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Надійшла до редакції 08.04.2017

ГІГІЄНІЧНЕ ОБҐРУНТУВАННЯ РОЗРАХУНКОВИХ МОДЕЛЕЙ ПРОГНОЗУВАННЯ ТОКСИЧНОСТІ ФУНГІЦИДІВ РІЗНИХ КЛАСІВ ЗАЛЕЖНО ВІД ЇХНІХ ФІЗИКО-ХІМІЧНИХ ВЛАСТИВОСТЕЙ

Вавріневич О.П., Антоненко А.М., Коршун М.М., Омельчук С.Т.

HYGIENIC SUBSTANTIATION OF CALCULATING MODELS FOR FUNGICIDES OF DIFFERENT CLASSES TOXICITY DEPEND ON THEIR PHYSICAL AND CHEMICAL PROPERTIES PROGNOSIS

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UDK 613:632.952:632.95.024:57.013

Key words: Fungicides, toxicology, calculation models, regression equations.

Foreign laboratories and institutes have for some time used calculation models of the toxicometric parameters dependence on the physico-chemical properties of xenobiotics [1, 2].

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. And actual methods for determining the toxicological parameters of pesticides are long-term and require significant financial costs, that is why laboratories do not always cope with the increasing flow of chemical plant protection products [3]. In solving this problem, the important role is played by methods of mathematical modeling and pre-

ГІГІЄНІЧНЕ ОБҐРУНТУВАННЯ РОЗРАХУНКОВИХ МОДЕЛЕЙ ПРОГНОЗУВАННЯ ТОКСИЧНОСТІ ФУНГІЦИДІВ РІЗНИХ КЛАСІВ ЗАЛЕЖНО ВІД ЇХНІХ ФІЗИКО-ХІМІЧНИХ ВЛАСТИВОСТЕЙ

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В Україні та багатьох інших країнах на сьогодні не існує методів математичного моделювання та прогнозування токсичності для фунгіцидів та гербіцидів, як і немає юридичних підстав для використання висновків та порогових величин, отриманих європейськими експертами.

Метою роботи *було гігієнічне обґрунтування розрахункових моделей прогнозування токсичності фунгіцидів різних класів залежно від їхніх фізико-хімічних властивостей.*

Матеріали та методи. *Для аналізу ми використовували параметри токсикометрії та фізико-хімічні показники, поширені у світовому сільському господарстві фунгіцидів. Для статистичної обробки результатів були використані пакети статистичних програм IBM SPSS StatisticsBase v.22 та MS Excel.*

Результати і обговорення. *Розроблено лінійні та нелінійні регресійні рівняння, що враховують кореляційні залежності між токсичними властивостями фунгіцидів класу піразол-карбоксамидів і карбоксамідів, триазолів, імідазолів, карбаматів і дитіокарбаматів, метоксиакрилатів та їхніми фізико-хімічними властивостями. У більшості випадків розраховані за нашими формулами значення корелюють з експериментально встановленими.*

Висновок*. Доведено, що запропоновані розрахункові моделі для прогнозування небезпеки вивчених фунгіцидів є адекватними та статистично достовірними. Розроблений алгоритм дає змогу істотно спростити проведення токсикологічних експериментів та прискорити процедуру реєстрації нових фунгіцидів досліджуваних класів за наявності даних про фізико-хімічні властивості досліджуваних сполук.*

Ключові слова: фунгіциди, токсикологія, розрахункові моделі, рівняння регресії.

diction 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 [4].

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 purpose of work was the hygienic substantiation of calculating models for fungicides of different classes toxicity depend on their physical and chemical properties prognosis.

Materials and methods. 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 we have selected fungicides, which belong to the most widely used in the world agriculture of next chemical classes [6-10]: 18 active ingredients (a.i.) of *carboxamide, pyrazole-carboxamide class* (sedaxane, penthiopyrad, fluopyram, carboxin, penflufen, benzovindiflupyr, isopyrazam, boscalid, isofetamid, bixafen, flutolanil, fluxapyroxad, mepronil, oxycarboxin, thifluzamide, furametpyr, fenfuram, benodanil); 26 a.i. of *triazole class* (fluquinconazole, triadimenol, mibenconazole, bitertanol, fenbuconazole, flusilazole, diniconazole, triadimefon, difenoconazole, ipconazole, tetraconazole, penconazole, prothioconazole, bromuconazole, tebuconazole, metconazole, triticonazole, propiconazole, hexaconazole, etaconazole, azaconazole), 5 a.i. of *imidazole class* (imazalil, triflumizole, oxpoconazole, fenamidone, prochloraz), 21 a.i. of *carbamate class* (metiram, zineb, valifenalate, maneb, iprovalicarb, diethofencarb, pyraclostrobin, fuberidazole, dasomet, propineb, benthiavalicarb, ziram, thiabendazole, prothiocarb, thiophanate-methyl, thiram, pyrametostrobin, mancozeb, carbendazim, benomyl, propamocarb).

In the initial stages of the study, we analyzed 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). 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. The substantiation of the calculation models for forecasting the hazard of the fungicides studied classes was based on correlation and regression analysis, taking into account the determination coefficient, which most closely approximates the relationship between the selected toxicological parameters and physical and chemical properties. The significance of the obtained regression equations was checked by Fisher's F-criterion, and the individual coefficients in the regression equation (a, b) – according to Student's t-criterion.

Results and discussion. In the first stage, we analyzed 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, which statistically significant results are given in table 1.

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. 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 [11-13], which leads to LD_{50} decrease.

Also, a positive correlation between NO(A)EL value and water

Table 1

Relationship between toxicological parameters of fungicides and their physical and chemical properties

Chemical class	Resulting variable	Factorial variable	Statistical parameters*: correlation coefficient	determination coefficient, %	observations number (n)
Carboxamides, pyrazole-carboxamides	LD_{50} per os, mg/kg	vapour pressure, mPa	0,53	28,5	17
	LD_{50} per cut, mg/kg		0,70	48,3	17
	NO(A)EL, mg/kg	water solubility, mg/l	0,62	39,0	15
Triazoles	NO(A)EL, mg/kg	molecular weight	-0,42	17,9	23
		water solubility, mg/l	0,52	27,3	23
Carbamates	LD_{50} per cut, mg/kg	surface tension, mN/m	0,89	80,1	7
	$ЛК_{50}$ inhal., mg/m^3		-0,97	93,5	7
	NO(A)EL, mg/kg	water solubility, mg/l	0,47	22,5	19

*Note: * – statistically significant results are given (p<0,05).*

solubility was found (r=0,62; p<0,05). The fraction of this index impact is 39% (table 1). The obtained results can be explained by the fact that water-soluble compounds are rapidly metabolized and excreted from the body without a tendency to accumulate [11-13], which reduces toxic manifestations and causes increasing of NO(A)EL.

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%. The revealed dependence 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 [11-13].

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%. 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) [11-13].

At the second stage, we carried out an estimation using regression analysis 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 2). The significance of the obtained regression equations was checked by Fischer's F-creterion,

Table 2

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

Chemical class	Observa-tions number (n)	№ of equation	Regression equation	Indices of model adequacy: Fischer's F-criterion, F	Fischer's F-criterion, $F_{cr.}$ **	approximation reliability (R^2)	Coefficients certainty indices: a, t	b, t	$t_{cr.}$ **
Carboxamides, pyrazole-carboxamides	17	1	LD_{50} per os = $-2x10^{+06} X_1^2 + 25046X_1 + 3355$	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 = $3x10^{-05} X_2^2 - 0,030X_2 + 4,753$	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 = 2Ч10^{-05} X_2 + 6,775	4,93*	4,45	0,225	2,95*	2,22*	2,11

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

Table 3

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

Chemical class	Observations number (n)	№ of equation	Regression equation	Index of the model adequacy (R^2)
Carboxamides, pyrazole-carboxamides	17	1	ЛД$_{50}$ per os = $-2x10^6 X_1^2 + 25046X_1 + 3355$	0,308
	17	2	ЛД$_{50}$ per cut = $11515X_1 + 2888$	0,483
	15	3	NO(A)EL = $3x10^{-5} X_2^2 - 0,030X_2 + 4,753$	0,462
Triazoles	23	4	NO(A)EL = $-6,11ln(X_3) + 37,40$	0,181
	23	5	NO(A)EL = $0,552ln(X_2) + 0,102$	0,338
Carbamates	7	6	ЛД$_{50}$ per cut = $24327ln(X_4) - 99022$	0,804
	7	7	ЛК$_{50}$ inhal. = $-29,3ln(X_4) + 126,1$	0,942
	19	8	NO(A)EL = $2x10^{-5} X_2 + 6,775$	0,224

Notes: X_1 – vapour pressure, mPa; X_2 – water solubility, mg/l; X_3 – molecular weight; X_4 – surface tension, mN/m.

and the individual coefficients in the regression equation (a, b) – by the Studentst-criterion.

Our assessment of the "a" and "b" coefficients adequacy has shown that in all regression equations they are significant for the 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 ta was less than tcr., which indicates the impossibility of using this regression equation to predict the risk of fungicides of the carbamates group.

Also, exponential, logarithmic, polynomial, and step functions were used to approximate the dependencies of the parameters of toxicometry and non-acting doses on the physical and chemical properties of the substances studied,

HYGIENIC SUBSTANTIATION OF THE CALCULATION MODELS FOR THE TOXICITY FORECAST OF DIFFERENT CLASSES' FUNGICIDES DEPENDING ON THEIR PHYSICAL–AND-CHEMICAL PROPERTIES

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***Background**. Today the methods of mathematical modeling and the forecast of xenobiotics' toxicity of fungicides and herbicides do not exist in Ukraine and many other countries, and there are no legal basis for the use of the conclusions and threshold values obtained by the European experts as well.*
***Objective**. We performed a hygienic substantiation of calculation models for the fungicides of different toxicity classes depending on their physical-and-chemical properties.*
***Materials and methods.** For the analysis we used the parameters of toxicometry and physical-and-chemical indices of the fungicides widely applied in the world agriculture. IBM SPSS Statistics Base v.22 and MS Excel statistical program packages were used for the statistical processing of the results.*
***Results and discussion.** The linear and non-linear regression equations, taking into account correlation dependences between the toxic properties of fungicides of the class of pyrazole-carboxamides and carboxamides, triazoles, imidazoles, carbamates and dithiocarbamates, methoxyacrylates and their physico-chemical properties, were developed. In the most cases the values, calculated by our formulas, correlates with experimentally established ones.*
***Conclusions**. It was proved that the proposed calculation models for the forecast of the hazard of studied fungicides were adequate and statistically reliable ones. The developed algorithm simplifies substantially the performance of the toxicological experiments and accelerates the procedure of the registration of new fungicides of studied classes if there are data on physical- and- chemical properties of the studied compounds.*

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

except for the linear one. In table 3 the mathematical models with the greatest values of accuracy of approximation (R^2) are given.

The verification of the possibility of using the calculation models for predicting the hazard of the studied groups of fungicides was carried out on the basis of comparison of the parameters of toxicometry, obtained experimentally (actual indices) and calculated on the proposed equations (fig. 1-2).

In most of cases, the calculated values correlated with experimentally established (table 3). For all valid pairs of resultant and factorial variables, a reliable correlation relationship was established ($r_{actual} > r_{table}$ at p=0.05) except LD_{50} per os and vapor pressure for pyrazolecarboxamides, carboxamides, and LD_{50} per cut and LC_{50} inhal. and surface tension for carbamates. However, for these pairs a reliable tendency of correlation was establish ($r_{actual} > r_{table}$ at $0.05<p<0.1$).

In isolated cases, calculated LD_{50} values for oral and percutaneous intake were higher than experimentally established, but this is due to the fact that practically all of the experimentally established indices of these parameters are presented in the form of "more than...".

It should be noted that the correlations we received (table 1) between the toxicity criteria of the studied fungicides and their physical and chemical properties, which are confirmed by the inverse calculations (figs 1-2), are similar to those previously proved for neonicotinoid insecticides [14].

Similar calculations for methoxyacrylates (dimoxystrobin, trifloxystrobin, fluoxystrobin, picoxystrobin, kresoxim-methyl, azoxystrobin, piraclostrobin) were also carried out by us, but no reliable correlation between their toxicological parameters and physical and chemical properties was detected. Taking into account that for most of the active substances of this chemical class, the threshold values for toxic effects were substantiated in the 1990s, often according to outdated approaches, in different species of animals (rats, mice, dogs), this exception only confirms the established correlations for modern fungicide class molecules.

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.

Table 4

Correlation between experimentally established and calculated values of toxicological *parameters*

Chemical class	Resulting variable	Factorial variable	Statistical parameters*: correlation coefficient (r_{actual})	correlation coefficient (r_{table}) at p: 0,05	0,1	observations number (n)
Carboxamides, pyrazole-carboxamides	LD_{50} per os, mg/kg	vapour pressure, mPa	0,438**	0,482	0,412	17
	LD_{50} per cut, mg/kg		0,717*	0,482	0,412	17
	NO(A)EL, mg/kg	water solubility, mg/l	0,675*	0,514	0,441	15
Triazoles	NO(A)EL, mg/kg	molecular weight	0,426*	0,413	0,352	23
		water solubility, mg/l	0,582*	0,413	0,352	23
Carbamates	LD_{50} per cut, mg/kg	surface tension, mN/m	0,700**	0,755	0,669	7
	$ЛК_{50}$ inhal., mg/m^3		0,753**	0,755	0,669	7
	NO(A)EL, mg/kg	water solubility, mg/l	0,474*	0,456	0,389	19

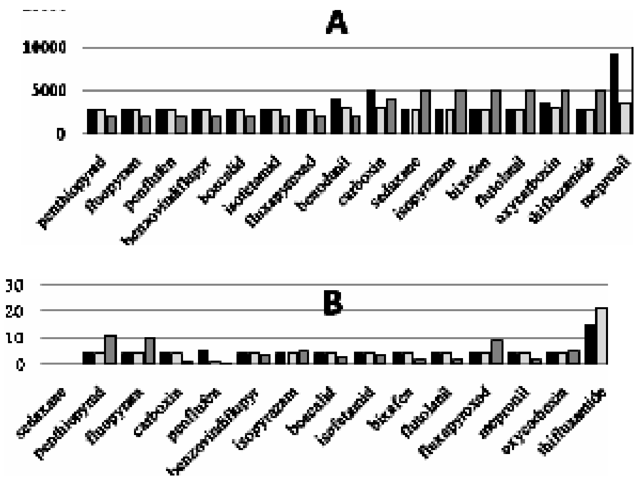
*Notes: * — results are significant at $p<0.05$;*
*** — tendency are present at $0.05<p<0.1$.*

3. There was 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 $p<0.05$.

4. 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.

Fig. 1

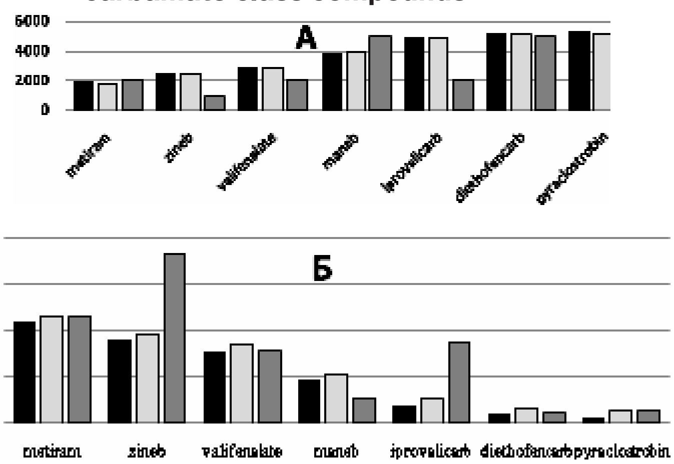
A comparative analysis of the experimentally established LD_{50} per cut (A) and NO(A)EL (B) values with calculated for pyrazolecarboxamides, carboxamides class compounds



- Indicators calculated according to linear models
- Indicators calculated on nonlinear models
- Current indicators

Fig. 2

A comparative analysis of the experimentally established LC_{50} inhal. (A) та NO(A)EL (B) values with calculated for carbamate class compounds



- Indicators calculated according to linear models
- Indicators calculated on nonlinear models
- Current indicators

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Надійшла до редакції 21.08.2017

FEATURES OF THE IMPACT OF OCCUPATIONAL NOISE AND ACCOMPANYING HYGIENIC FACTORS ON THE STATE OF THE ACOUSTIC ANALYZER AND THE MORBIDITY OF THE OPERATORS OF NON-ALCOHOLIC AND LOW-ALCOHOL BEVERAGES' BOTTLING AT OBOLON CORPORATION

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ОСОБЛИВОСТІ ВПЛИВУ ВИРОБНИЧОГО ШУМУ І СУПУТНІХ ГІГІЄНІЧНИХ ФАКТОРІВ НА СТАН СЛУХОВОГО АНАЛІЗАТОРА І ЗАХВОРЮВАНІСТЬ ОПЕРАТОРІВ З РОЗЛИВУ БЕЗАЛКОГОЛЬНИХ ТА СЛАБОАЛКОГОЛЬНИХ НАПОЇВ КОРПОРАЦІЇ «ОБОЛОНЬ»

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УДК:613.6:612.85:314.4:6 63.86-058.234.2

Ключові слова: гігієнічна оцінка, виробничий шум, сенсоневральна приглухуватість, захворюваність.

Інтенсивний виробничий шум є одним з пріоритетних факторів ризику у розвитку професійних захворювань на сучасному виробництві [2]. Він є провідним шкідливим виробничим фактором на підприємствах вугільної, транспортної, машинобудівної, харчової та інших галузей промисловості [2-4]. Крім того, з року в рік зростає кількість людей, які працюють в умовах впливу виробничого шуму. За даними багатьох авторів, в окремих країнах світу до 25% працівників, зайнятих у промисловості, зазнають впливу інтенсивного виробничого шуму [1, 5].

Внаслідок цього зберігається тенденція до зростання числа осіб з професійною приглухуватістю. У ряді країн Європи сенсоневральна приглухуватість професійного генезу посідає 1 або 2 місце за поширеністю серед професійних захворювань [6-8].

ОСОБЕННОСТИ ВОЗДЕЙСТВИЯ ПРОИЗВОДСТВЕННОГО ШУМА И СОПУТСТВУЮЩИХ ГИГИЕНИЧЕСКИХ ФАКТОРОВ НА СОСТОЯНИЕ СЛУХОВОГО АНАЛИЗАТОРА И ЗАБОЛЕВАЕМОСТЬ ОПЕРАТОРОВ РОЗЛИВА БЕЗАЛКОГОЛЬНЫХ И СЛАБОАЛКОГОЛЬНЫХ НАПИТКОВ КОРПОРАЦИИ «ОБОЛОНЬ»

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***Цель**: изучение состояния слухового анализатора и заболеваемости работников «шумовых» профессий пищевой промышленности.*

***Материалы и методы.** Проведены гигиенические исследования условий труда, анализ заболеваемости, углубленное клиническое обследование состояния слухового анализатора, определен биологический возраст работников «шумовых» профессий ПАО «Оболонь».*

***Результаты**. Установлено, что ведущим вредным фактором производственной среды работников «шумовых» профессий ПАО «Оболонь» является шум, уровни которого превышают допустимые величины на 1-11 дБА. У обследованных работников «шумовых» профессий выявлены ухудшения слуховой функции, особенно на тона в расширенном диапазоне частот, и признаки воздействия шума на центральные отделы слухового анализатора, проявляющиеся в нарушении функции его стволовых и корковых структур. Установлено, что частота выявления у операторов розлива напитков сенсоневральной тугоухости и болезней системы кровообращения статистически достоверно выше частоты выявления этих болезней в контрольной группе ($p \leq 0,05$). Обнаружены ускоренные темпы старения работников "шумовых" профессий.*

***Заключение**. Установлена причинно-следственная связь между условиями, характером труда и частотой выявления заболеваний, изменениями на разных уровнях слухового анализатора, темпами старения работников «шумовых» профессий.*

Ключевые слова: гигиеническая оценка, производственный шум, сенсоневральная тугоухость, заболеваемость.