Anton A. Tonshin[1], Tatiana A. Tkacheva[1], Svetlana V. Kautina[1], Margarita I. Golubeva[2]

Development of new methods for predicting hygienic standards for the content of medicines in the air of the working area on the example of non-steroidal anti-inflammatory drugs

[1]Izmerov Research Institute of Occupational Health, 31, Budyonnogo Ave., Moscow, 105275;
[2]All-Union Scientific Center for the Safety of Biologically Active Compound, 23, Kirova St., Staraya Kupavna, 142450

Introduction. Experts predict the hygienic standards of medicines in Russia in accordance with the methods common to all medicines (MG 1.1.726-98), developed more than 25 years ago on the basis of experimental materials obtained during the rationing of 66 medicines. By 2023, the content of more than 230 medicines of various pharmacological orientation has already been normalized in the air of the working area. Such an array of experimental materials makes it possible to study the relationship between the values of standard toxicological and pharmacological indicators and hygienic standards approved by law, already within the framework of individual pharmacological groups of drugs with the same mechanism of action, as well as to develop new forecasting approaches taking into account the specifics of pharmacological actions.

The study aims to evaluate existing and develop new computational methods for predicting hygienic standards for the content of medicines in the air of the working area, taking into account the specifics of pharmacological action on the example of a group of nonsteroidal anti-inflammatory drugs.

Materials and methods. Scientists studied the pharmacological group of nonsteroidal anti-inflammatory drugs. The main method of the study was a multiple correlation and regression analysis of the relationship between the values of hygienic standards and the values of toxicological and pharmacological parameters. As a mathematical model, the authors adopted a double logarithmic model. We evaluated the suitability of the mathematical model by Fisher's F-criterion, the statistical significance of the regression coefficients by the Student's t-criterion, the quality of approximation by the standard deviation, and the accuracy of the calculation by the average multiplicity of differences.

Results. Experts have identified in a group of 15 non-steroidal anti-inflammatory substances normalized in the air of the working area, a reliable relationship between the values of toxicometry parameters and the values of therapeutic doses, on the one hand, and the values of hygiene standards, on the other. Scientists have developed and selected the most accurate and statistically significant formulas for calculating the safe concentrations of this group of drugs in the air of the working area. We found that the accuracy of the formulas developed by us, taking into account the specifics of the pharmacological action, is higher than that of the formulas from MG 1.1.726-98. From the formulas developed earlier, equations with greater accuracy for the hygienic rationing of nonsteroidal anti-inflammatory drugs have been identified.

Conclusion. *Taking into account the specifics of the pharmacological action of medicines when developing mathematical models for calculating the hygienic standard increases the accuracy of the forecast.*

Keywords: *prediction of hygienic standards; parameters of toxicometry; nonsteroidal anti-inflammatory drugs; air of the working area*

For citation: Tonshin A.A., Tkacheva T.A., Kayutina S.V., Golubeva M.I. Development of new methods for predicting hygienic standards for the content of medicines in the air of the working area on the example of non-steroidal anti-inflammatory drugs. *Med. truda i prom. ekol.* 2023; 63(9): 574–585. https://elibrary.ru/yqucan https://doi.org/10.31089/1026-9428-2023-63-9-574-585

For correspondence: *Anton A. Tonshin,* Head of the Toxicology Laboratory at Izmerov Research Institute of Occupational Health, Cand. of Sci. (Biol.). E-mail: atonshin@yandex.ru

Author IDs: Tonshin A.A. https://www.scopus.com/authid/detail.uri?authorId=6603187160

Contribution:
Tonshin A.A. — research design, mathematical calculations and writing the text;
Tkacheva T.A. — research concept, editing;
Kayutina S.V. — data collection and processing;
Golubeva M.I. — research concept, editing.

Funding. The study was carried out within the framework of the State Task of research No. FGFE-2022-0006.

Conflict of interests. The authors declare no conflict of interests.

Received: 02.08.2023 / Accepted: 11.08.2023 / Published: 05.10.2023

Introduction. Accelerated hygienic rationing of medicines in the air of the working area (AWA) is an important direction in the development of preventive toxicology at the present stage. The State Program "Development of the pharmaceutical and medical industry" (Decree of the Government of the Russian Federation dated 12/28/2017 No. 1673 as amended on 03/31/2020 No. 396) outlines prospects for increasing "by 2024 the share of high-tech and high-tech products in the total production of the pharmaceutical and medical industry by 7 times in relation to 2011, an increase by 2024 to 53 percent of the share of medicines of domestic production in total consumption (in monetary terms)".

In this regard, the program separately formulated the task "... improvement of regulatory and legal regulation in order to stimulate innovation activity, improve the quality and safety of pharmaceutical products." The principle of anticipating the development and implementation of preventive measures (which include the development of safe values of the content of harmful substances in the air of the working area) in comparison with the moment of contact of workers with a new substance at work is one of the fundamental in preventive toxicology.

Scientific work on the justification of the hygienic standard (HS) according to the full scheme with the experimental establishment of the threshold of chronic action is very long and expensive. Therefore, experts have established criteria at the legislative level under which an accelerated justification of hygiene standards (HS) in the air of the working area (AWA) can be carried out [1]. Experts carry out a preliminary calculation of the value of hygienic standards in accordance with the physico-chemical constants of the substance, its biological activity, the characteristics of the structural components of the molecule.

However, the most reliable forecasts of hygienic standards with accelerated hygienic rationing are associated with the use of toxicometric parameters obtained during an experimental study of the toxicity and danger of the substance.

The development of methods for calculating HS based on the processing of experimental data obtained by statistical methods dates back to the 60s of the last century [2–6].

The result of many years of research was the approval at the legislative level in the form of Methodological guidelines of 100 formulas for predicting hygienic standards of harmful substances in the air of the working area [7].

The principal approaches to hygienic rationing of drugs do not differ from the general methodology of hygienic standards of industrial chemical compounds.

At the same time, there are some specific features of hygienic rationing of medicines. In particular, to calculate the hygienic standards of medicines, along with the above indicators, experts suggested using the pharmacological parameters established for each drug — the minimum and highest daily therapeutic doses (MDTD and HDTD). In this regard, specialists have developed additional special formulas for determining the hygienic standards of medicines [8], most of which have also been approved at the legislative level in the form of Methodological Guidelines 1.1.726-98 [9]. As of the beginning of the two thousandth years, the multiplicity of differences between the hygiene standards calculated according to these formulas and the approved values in most cases did not exceed 2, although for some compounds they could range from 3 to 3.8 [10]. Obviously, this is due not only to the insufficient accuracy of the formulas, but also to the correction of the calculated values of hygiene standards with mandatory expert evaluation of materials on the justification of hygiene standards by the main experts of Rospotrebnadzor, taking into account the unique combination of toxicological and pharmacological parameters for each substance.

Due to the small sample amount (66 drugs), the formulas developed earlier (MG 1.1.726-98) are common to all drugs and do not take into account the specifics of the pharmacological action of the normalized compound [8]. Since the approval of Methodological Guidelines 1.1.726-98, specialists have conducted studies to substantiate more than 170 hygienic standards for the content of medicines in the air of the working area [11]. Such an array of data makes it possible for the first time to set the task of improving the prediction of hygiene standards based on the general mechanisms of action of medicines.

The study aims to evaluate existing and develop new computational methods for predicting the hygienic standards of medicines in the air of the working area, taking into account the specifics of pharmacological action on the example of a group of nonsteroidal anti-inflammatory drugs.

Materials and methods. As the studied group of substances with similar specificity of pharmacological action, the scientists chose the pharmacological group of nonsteroidal anti-inflammatory drugs (NSAIDs) as one of the most numerous groups of standardized drugs with a similar mechanism of action.

The main research method was a multiple correlation and regression analysis of the relationship between the values of hygienic standards, on the one hand, and the toxicological and pharmacological parameters (TPP) of substances, on the other. The following were selected as TPP:

1. Lim_{ac}, mg/m^3 — the threshold of a single (acute) inhalation action is the minimum concentration of drugs in the air, causing changes in biological parameters that go beyond adaptive physiological reactions;

2. DL_{50}, mg/kg — the dose of drugs that causes the death of 50% of experimental animals within 2 weeks after the introduction of drugs into the stomach;

3. K_{kum} is the cumulation coefficient established by the Lim method [12];

4. MDTD, g — the minimum daily therapeutic dose;

5. HDTD, g — the highest daily therapeutic dose.

To obtain information about the parameters of toxicometry, specialists used the archive of the section "Industrial Toxicology" of the Problem Commission "Scientific foundations of Occupational Hygiene and Occupational Pathology", which contains official materials on the justification of the maximum permissible concentration (MPC) and approximate safe exposure levels (ASEL) to harmful substances in the air of the working area. Legally approved values of HS (ASEL or MPCm.r. in the air of the working area) were borrowed from SanPiN 1.2.3685-21 [13]. The researchers obtained the values of therapeutic doses from the instructions for the use of medicines from open sources [14–17].

As a mathematical model of the dependence of hygienic standards (HS) on toxicological and pharmacological parameters (TPP), a double logarithmic model was assumed, the most common in the calculations of hygienic standards:

$$\lg(Y) = \beta_0 + \sum_{i=1}^{n} \beta_i \lg(X_i) \qquad (1)$$

where Y is the value of HS, β_0 is the intercept, β_i are regression coefficients (slope), X_i is TPP, n is the number of TPP (from one to five). The calculation was carried out in four stages.

At the first stage, we calculated the Pearson correlation coefficients (R) between the logarithm of HS and the logarithm of each of TPP. In the second stage, the TPP's were ranked in descending order of R (number 1 was assigned to the TPP with the largest R). At the third stage, the specialists calculated the regression coefficients (slope) and intercept sequentially by multiple regression analysis for models with different numbers of TPPs (in formula (1) n=1,2,3,4,5). In addition, the calculation of one-parameter models for TPP with a "very high" and "high" degree of correlation on the Chaddock scale was additionally carried out.

The suitability of the mathematical model for each equation was evaluated by specialists by calculating the Fisher F-criterion and comparing it with a tabular value (at a significance level of 0.01). For each regression coefficient (slope) β_i and the intercept β_0, we determined the level of statistical significance p for the Student's t-test. At the fourth stage, the researchers evaluated the quality of approximation and the accuracy of calculation of each of the models. As a criterion for the quality of approximation, the authors used the mean square deviation (S) of the logarithm of the calculated HS from the approved one. As a criterion for the accuracy of the calculation, we used the average multiplicity of differences (<K>) between the calculated and approved HS values. The multiplicities of the differences (K) were defined as:

$$K = HS_{Tabular}/HS_{Approved}, \text{ if } HS_{Tabular} \geq HS_{Approved} \qquad (2)$$

or

$$K = HS_{Approved}/HS_{Tabular}, \text{ if } HS_{Tabular} < HS_{Approved} \qquad (3)$$

The obtained values of S and <K> according to the formulas justified in this study and approved earlier (MG 1.1.726-98 [9]) were compared with each other.

Specialists have carried all calculations using Microsoft Excel 2013 programs.

Results. The list of drugs included in the study group, as well as the values of TPP and approved HS are shown in ***Table 1***.

The group included all drugs belonging to the pharmacological group of NSAIDs that have an approved HS (MPC or ASEL) in the AWA.

The calculated values of the Pearson correlation coefficient (R) between the logarithm of the HS and the logarithm of each of the TPP are given in ***Table 2***.

According to the value of R, the ranked TPP series descending R looks like this: Lim_{ac} — 1, MDTD — 2, HDTD — 3, K_{kum} — 4, DL_{50} — 5.

The values of the regression coefficients (s`lope) β_i and intercept β_0 for five mathematical models with the number of TPPs from one to five, as well as for an additional one-parameter model with MDTD are presented in ***Table 3***. If the parameter was not taken into account in the mathematical model, its coefficient β_i was assumed to be zero. Due to the fact that not all TPP values were known for methyl salicylate and phenylbutazone, information about these substances was used in the calculations of only one-parameter models. Methyl salicylate is for the Limac model, and phenylbutazone is for the MDTD model.

As follows from ***Table 3***, for example, the column "*n*=4" corresponds to the equation:

$$\lg(HS)=-0.615+0.491\lg(Lim_{ac})+0.727\lg(MDTD) -0.317\lg(HDTD)+0.038\lg(K_{kum}) \quad (4)$$

The levels of statistical significance *(p)* of the Student's *t*-test for the coefficients β_i and β_0 from ***Table 3*** are presented in ***Table 4***.

The multiplicity of differences (K) between the calculated and approved HS values for each of the models is shown in ***Table 5***.

Table 5 shows that the greatest multiplicity of differences between the approved and calculated HS is characteristic of ketorolac, which has the strictest standard and, therefore, is located at one end of the regression line, and for two representatives of salicylates.

The mean square deviation (S) of the logarithm of the calculated HS from the approved one, as well as the average multiplicity of differences (<K>) between the calculated and approved HS values, calculated (F) and tabular (F_{table}) with a significance level of 0.01 of the Fisher criterion for each of the models are shown in ***Table 6***.

For the studied pharmacological group, the calculations of HS were carried out using formulas from MG 1.1.726-98 [9], including the same TPP as in this study:

$$\lg(HS)=0.77\lg(MDTD)+0.34 \quad (5)$$

$$\lg(HS)=0,8\lg(HDTD)-0.06 \quad (6)$$

$$\lg(SH)=0.45\lg(Lim_{ac})+0.5\lg(MDTD)-0.43 \quad (7)$$

$$\lg(HS)=0.49\lg(MDTD)+0.42\lg(Lim_{ac}) +0.11\lg(LD_{50})-0.75 \quad (8)$$

The mean square deviation (S) of the logarithm of the calculated HS from the approved one, as well as the average multiplicity of differences (<K>) between the calculated and approved HS values, for each of the formulas is given in ***Table 7***.

Discussion. The study group included 15 drugs belonging to different classes of chemical compounds: acetic acid derivatives (indomethacin, diclofenac, ketorolac); propionic acid derivatives (ibuprofen, naproxen, ketoprofen); salicylic acid derivatives (mesalazine, acetylsalicylic acid, salicylamide, lysine acetylsalicylate, methyl salicylate), pyrosolones (sodium metamizole, dimethylaminopyrazolone,

Table 1

Values of HS, toxicological and pharmacological parameters of drugs included in the NSAID group

№	Title	CAS	HS (mg/m³); hazard class	Lim_{ac} (mg/m³)	MDTD (g)	HDTD (g)	K_{kum}	DL_{50} (mg/kg)
1	Ketorolac⁺	74103-07-4	0.01	0.47	0.01	0.04	1.91	190
2	Indomethacin⁺	53-86-1	0.05; 1	0.52	0.05	0.2	2.6	15
3	Diclofenac	15307-79-6	0.2; 2	3.12	0.075	0.15	3.3	250
4	Ketoprofen	22071-15-4	0.2	5.54	0.15	0.2	9.4	43
5	Naproxen	22204-53-1	0.5; 2	8.6	0.55	0.825	4.3	1284
6	Lysine acetylsalicylate	34220-70-7	0.5; 2	19.3	1	6	3.64	3,600
7	Metamizole sodium	68-89-3	0.5; 2	22.6	0.5	3	2.92	3,120
8	Salicylamide	65-45-2	0.5; 2	25	0.5	8	12.8	1,147
9	Dimethylaminopyrazolone	58-15-1	0.5; 2	25.1	0.75	3	11.5	700
10	Acetylsalicylic acid	50-78-2	0.5; 2	40	0.1	0.3	3.13	2,990
11	Phenylbutazone	50-33-9	0.5; 2	no data	0.45	0.6	no data	no data
12	Methyl Salicylate⁺	119-36-8	1; 2	18	no data	no data	11.5	700
13	Ibuprofen	15687-27-1	1	21	0.6	1.2	12.8	1,000
14	Salazopyridazine	22933-72-8	1; 2	38.5	1	2	5.5	540
15	Mesalazine	89-57-6	1.5; 2	30.4	1.5	3	6.5	150

Note: ⁺ — substances that require special skin and eye protection when working with; no data — no data available.

Table 2

Значения коэффициентов корреляции Пирсона *(R)* между *lg*(ГН) и *lg*(ТФП)

	$lg(Lim_{ac})$	lg(MDTD)	lg(HDTD)	$lg(K_{kum})$	$lg(DL_{50})$
R	0.920	0.917	0.764	0.609	0.505

Table 3

Values of regression coefficients β_i and intercept terms β_0

Coefficient	*n*=1 *(Lim_{ac})*	*n*=2	*n*=3	*n*=4	*n*=5	*n*=1 (MDTD)
β_0	–1.298	–0.708	–0.586	–0.615	–0.507	–0.012
β_1 ($lg(Lim_{ac})$)	0.831	0.467	0.493	0.491	0.555	0
β_2 (lg(MDTD))	0	0.439	0.735	0.727	0.679	0.846
β_3 (lg(HDTD))	0	0	–0.317	–0.316	–0.279	0
β_4 ($lg(K_{kum})$)	0	0	0	0.038	–0.020	0
β_5 ($lg(DL_{50})$)	0	0	0	0	–0.058	0

Table 4

P-values of Student's *t*-test of regression coefficients (slope) β_i and intercept terms β_0 from *Table 3*

Коэффициент	*n*=1 *(Lim_{ac})*	*n*=2	*n*=3	*n*=4	*n*=5	*n*=1 (MDTD)
β_0	<0.001	0.009	0.015	0.045	0.192	0.88
β_1 *($lg(Lim_{ac})$)*	<0.001	0.008	0.003	0.005	0.021	0
β_2 *(lg*(МСТД))	0	0.013	0.003	0.007	0.023	<0.001
β_3 *(lg*(ВСТД))	0	0	0.059	0.076	0.167	0
β_4 ($lg(K_{кум})$)	0	0	0	0.856	0.938	0
β_5 *($lg(DL_{50})$)*	0	0	0	0	0.639	0

Table 5

The multiplicity of differences (K) between the calculated and approved values of HS for regression models from *Table 3*

№	Title	*n*=1 (Lim_{ac})	*n*=2	*n*=3	*n*=1 (МСТД)
1	Ketorolac	2.69	1.82	1.68	1.98
2	Indomethacin	1.71	1.29	1.45	1.55
3	Diclofenac	1.54	1.87	1.62	1.84
4	Ketoprofen	1.04	1.05	1.25	1.02
5	Naproxen	1.66	1.21	1.03	1.17
6	Lysine acetylsalicylate	1.18	1.56	1.27	1.94
7	Metamizole sodium	1.35	1.24	1.02	1.08
8	Salicylamide	1.46	1.30	1.27	1.08
9	Dimethylaminopyrazolone	1.47	1.56	1.45	1.52
10	Acetylsalicylic acid	2.16	1.25	1.16	3.60
11	Phenylbutazone	—	—	—	1.01
12	Methyl salicylate	1.80	—	—	—
13	Ibuprofen	1.58	1.54	1.32	1.59
14	Salazopyridazine	1.05	1.08	1.26	1.03
15	Mesalazine	1.74	1.30	1.13	1.10

salazopyridazine) and butylpyrazolidones (phenylbutazone). Two substances (ketorolac and indomethacin) by the magnitude of HS belong to the first class of danger, the rest — to the second. It should be pointed out that not a single substance belonging to NSAIDs from the chemical class of oxycams and coxibs has yet been normalized in the AWA and, therefore, was not included in the study group. The range of variation in the values of HS for the studied group of NSAIDs is two orders of magnitude (from 0.01 mg/m^3 for ketorolac to 1.5 mg/m^3 for mesalazine). The variability of most TPP is also significant and is about two orders of magnitude. The mechanism of pharmacological action, consisting in inhibition of cyclooxygenase one and two activity, mainly in peripheral tissues, is similar for all drugs included in the study group, resulting in inhibition of prostaglandin biosynthesis.

As a result of assessing the closeness of the relationship of the parameters on the Chaddock scale by the degree of correlation between the logarithms of the TPP selected for

Table 6

The mean square deviation (S) of the logarithm of the calculated HS from the approved one, the multiplicity of differences (<K>) between the calculated and approved HS values, calculated (F) and tabular (F_{table}) with a significance level of 0.01 Fisher criteria for regression models from *Table 3*

Criteria	*n*=1	*n*=2	*n*=3	*n*=4	*n*=5	*n*=1 (MDTD)
S	0.219	0.162	0.128	0.128	0.125	0.219
<K>	1.60	1.39	1.30	1.30	1.30	1.54
F	66	61	57	38	27	63
$F_{table}(0,01)$	9	8	7	7	7	9

Table 7

The mean square deviation (S) of the logarithm of the calculated HS from the approved one, as well as the average multiplicity of differences (<K>) between the calculated and approved HS values for *Formulas* 5–8

Criteria	*Formula 5*	*Formula 6*	*Formula 7*	*Formula 8*
S	0.223	0.370	0.159	0.189
<K>	2.85	3.33	1.82	1.73

analysis and the logarithms of the HS, we have found that for Limac and MDTD it is "very strong" (0.9–0.99), for HDTD — "strong" (0.7–0.9), and for K_{kum} and DL_{50} — "moderate" (0.5–0.7).

During the regression analysis, regression coefficients (slope) and intercept were calculated for six mathematical models, including from one to five TPP.

For multiparametric models, the authors have obtained the highest absolute values of regression coefficients for the Limac and MDTD parameters with the highest degree of correlation (β_1, β_2, ***Table 3***). The absolute values of the regression coefficients for the HDTD parameter with a lower degree of correlation were lower (β_3 ***Table 3***). The smallest absolute values of regression coefficients were obtained for the parameters of the K_{kum} and DL_{50} having the lowest degree of correlation (β_4, β_5 ***Table 3***) and not having statistical significance ***(Table 4)***. Thus, the greatest contribution to the calculated value of HS is made by the most correlated TPPs with it.

When considering the quantitative characteristics of the equations, it can be seen that for all of them the mathematical model is suitable according to the Fisher *F*-criterion. A significant decrease in S and <K> occurs during the transition from a two-parameter (*n*=2) to a three-parameter (*n*=3) model. With a further increase in the number of parameters, the values of S and <K> practically do not change.

Thus, the most suitable for calculating the value of HS for NSAIDs is a three-parameter formula:

$$\lg(HS)=-0.586+0.493\lg(Lim_{ac}) +0.735\lg(MDTD)-0.317\lg(HDTD) \quad (9)$$

In this formula, the highest quality of approximation and calculation accuracy are achieved. The disadvantage of this model is the insufficient statistical significance of the regression coefficient β_3 at lg HDTD slightly exceeding the value of 0.05, usually taken as a threshold in statistical calculations of this kind.

In a two-parameter model

$$\lg(HS)=-0,744+0.483\lg(Lim_{ac}) +0.408\lg(MDTD) \quad (10)$$

the quality of the approximation and the accuracy of the calculation are also quite high. At the same time, in this formula, the high quality of approximation and the accuracy of calculation are preserved when the statistically less significant parameter (HDTD) is excluded from formula nine. As shown above, the degree of correlation of HDTD and HS is significantly lower than MDTD and HS. In addition, the statistical significance of the β coefficient for lg HDTD does not decrease below 0.059 in any model ***(Table 4)***.

If accurate data on therapeutic doses are not available, for example, for external medicinal products (which, in our case, is methyl salicylate), a one-parameter model can be used (along with other forecasting methods with a sufficient set of experimental material).

$$\lg(HS)=-1.298+0.831\lg(Lim_{ac}) \quad (11)$$

It has sufficient approximation quality and calculation accuracy. It should be noted that previously, single-parameter formulas that take into account only Lim_{ac} were not used for hygienic rationing of drugs.

The one-parameter formula has almost the same quality of approximation and even greater accuracy of calculation:

$$\lg(HS)=-0.012+0.846\lg(MDTD) \quad (12)$$

We believe that two circumstances may be a limitation for the application of the equations we have developed. The accumulation coefficient of the NSAIDs selected for the study was at least 1.9 (according to Lim), and all substances belonged to hazard class one-two. The studied group did not include NSAIDs related to coxibs and oxycams. For such NSAIDs, the use of formulas developed by us should be limited and requires further research.

Table 3 shows the multiplicities of the differences between the calculated according to formulas 9–12 and the approved value of HS. It can be seen from the table that there are practically no drop-down values, which indicates a high degree of stability of the obtained formulas when calculating HS for NSAIDs.

When considering S and <K> for formulas from MG 1.1.726-98 [9] ***(Table 7)*** it can be seen that formulas seven and eight have the highest approximation quality and calculation accuracy. Therefore, when calculating the HS of NSAIDs according to MG 1.1.726-98, these formulas should be preferred.

If we compare <K> for formulas from MG 1.1.726-98 [9] ***(Table 7)*** and mathematical models obtained in this study ***(Table 6)***, while comparing formulas with the same number and set of TPPs, that is, formulas five and six are compared with models *n*=1, formula seven with model *n*=2, formula eight with model *n*=3, then it can be seen that the formulas obtained in this study have significantly greater calculation accuracy. Therefore, taking into account the specifics of the pharmacological action of drugs when developing formulas for calculating HS by the method of multiple correlation and regression analysis can increase the accuracy of the calculation, which is advisable to take into account in future editions of the guidelines on hygienic rationing of drugs.

Conclusion. *As a result of the conducted research, new formulas have been developed for calculating the HS of drugs of the pharmacological group of NSAIDs, which have higher accuracy compared to the equations previously justified for all drugs. Formulas with the highest accuracy for predicting the values of HS for drugs of the pharmacological group of NSAIDs were determined from MG 1.1.726-98. It is shown that taking into account the specifics of the pharmacological action of drugs increases the accuracy of calculating safe concentrations for the air of the working area.*

References

1. Hygienic standards GN 1.1.701-98 Hygienic criteria for substantiating the need to develop MPC and SHEL (ODU) for harmful substances in the air of the working area, atmospheric air in populated areas, water in water bodies: Approved and put into effect by the Decree of the Chief State Sanitary Doctor of the Russian Federation of April 30, 1998 No. 15. Elektronnyy fond pravovoy i normativno-tekhnicheskoy dokumentatsii. https://docs.cntd.ru/document/1200011526 (Accessed: 22.11.2022) (in Russian).
2. Golubev A.A. The use of calculation methods in industrial toxicology to establish the approximate value of a number of constants and indicators. In: *"Issues of general industrial toxicology"*. L., 1963: 23–31 (in Russian).
3. Zaeva G.N. On the application of calculation methods. In: *"Toxicology of new industrial chemicals"*. M.; 1964: 150–164.
4. Ivanov N.G., Sidorov K.K., Maksimov G.G. Scientific foundations of accelerated methods for substantiating sanitary standards in the USSR. In: *"Principles and methods for establishing MPCs for harmful substances"*. M., 1983: 25–29 (in Russian).
5. Ivanov N.G. Accelerated methods for establishing sanitary standards for industrial chemicals. In: *"Preventive toxicology"*. Ed N.F. Izmerov. M. Tsentr mezhdunarodnykh proektov GKNT. 1984; 1: 138–151 (in Russian).
6. Lyublina E.N., Mikheev M.I. Dvorkin E.A. et al. Possibility to calculate indicative safe exposure levels (SEL) of organic substances from available physicochemical constants and acute toxicity parameters. In: *"Some issues of experimental industrial toxicology"*. M.; 1977: 28–44 (in Russian).
7. Guidelines MU N 4000-85 for establishing approximate safe levels of exposure to harmful substances in the air of the working area: Approved by the Deputy Chief State Sanitary Doctor of the USSR A.I. Zaichenko November 4, 1985. Electronic fund of legal and normative-technical documentation. https://docs.cntd.ru/document/1200067849 (Accessed: 22.11.2022) (in Russian).
8. Shashkina L.F., Novikov S.M., Rozhnov G.I. Accelerated methods of substantiation of hygienic standards for drugs in the air of the working area. *Gigiena i sanitariya.* 1993: 11: 23–26 (in Russian).
9. Guidelines MU 1.1.726-98 Hygienic regulation of medicines in the air of the working area, the atmospheric air of populated areas and the water of water bodies: Approved and put into effect by the Chief State Sanitary Doctor of the Russian Federation, First Deputy Minister of Health of the Russian Federation on December 28, 1998. Electronic fund of legal and normative-technical documentation. https://docs.cntd.ru/document/1200036512 (Accessed: 22.11.2022) (in Russian).
10. Golubeva M.I., Shashkina L.F., Rozhnov G.I., Novikov S.M. Features of substantiation of safe levels of drugs in the air of the working area. *Toksikologicheskiy vestnik.* 2001; 1: 14–20 (in Russian).
11. Tkacheva T.A., Bidevkina M.V., Golubeva M.I., Karpukhina E.A., Kayutina S.V., Gritsun E.N. Hygienic standards for the content of pharmacological substances and intermediate products of their synthesis in the air of the working area of the Russian Federation. Database. Certificate of state registration No. 2020621711 (in Russian).
12. Lim R.K., Rink K.G., Glass H.G., Soaje-Echague E. A method for the evaluation of cumulation and tolerance by the determination of acute and subchronic median effective doses. *Arch. Int. Pharmacodyn. Ther.* 1961; 130: 336–53.
13. Sanitary rules and norms SanPiN 2.1.3685-21 Hygienic standards and requirements for ensuring the safety and (or) harmlessness of environmental factors for humans: Approved by the Decree of the Chief State Sanitary Doctor of the Russian Federation dated January 28, 2021 No. 2. Electronic fund of legal and normative-technical documentation. https://docs.cntd.ru/document/573500115?marker=6560IO (Accessed: 22.11.2022) (in Russian).
14. https://grls.rosminzdrav.ru (Accessed: 22.11.2022) (in Russian).
15. https://www.rlsnet.ru (Accessed: 22.11.2022) (in Russian).
16. https://www.vidal.ru (Accessed: 22.11.2022) (in Russian).
17. https://бмэ.орг (Accessed: 22.11.2022) (in Russian).