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System approach to the hygienic standards of xenobiotics in different environments

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Abstract

Based on the own experimental data and comprehensive analysis of national toxicometric indicators and MPC of 330 chemicals in different media (working area, atmospheric air and water reservoirs), as well as 265 standards used in the US and the EU, a systematic approach was designed and implemented with the purpose of substantiating the chemicals hygienic standards in different media. It takes into consideration the parameters of toxicity and cumulative properties of standardized substances which are manifested integrally by the reliability standard value, determined by the ratio of LC50 (LD50)/MPC_{wz}, which correlates with the corresponding relations of foreign standards. At the same time, MPC_{wz} plays an important part in the parameters of the system creation.

Implementation of the methodological guide developed by the authors and approved by the Ministry of Public Health of Ukraine provided the opportunity to significantly reduce uncertainties in the process of hygienic standardization, improving the reliability of newly developed standards and correction of existing standards on the basis of newly accumulated experimental and clinical data.

Further development of systematic approach to the hygienic standards will more successfully solve challenges of hygiene and quantitative toxicology, as the assessment of acceptable risk, the combined effects of chemical substances, the substantiation of regional, emergency standards, integrated regulatory support of chemical safety of the workers and the population as whole.

Key words

chemicals, hygienic standards, the reliability, standardization, system approach, cumulative toxicity

INTRODUCTION

Chemical safety in the modern industry, agriculture, construction and transport is not only a relevant hygienic and toxicological but also an global comprehensive social problem. Chemicals are an integral part of modern daily life with over 100,000 different substances [1]. About 15% territory of Ukraine with a population over 10 million people are in critical environmental conditions [2]. This highlights the need to determine the toxicity of new implemented in all spheres of life chemicals, types, mechanisms, occupational and ecological exposure limits established hygienic standards, risk assessment for the health of present and future generations of population.

Despite the implementation into hygienic science and practice the new technologies, criteria and methods in toxicometry, interest in the problem of the chemicals regulation and management has not waned, and new approaches to it solution continues [3, 4]. Many of theoretical and applied questions require a systematic approach for the integration of the accumulated data, as well as new paradigm substantiation at the national and international levels. Development of the hygienic standards system was and remains one of the leading and effective preventive measures and future trends in preventive toxicology.

Therefore, **the aim of the research** was to develop a unified system of xenobiotics hygienic standardization in different environments on the basis of quantitative toxicology and biological patterns, as well as recognition of the role of maximum permissible concentrations in the air of the working zone as a system creating factors.

MATERIALS AND METHODS

As quantitatively, the most representative was the normative base substantiated in the former Soviet Union, supplemented in Russia and Ukraine, on the one hand, and tried and tested in the United States and the European Community, on the other. Both of them were used for critical analysis and systems research and construction. The all available data for 330 industrial chemicals and pesticides were taken: Maximum permissible concentrations in the working zone (MPCwz) [predelno dopustimaya kocentracia v vosduche rabochey zony – PDCrz], the same in atmospheric air (MPCaa) and in drinking water (MPCdw), as well as foreign hygienic standards and key toksicometric indices, such as Occupational exposure limit (OEL), Threshold limit value (TLV), Permissible exposure limit (PEL), Recommended exposure limit (REL) or Immediately dangerous to life or health concentration (IDLH) for 265 chemicals. Part of the used standards was previously experimentally established by authors. Mathematical processing was performed by methods of variation, regression, and correlation analysis [5, 6].

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THE RESULTS OF THE RESEARCH

The analysis of the literature sources and our own researches showed that general tendency to ranking, grouping and systematization of the standards can be illustrated by successful search of relationship between chemical structure and biological effects of toxic compounds (QSAR models) [7, 8], their combinations [9, 10]; the initial and intermediate parameters of toxicometry, or defined normative values in the same environment between the standards of substances in various media and with subsequent development of the calculated and experimentally estimated methods for hygienic standards of xenobiotics [11, 12].

Meanwhile it should be recognized that the operational use of the calculating equation of the hygienic standards, existing up to now, is failed due to a significant variation of the data, when compared with those obtained in the experiment. These equations are mainly associated to the physical and chemical properties and chemical structure of the substance and to a much lesser extent – to their biological activity and toxicity. Biomarkers provide more reliable information in this regard [13, 14, 15]. The methods and results of this analysis and calculations remain particular solutions and don't allow to indicate a common conceptual and methodological basis of an unified system of standards.

Therefore, it have to be a tool for operational procedures and a precursor of a new approach to the standardization of xenobiotics. Such is systematic approach (adequate in terms of toxicological, and to a large extent, an alternative solution), based on conception, criteria and methodology for experimental evaluation of the toxicity of chemicals, creation of predictive models, checking the reliability of the system of standards and its invalid elements correction.

System approach, presented in this report, is understood throughout the organization of the entire regulatory infrastructure of xenobiotics based on methodologically defined quantitative relationships between hygienic standards (MPC) of different substances in the same environment and / or the same substance in different environments in the toxicological evidence depending on the medium lethal inhalation value (LC_{50}, mg/m^3 of air in experimental condition with the 2 h exposure in mice and 4 h – in rats) and / or by oral pathway (LD_{50}, mg/kg of animal body weight) [16, 17].

In this study, as the initial (maximum), based on the toxicity, parameters were taken mean lethal dose (LD_{50}) and/or the concentration (LC_{50}). In quantitative terms, toxicity is considered as an inverse parameter to the lethal dose (concentration) [18]. Indicators LD_{50} (LC_{50}) are measured objectively, as statistically significant values, which correspond to the maximum value of toxicity, and their relationship to the MPC indicate the range of values of the substance toxic properties (like other derived indicators in toxicometry).

The proposed approach is extended to the hygienic standards such as MPC (its national and international equivalents). It allows you to specify theoretically grounded position in the system of a particular standard in its toxicologically based coordinates. In this vein, the authors further develop the systems concept of the hygienic standards of xenobiotics and discussed a system of connections between the top (at lethal doses and concentrations) toxicity limits and permissible (safe) levels of substances in occupational practice (in the working environment).

Virtually in all countries the standards like MPCwz are oriented on the absence of harmful effects in workers (safety level), which are determined in toxicological experiments on the physiological, biochemical, morphological biomarkers. The more sensitive, specific, and adequate used in experimental studies complex of indices, the more reliable is established standard. Unlike MPC_{wz} the standarts of MPC_{aa} and MAC_{dw} designed for chemical safety of the whole population and are focused on the lack of any possible effect (the level of practical indifference). In connection with the latter it should delimited the author positions and the requirements of "zero" concept, which has long been subjected to reasoned criticism. However, regardless of this, daily intake of some substance in the relevant MPC_{wz} quantities serves as a maximum allowable in general, and its entry in the MPC_{aa} or MPC_{dw} shall be (on a comparable basis), some part of MPC_{wz}. This, in principle, predetermines the status of MPC_{wz} as a system configurative factor.

Relations between lethal and normative values such as LC_{50} / MPC_{wz} or LD_{50} / MPC_{wz} are a reflection of "reliability" standards and at the same time – inverted characteristics of toxigenic risk. Since these values are stochastic in nature, reliability in their most general meaning is seen as a numerical measure of the objective probabilities of each event (in this context – poisoning). If all other parameters are equal, the numerically greater this ratio, the more reliable is the standard (the less toxigenic risk), and vice versa. Since, as we are talking about a possible source alternative – LD_{50} or LC_{50}, it is important to establish and incorporate the actual relationship between the inhalation and oral toxicity of substances to lethal level – inhalation-oral coefficient (Ki/o). It reflects the ratio of toxicity under the main routes of exposure. In terms of, for example, a person weighing 70 kg, inhales for 10^3 air per day, this index [16], similarly as for mouse is equal to:

$$Ki/o = 0{,}15\ LC_{50}/\ LD_{50}. \quad (1)$$

The inhalation toxicity in fact exceeds the oral one. Very rare, in contrast, the oral toxicity exceeds inhalation toxicity. In the case of non volatile substances it is impossible to establish LC_{50}. Then, to go from the known LD_{50} to the unknown LC_{50} is advisable to estimate Ki/o at izoeffective quantities in parallel acute experiments under both ways of exposure (inhalation and oral). The differences in the estimates of Ki/o depends on the inevitable influence of random factors, due to which the toxicometric parameters are reproduced in acute experiments with accuracy in the range of 2–3 times, in chronic – up to 5- times [16].

The toxicological essence of considered ratios is defined by, that all known forms of chemical hazard are dependent not only on the dose (concentration) of the material, but also on the exposure time. In the three-pronged relationship "dose – time – effect", the dose reflects the toxicity, time predominantly is associated with cumulative properties of substances in primary toxigenic reactions. The toxicity is realized through a number of simultaneously exposed receptors (dose), through duration (time) of binding – the primary cumulative effect is defined. Its measurable characteristics is the period of half- existence of the altered biological object, which may coincide or not coincide in different way with half-period of the substance location at the cell receptor field (in the bioobject). Virtually, is said to be a biological time, in the scale of which all of the metabolic

and physiological processes in cells, organs and systems, in the organism as a whole are developing [19].

The longer period of the primary reaction is, the stronger and diverse the effects of derivatives, powerful the chemical pressure on the biological systems as a whole and, in particular, displays the cumulative effect at the organism level. During the acute and chronic toxicity, the development of long-term effects of cumulation phenomena manifests themselves in different ways and to varying degrees to calculate them. Therefore, as it has been emphasized earlier [20, 21], a detailed description of cumulative effects can't be obtained by only on any one of the indicators, for example, such as well known in toxicometry coefficient of cumulation at lethal levels set by one of the common scheme of subacute experiment. To complete their qualitative assessment should specifically conduct a comprehensive study of the cumulative properties of substances on their qualitative characteristics and to set quantitative criteria (from the cumulation index and the average time of death of animals in the acute and subacute experiments to possible characteristics of the rate of aging in gerontological and toxicological studies). It is important also to take into account the difficulties associated with the extrapolation of of toxicological data from animals to humans [22].

In general, the toxicity of a substance, usually is associated with its ability to cause a cumulative effect, i.e., lead to increased its action in time without increasing the dose. Thus is the systematization of standards of proof only acquire a maximum after differentiation agents on the severity of their cumulative properties – weak, medium, strong or very strong (extreme) degree. In accordance with the results of our own many years experimental studies, we developed the concept that a higher or lower ratio of lethal and normative values reflect their cumulative toxicity. To some extent it is inherent in each of the substances, and therefore leads to their conjugate grouping. The latter is, in turn, a part of the standards system in one environment (adopted system of coordinates). If the system is based on the same sign (e.g., toxicity in inhalation or oral exposure), there is a basis for chemicals standardization and ranking in any environment, and consequently, for the creation of a unified system of hygienic standardization of xenobiotics in all environments.

Optimism in this issue is inspired by the results of calculations based on the linear model:

$$y = (\alpha \pm \Delta\alpha)\, x + (b \pm \Delta b) \qquad (2)$$

where the dependent (y) and independent (x) variable – logarithm of concentrations (doses), α – the angular coefficient, b – the free term. For α close to 1 (angle of the slope – about 45 degrees), the resulting equality (2), it is easy to present by numerical expression of standard in units of LC_{50} or LD_{50}. If α definitely differs from 1, the toxicological control sense may be clarified by the standard errors Δa and Δb, where there is pronounced, in particular, the high correlation coefficient (r) between the variables for a particular group from n agents. This is confirmed by the results of analysis given in the Table 1.

Distribution of substances by the relations of reliability and correlation with MPC_{wz} with LC_{50} of industrial chemicals and LD_{50} of pesticides in mice and rats

In assessing the presented in the table data should pay attention to three of the most important points. First one, the group obtained a ratio to increase the reliability of the correlation coefficient to the most high (from 0.49 to 0.98). The value of the reliability index in 90–95% of cases in the range of 500–12500, i.e. sufficiently high. Second, the number of relations LC_{50}/MPC_{wz} is only 7.8% of the population ratio, i.e., almost no effect on the character of the distribution (the exponent of reliability in three main groups (500–12500), which may be related deviations from the general principles of justification toxicometric standards or receipt of information (the latter is less likely). Third, although there are certain features in establishing MPC_{wz} for pesticides [21], the two halves of the table (for industrial toxins and pesticides, as well as animals of different species) are nearly identical, which indirectly confirms the universality of the used by authors the indices of standards reliability.

Table 1. Distribution of substances by the relations of reliability and correlation with MPC_{wz} with LC_{50} of industrial chemicals and LD_{50} of pesticides in mice and rats

Reliability factor	LC_{50}/MPC_{wz} (industrial substances)			LD_{50}/MPC_{wz} (pesticides)		
	n	%	r	n	%	r
Mice						
all WPC_{wz}	255	100,0	0,74	159	100,0	0,49
≤500*	96	37,6	0,93	38	23,9	0,93
501–2500	89	34,9	0,98	73	45,9	0,92
2501–12500	46	18,1	0,98	37	23,3	0,96
> 12500**	24	9,4	0,72	11	6,9	0,82
Rats						
all WPC_{wz}	130	100,0	0,71	188	100,0	0,49
≤500*	42	32,3	0,88	21	11,2	0,73
501–2500	59	45,4	0,98	88	46,8	0,92
2501–12500	23	17,7	0,98	59	31,4	0,94
> 12500**	6	4,6	-	20	10,6	0,79

* Including for 3 substances $LC_{50}/MPCwz \leq 80$.
** Including for 5 substances $LC_{50}/MPCwz > 62500$; for the remaining 19 substances in the range of $LC_{50}/MPCwz = 12501…62500$ we have r = 0,96

Basically, it corresponds with the detailed consideration of I.V. Sanotsky and I.P. Ulanova [23], proposed by K.K. Sidorov classification of cumulative activity (degree of cumulation) by the index of biological action zone (Zbiol) to the substances standards in the working zone, the atmosphere and drinking water reservoirs. As applied to the air sphera it was identified four cumulative grade, and to the water – five. Zbiol values are found from the conditions:

$$Z_{biol} = LC_{50} / Lim_{chr} = LD_{50} / Lim_{chr} \qquad (3)$$

where, almost regardless of the pathways of exposure of the chemical agent the threshold concentration (inhalation – in mg/m^3 air or threshold dose (for ingestion – in mg/kg of body weight) – indicators of chronic hazards of the substances. Zbiol reflects the cumulative properties of toxicant and is also a measure of the activity of the organism's defenses. Therefore the wider Zbiol is, the higher the risk of chronic poisoning. In the considered as an example K.K. Sidorovs' classification interval values between classes on Zbiol differ by an order of magnitude (10, 100, 1000, and more than 1000 for the substances in the working zone with varying degrees of cumulation). It reflects the logarithmic (or rather, exponential) principle variation of toxicity and can be accepted for any classification (or system) in quantitative toxicology. This again shows that a systematic approach to the

hygienic standards originated in the practice of experimental validation of toxicity

The considered principle has been used by the authors of this research. According to equation (2) it was obtained 4 general and 16 quotient grouped equations, the regression analysis of which showed that the consequence of increasing the correlation coefficient becomes approximation of the angular coefficients to 1,0. In general, the considered dependence is determined by the equation:

$$\lg MPC_{wz} = \lg LC_{50} - (b \pm \Delta b), \quad (4)$$

where the remote of normative values from the top of the inhalation toxicity border is determined by the absolute values of the free terms (b + Δb), according to the four degrees of cumulative substances (mild, moderate, severe, very severe) under the following conditions: first, the mean average of free members (b) are central to the permitted range (b + Δb) for each degree of accumulation of substances, and secondly, all 4 bands are docked and overlap all known (calculated from pooled data) reliability ratios of MPC_{wz}, and thirdly, as it is shown by the calculations for the most cumulative substances actual ratio of LC_{50}/ MPC_{wz} > 62500, but generally does not exceed 100,000.

The above mentioned conditions satisfies a solution, in which for highly cumulative chemicals the geometric mean of the absolute value of b = lg 35 000 = 4.54. Its consequent meaning reducts in each adjacent group of less cumulative substances (lg 5 = 0.7), and the absolute value of Δb = 0,5 lg 5 = 0.35, which applies to all 4 groups. As a result, according to the four groups of substances which have different degrees of cumulative properties, there are:

$$\lg MPC_{wz} = \lg LC_{50} - (4{,}54 \pm 0{,}35), \quad (5)$$

$$\lg MPC_{wz} = \lg LC_{50} - (3{,}84 \pm 0{,}35), \quad (6)$$

$$\lg MPC_{wz} = \lg LC_{50} - (3{,}14 \pm 0{,}35), \quad (7)$$

$$\lg MPC_{wz} = \lg LC_{50} - (2{,}44 \pm 0{,}35). \quad (8)$$

Thus, there are obtained four basic equations of reliability (5) – (8), forming a matrix of MPC_{wz}. It covers all the possible values LC_{50}/ MPC_{wz} from 77,63 to 123,0 (otherwise, from MPC_{wz} = 0.000013 to 0.00813 LC_{50}), and compatible with it any private regression establishes a relationship of MPC_{wz} from LC_{50}. However, the sheer expression (5) – (8), although similar to the regression equation in the form they are known to be either in the genesis or by the final content. These basic equations are generalized toxicological legitimate regulatory decisions that determine the ranges should theoretically allowed values of MPC_{wz} to the substances of varying cumulation degrees (in counts is the minimum of the actual values of LC_{50} for mice or rats). The decision to classify a substance to the one of groups in terms of cumulative toxicity remains (within the allowed values for substances of this group) is up to developer of MPC_{wz}. The last, in principle, also determined the objective need for periodic revision of the national regulatory framework of any country, where is developed own legislation on the chemical safety, and the relevant international documentation too, in order to their harmonization and renovation.

The principal consistency of the whole proposed system of standards provides the logic of successive transitions from relations reliability of MPC_{wz} to co-organizing relations of MPC_{aa} (as the way of entering to the organism of xenobiotics is the same). The system then allows to go to the relations regarding the reliability MPC_{dw} to LC_{50} and further, given Ki/o, to the relations in the form of reliability MPC_{dw} as maximum ineffective dose (MID) and the acceptable daily intake (ADI), because these standards, so as MPC_{dw}, apply to whole population. Methods of hygienic standards of chemicals study of in different media described by the authors of this work in the Ministry of Health approved the Methodological guidance [23]. However, their detailed analysis is beyond the scope of this paper.

The high degree of commonality of systems approach in relation to different normative databases (other systems) used in international practice, traced by comparing the quantitative parameters by calculating the applicable U.S. counterparts of MPC_{wz}. There were established for this relationship between the numerical values of the IDLH ratio and three analogues MPC_{wz} by U.S. standards (TLV, PEL, REL) with each other and IDLH / MPC_{wz}. The analysis showed that out of 265 agents to 134 agents (50.6%), all three standards (TLV, PEL, REL) are numerically the same (they are marked as TPR). Between the remaining (49.4%) at least one of the three ratios was significantly different from others. For 39 substances all three standards were differ. MPC_{wz} were known for 189 of the 265 substances. The results of the group of these relations are presented in the Table 2.

Table 2. Distribution of substances (%) of their relationship to IDLH/MPC_{wz}

Groups (to the IDLH ratio)	IDLH/USA standard				IDLH/MPC_{wz} (n= 189)
	TPR (n = 134)	TLV (n = 131)	PEL (n = 131)	REL (n = 134)	
≤50	35,1	14,1	≤50	35,1	14,1
51…300	44,0	48,1	51…300	44,0	48,1
301…1500	16,4	25,2	301…1500	16,4	25,2
1501…7500	3,7	10,7	1501…7500	3,7	10,7
> 7500	0,8	1,5	> 7500	0,8	1,5

As it is seen from the data in Table 2, the grade of the received data on 5 groups with 5–6-fold intervals covers all the factual materials and does not contradict the logic of relations of the proposed system. Only 1,0–11,0% of substances yield ratio is higher than the reliability of the reporting range (50–7500). Moreover, about 70–90% of the values are within the limits of 1500.

Only heterogeneous ratio IDLH / MPC_{wz} almost uniformly distributed in the range of 51–7500. In other words, the productivity of the systems approach is confirmed on a sufficiently large set of databases on the health standards in different countries.

DISCUSSION

Comparison of the data, summarized in Tables 1 and 2, which, in spite of criterial and methodological bases differences in justifying the hygienic standards, they are not only satisfactorily arranged in the proper system, but quite clearly matched to each other. This, in particular, is a quantitative expression of the distribution of the reliability standards, depending on the cumulative properties of the chemicals.

CONCLUSION

1. Toxicologically informative developed and proposed for use in the practice of hygienic standardization system has successfully solved the problem of forecasting the values of specific regulations in the same environment and different environments with the limited set of toxicometric data.
2. The systems approach to the hygienic standards reasoning makes it easy to move from one regulation system to another, as well as adjust some standard value if it do not fit into the logic of comparative evaluation (the location in the series of cumulative toxicity and reliability).
3. These opportunities are of interest not only for toxicologists and hygienists, but the designers of industrial, transportation and public projects, specialists providing health and chemical safety, including in divisions on the liquidation and prevention of emergency situations. This is evidenced by 10 years of experience in systematic approach and Methodical Guidance application [23].
4. However, the activity of the systems approach improving and optimization should be considered in terms of experimental data acquisition, correction of individual invalid standards, harmonization of national and international databases, the wider application in the task of the risk assessment for the health of workers and the population.
5. It is necessary to clarify the biological (toxicological) significance of relations such as LC_{50} (LD_{50}) / MPC, applied to different standards (in various media), as well as opportunities to display it on a logarithmic scale, the use for predicting the degree of cumulative activity of new chemical compounds. While still controversial assessment of the importance of reliability, its numerical expression and interpretation in solving applied (practical) problems.

The authors are optimistic about the prospect of the „removal" of emerging issues and continue to work in this direction.

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Systematyczne podejście do standaryzacji higienicznej ksenobiotyków

Streszczenie

Na podstawie własnych danych doświadczalnych, analizy parametrów krajowych, toksymetrów oraz na podstawie dopuszczalnych poziomów 330 substancji chemicznych w różnych środowiskach (w strefie roboczej, atmosferze i wodzie) i 265 norm stosowanych w USA i UE, zostało opracowane i zrealizowane systemowe podejście do określenia standardów higieny chemikaliów w różnych mediach. Bierze ono pod uwagę parametry toksyczności standardowych materiałów i ich kumulacyjne właściwości, które reprezentowane są poprzez integralną wartość norm niezawodności. Określa się je przez stosunek LC50 (LD50)/MPLwz, co koreluje z odpowiednimi przepisami norm zagranicznych. Wykazano, że MPLwz odgrywa istotną rolę jako parametr tworzenia systemu.

Wdrożenie instrukcji opracowanych przez autorów i zatwierdzenie ich przez Ministerstwo Zdrowia Ukrainy dało możliwość znacznego zmniejszenia stopnia niepewności w opracowywaniu norm higienicznych, niezawodność nowych opracowań i korektę istniejących standardów w oparciu o nowe dane, zebrane eksperymentalnie i klinicznie.

Dalszy rozwój systemowego podejścia do opracowywania standardów higienicznych daje możliwość bardziej skutecznego rozwiązywania złożonych zadań w zakresie higieny i toksykologii. Pozwoli, także w kontekście regionalnym, na ocenę skutków oddziaływania substancji chemicznych, przy pomocy standardów ratowniczych, oraz zapewnienie pracownikom i ludności bezpieczeństwa chemicznego.

Słowa kluczowe

substancje chemiczne, standardy higieniczne, niezawodność, standaryzacja podejścia systemowego, skumulowana toksyczność, stosowana standaryzacja