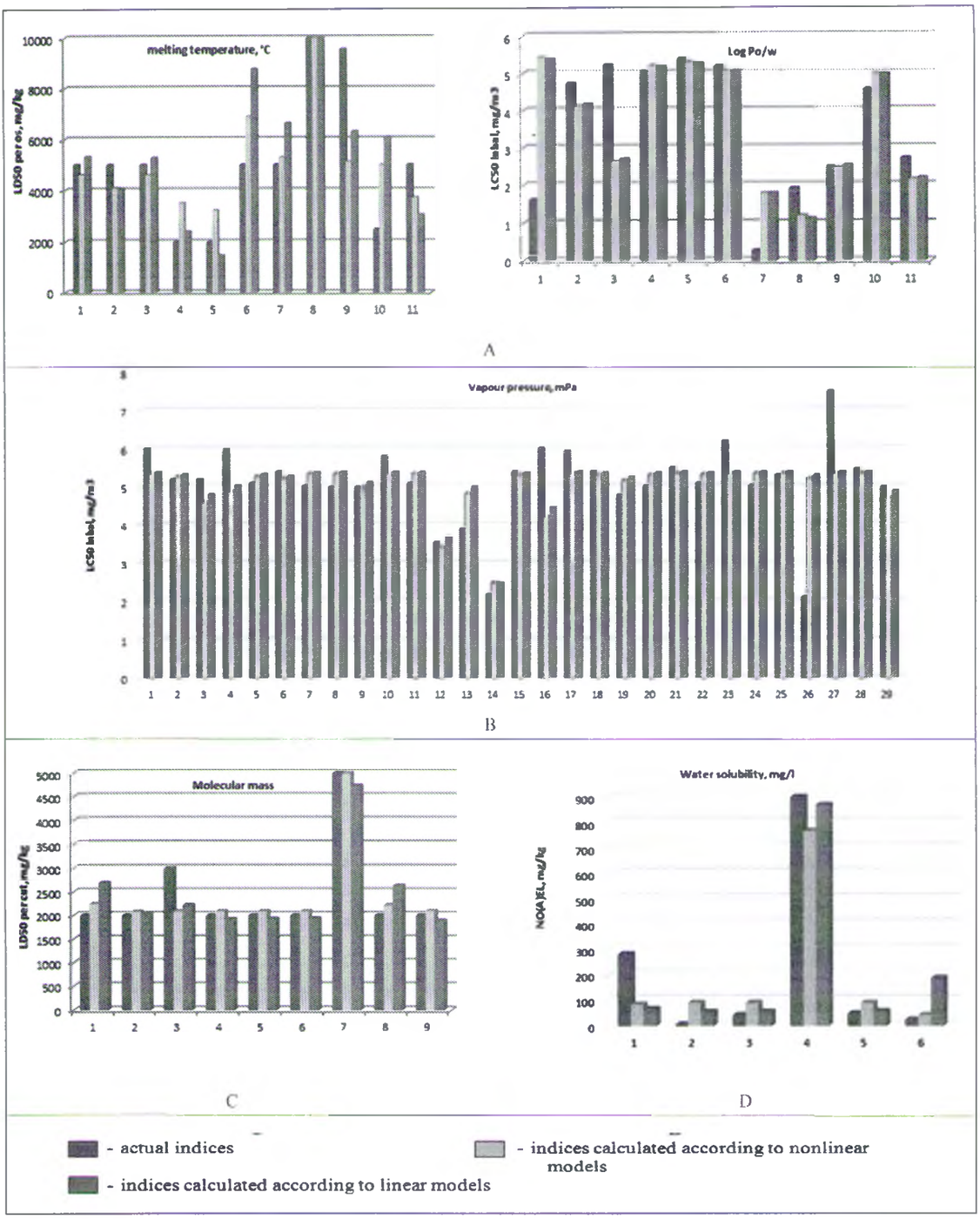

Figure 1. — Comparison of actual and estimated indicators of toxicological parameters for: A — pyrazoles and triketones; B — sulfonylureas; C — ureas; D — imidazolinones

Table 4. — Relationship between experimentally established and estimated values of toxicological parameters

Compound class	Resulting variable	Factorial variable	Statistical parameters				
			correlation coefficient				n
			r_{actual}		r_{table} at p		
			nl	l	0.05	0.1	
Pyrazoles and triketones	LD_{50} per os. mg/kg	melting temperature, °C	0.863*	0.774*	0.602	0.521	11
		log $P_{o/w}$	0.788*	0.711*	0.602	0.521	11
	LD_{50} per cut, mg/kg	melting temperature, °C	0.770*	0.763*	0.602	0.521	11
	LC_{50} inhal., мг/м^3	log $P_{o/w}$	0.581**	0.591**	0.602	0.521	11
		vapour pressure, mPa	0.880*	0.670*	0.602	0.521	11
	NO(A)EL, mg/kg	molecular mass	-0.100	0.016	0.602	0.521	11
		log $P_{o/w}$	0.907*	0.810*	0.666	0.582	9
		vapour pressure, mPa	0.651*	0.647*	0.602	0.521	11
Sulfonylureas	LD_{50} per os, mg/kg	log $P_{o/w}$	0.308**	0.292	0.361	0.296	31
	LD_{50} per cut, mg/kg	vapour pressure, mPa	0.428*	0.420*	0.361	0.296	33
	LC_{50} inhal., mg/m^3	vapour pressure, mPa	0.561*	0.575*	0.361	0.296	29
Ureas	LD_{50} per cut, mg/kg	molecular mass	0.939*	0.899*	0.666	0.582	9
		log $P_{o/w}$	0.882*	0.769*	0.666	0.582	9
	NO(A)EL, mg/kg	molecular mass	0.852*	0.996*	0.811	0.729	6
SCT	LD_{50} per cut, mg/kg	molecular weight	0.998*	0.998*	0.997	0.988	3
		water solubility, mg/l	0.999*	0.999*	0.997	0.988	3
	LC_{50} inhal., mg/m^3	water solubility, mg/l	0.999*	0.999*	0.997	0.988	3
Imidazolinones	LD_{50} per cut, mg/kg	molecular mass	0.819*	0.830*	0.811	0.729	6
	NO(A)EL, mg/kg	water solubility, mg/l	0.958*	0.936*	0.811	0.729	6
		log $P_{o/w}$	0.995*	0.973*	0.878	0.805	5

* — results are significant at $p<0.05$;
** — tendency, $0.05<p<0.1$.
Notes:
1) SCT — sulfanylcarbonyl-triazolinones;
2) l — correlation coefficient when calculating according to linear model;
3) nl — correlation coefficient when calculating according to nonlinear model;
4) n — number of observations.

In order to verify toxicometry indices of adequacy values calculated using proposed equations, we made the following calculations, and the results were compared with the actual values of oral and dermal LD_{50}, inhalation LC_{50} and NO(A)EL (Figure 1).

In most cases, the calculated values correlated with the experimental ones (Table 4). For all valid pairs of resultant and factorial variables, a reliable correlation relationship was found (ractual>rtable at p = 0.05) except LD_{50} per os and log Po/w for sulfonylureas and LC_{50} inhal. and log Po/w for pyrazoles and triketones. However, for these pairs, there is a reliable tendency of correlation (ractual>rtable at p = 0.1). The only exception is the absence of a correlation between NO(A)EL and the molecular weight of pyrazoles and triketones.

Although in the obtained linear regression equations № 13; 14; 19; 20 (Table 2) and 9; 10; 11 (Table 3), the coefficients were not reliable and reliability of the approximation was low, respectively, they could be used for calculation of the toxicometry parameters of studied pesticides classes. In order to check the formulas and compare obtained values with experimentally established ones, high correlation coefficients were obtained, which indicates the reliability of the relationship between the parameters under investigation. We do not recommend not to use only the equation number 6, since in addition to a rather small approximation coefficient, when using it for calculations, the minimum non-reliable correlation indices were obtained.

It should be noted that the correlation relations we received (Table 1) between the toxicometry indices and the threshold doses of the studied herbicides and their physical and chemical properties, which are confirmed by the inverse calculations (Fig. 1) — a direct correlation between the toxicological parameters and water and fat solubility — are similar to previously substantiated for neonicotinoid insecticides [16]. We also found a similar direct correlation between the values of fungicides threshold doses and molecular weights, its vapor pressure and toxicometry parameters.

Similar calculations for triazolpyrimidines (chlorosulam methyl, diclosulam, methsulam, pyroxsulam, florasulam, flumetsulam, penoxsulam, n = 7) were also performed by us, but no reliable correlation between their toxicological parameters and physicochemical properties was found. This can be explained by the fact that for most of the active ingredients of this chemical class, the threshold values of toxic effects were substantiated in the 1990s–2000s, often according to outdated approaches. In addition, the NO(A)EL values were substantiated on different species of animals (rats, mice, dogs). However, such an exception only confirms the established correlations for molecules of modern herbicide groups.

Conclusions:

1. Significant positive correlation between the toxicometry parameters of the studied herbicides (LD_{50} per os, LD_{50} per cut, LC_{50} inhal., NO(A)EL) and molecular weight, water solubility, vapor pressure, solubility in fats ($r = 0.40–1.00$ at $p \leq 0.05$) were established.

2. There was a significant negative correlation between NO(A)EL and molecular weights ($r = -0.70$ at $p<0.05$), LD_{50} per os, LD_{50} per cut and melting point ($r = -0.77$ and -0.76 respectively at $p<0.05$), LC50 inhal. and fat solubility and vapor pressure ($r = -0.92$ and -0.70, respectively, at $p<0.05$).

3. A significant positive correlation between LD_{50} per cut and LC_{50} inhal. and the solubility of sulphonylcarbonyl-triazolinone herbicides in water ($r = 1.0$ at $p<0.05$) were established.

4. It was proved that the proposed calculation models for predicting the toxicity of fungicides of pyrazole and triketon, sulfonylurea, urea, sulfonyl-carbonyl-triazolnion, imidazolinone classes are adequate for Fisher's criterion, and the coefficients of regression equations are reliable on the Student's criterion at $p < 0,05$.

5. The developed algorithm makes it possible to substantially simplify the procedure for establishing a hazard class for toxicological parameters, reduce the time spent on research and reduce the number of used laboratory animals, provided that there are data on the physical and chemical properties of the substances being studied, which is consistent with modern approaches on toxicological assessment and bioethics principles.

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ГИГИЕНИЧЕСКОЕ ОБОСНОВАНИЕ РАСЧЕТНЫХ МОДЕЛЕЙ ПРОГНОЗИРОВАНИЯ ТОКСИЧНОСТИ ГЕРБИЦИДОВ РАЗНЫХ КЛАССОВ

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Реферат. Была выявлена достоверная положительная корреляция между параметрами токсикометрии изученных гербицидов (LD_{50} per os, LD_{50} per cut, LC_{50} inhal., NO(A)EL) и молекулярной массой, растворимостью в воде, давлением паров, растворимостью в жирах ($r = 0,40–1,00$ при $p \leq 0,05$). Также была установлена достоверная отрицательная корреляция между NO(A)EL и молекулярной массой ($r = -0,70$ при $p<0,05$), LD_{50} per os, LD_{50} per cut и температурой плавления ($r = -0,77$ и $-0,76$ соответственно при $p<0,05$), LC_{50} inhal. и растворимостью в жирах и давлением пара ($r = -0,92$ и $-0,70$ соответственно при $p<0,05$). Установлена достоверная положительная корреляция между LD_{50} per cut и LC_{50} inhal. и растворимостью сульфонил-карбонил-триазолиноновых гербицидов в воде ($r = 1,0$ при $p<0,05$). Нами были разработаны расчетные модели для прогнозирования токсичности гербиидов классов пиразолов и трикетонов, сульфонилмочевин, мочевин, сульфонил-карбонил-триазолнионов, имидазолинонов, их надежность была статистически подтверждена.

Ключевые слова: гербициды, токсикология, расчётные модели, уравнения регрессии.

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