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Substantiation of the algorithm for identifying high-risk groups among the personnel of chemically hazardous facilities

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ABSTRACT

Introduction. Studies of the impact of chemicals on the health of employees of chemical industry enterprises based on biomonitoring are an urgent medical and social problem. The article is devoted to the substantiation of the algorithm for examining personnel at chemically hazardous facilities to identify high-risk groups due to the effects of industrial poisons.

Material and methods. The article presents an analysis of domestic and foreign scientific literature devoted to the problems of identifying high-risk groups among workers in chemical enterprises based on biomonitoring methods.

Results. Identification of high-chemical risk groups among chemically hazardous facilities employees involves the following steps: assessment of the level of external chemical exposure, identification of priority pollutants, substantiation of the most informative bioenvironments and the time of analysis, determination of exposure/effect biomarkers, and clinical examination of personnel.

Limitations. The proposed algorithm for identifying high-risk groups applies only to persons who are professionally in contact with hazardous chemicals.

Discussion. The article presents an analysis of the scientific literature on the problem of identifying high-risk groups based on biomonitoring.

Conclusion. In order to identify high-risk groups among the personnel of chemical enterprises, it is necessary to introduce the proposed algorithm and develop quantitative criteria for biomonitoring – biological maximum permissible concentrations (BEI) or biological exposure indices into the practice of toxicological and hygienic assessment of the health of workers.

Keywords: chemicals; biological monitoring; biomarkers of exposure/effect; biological media of exposure; biological exposure indices; risk groups

Compliance with ethical standards. The presented materials do not analyze specific individual data from clinical or experimental studies, therefore the article does not require the presentation of a conclusion on biomedical ethics.

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Introduction

Preserving the health of the working population, ensuring safe working conditions and preventing occupational morbidity are priority areas of state policy towards workers. Decree of the President of the Russian Federation No. 97 dated 03/11/2019 “On the fundamentals of the State policy of the Russian Federation in the field of chemical and biological safety for the period up to 2025 and beyond” defines the main directions of the state strategy in the field of chemical safety, among which are: the development of modern methods for the indication of chemicals in the environment and biological media (point 4 of paragraph 13); development of procedures for the chemical analysis of toxicants in the environment and biological material (point 35 of paragraph 13). Thus, the listed directions of state policy on the study of the effect of chemicals on the health of employees of chemical industry enterprises based on biomonitoring are an urgent medical and social problem.

Biomonitoring as a methodological approach to assessing the harmful effects of chemical environmental factors has been known since the nineteenth century. In the United Kingdom, canaries were used to monitor the safety of working conditions in coal mines, which reacted to dangerous concentrations of carbon monoxide in the air. Later, during World War II, carbon monoxide levels in submarines were assessed by the behavior of long-tailed parrots [1]. In relation to production conditions, the most common method for quantifying concentrations of chemicals in the air of the working area and comparing the results obtained with acceptable levels is $MAC_{w.z.}$ (maximum allowable concentration of a harmful substance in the air of the working zone is a term used in the Russia). However, the determination of chemicals in the air of the working area allows to assess the level of external exposure only in a specific place and at a certain time, and does not give an exhaustive idea of the amount of chemical actually entering the body, especially in cases where a complex effect of the toxicant on the body is possible (simultaneous intake of the toxicant by inhalation, through the skin and through the gastrointestinal tract). Therefore, in the practice of assessing the real hazard of chemicals, biological control methods have been proposed, with the help of which it is possible to estimate the amount of toxicants in the biological environments of the human body.

Research using biological control methods for the health of employees of chemical enterprises became possible due to the successes of analytical chemistry, when sensitive methods for the determination of chemicals and their metabolites in biological media were developed. The first to propose the introduction of

biomonitoring as a necessary element of toxicological and hygienic research in production were J. Teisinger and H.B. Elkins, who conducted research to identify correlations between the level of exposure to industrial substances in the air of the work area and their content in the biological environments of the human body [2, 3]. A significant contribution to the development of the methodology of biomonitoring (determination of exposure tests or biomarkers of exposure) was made by the work of E. Piotrowski and his staff [4]. In our country, under the leadership of I.D. Gadaskina, in the 60s of the twentieth century, research was conducted to study the “fate” of poisons in the body and to determine organic and inorganic compounds in biological media. As a result of the research carried out by I.D. Gadaskina and V.A. Filov, monographs were published, which were the first attempt to substantiate biomarkers of exposure in Russia [5, 6].

An active discussion of the need to use biomonitoring to assess the occupational effects of chemicals on the health of workers began in 1959 at an International Symposium in Prague, when a new approach, based on monitoring harmful chemicals in the air of the work area (in comparison with $MAC_{w.z.}$), was proposed to the practice of toxicological and hygienic control using such an indicator as the “Maximum permissible biological concentration” (MPBC), which characterizes the safe content of a chemical or its metabolites in the biological environment of the working body. Exceeding the MPBC was recommended to be considered as an indicator of the unfavorable working environment, requiring increased attention to working conditions and staff health [4]. A new approach to assessing the effects of chemicals on the health of workers has found support among researchers, and initially it was even proposed to replace the $MAC_{w.z.}$ to the biological standard MPBC, which was a more informative and objective characteristic of the harmful effects of toxicants. Later it became clear that biomonitoring studies cannot replace chemical control of the working area air and are an addition to chemical monitoring when assessing the health status of workers. Without analyzing chemical monitoring data, it is not possible to assess the toxicity and hazard of chemicals present in the air or other object of the production environment and identify a priority pollutant from them, which in turn is determined in the biological environment of the human body. Based on the results of the performed study, the biomarker of exposure and/or effect, the most informative biological environment and the time of determination of the toxicant are substantiated [7, 8].

Despite the obvious need to introduce biological control over the level of chemical load in workers and, first of all, in persons working at chemically hazardous facilities, in the Russian Federation, unlike

the countries of the European Union and the United States, a system for assessing the content of chemicals in the biological environment of the human body has not been developed. There is practically no methodological basis for conducting surveys of various professional groups of the working population using biomonitoring methods, requirements for substantiating biomarkers of exposure and effect depending on toxicokinetics, the mechanism of toxic action and clinical manifestations of toxicants have not been developed and implemented. This problem is especially relevant for assessing the health of personnel of enterprises using technologies with the use or production of chemicals of hazard class 1 and 2 [7, 8].

Objective. To substantiate the algorithm of personnel examination to identify high-risk groups among people in contact with the most toxic and hazardous pollutants of the production environment.

Materials and methods

The research methods were the analysis of scientific literature, domestic and foreign methodological materials on biomonitoring.

Results

Currently, there are many articles in the scientific literature devoted to the problem of biomonitoring. Most of all, studies on the assessment of the risk of chemical exposure are presented, which provide an analysis of domestic and foreign studies using biomonitoring methods, which confirms a reasonable interest in this problem [9, 10, 11, 12, 13, 14]. The articles mainly discuss methodological issues of determining toxicants or their metabolites in biological media, as confirmation of the presence of a chemical in the body, which corresponds to the definition of the term exposure biomarker [15, 16, 17, 18, 19].

Much less attention is paid in the scientific literature to biomarkers of effect or damage, which characterize not only the fact of detection of a toxicant in biological media, but also the specific or non-specific response of the body to the action of a chemical substance. Quite often, researchers do not distinguish between exposure biomarkers and effect biomarkers, using the general term biomarkers [10, 16].

Not enough attention is paid to such important characteristics as the time of biomaterial selection and the rationale for choosing a biological medium for performing biomonitoring studies. If the rate of excretion of the substance is high and is limited by hours (for example, when personnel work with chromium, manganese, alcohols, aniline, fluorine, carbon monoxide, etc.), sampling is carried out

during a shift or immediately after a work shift. For substances with a long half-life (weeks, months, as, for example, for lead), the sampling time of experienced workers is not of great importance, but for newly hired workers, the first determination is carried out no earlier than after two weeks of exposure [20].

An analysis of domestic and foreign literature has shown that the justification and development of MPBC for all regulated industrial poisons is not required.

Discussion

To fully understand the nature of the toxic effect of a chemical, quantitative characteristics of biomonitoring are equally necessary, supplemented with information about the mechanism of the toxic effect of the toxicant, what is called in the scientific literature a biomarker of the effect. Quantitative characteristics of biomonitoring – Biological Exposure Indices (BEI) were adopted and justified in the USA in the 90s of the last century by the American Conference of Governmental Industrial Hygienists (ACGIH). BEI are a quantitative expression of the content of a chemical substance and/or its metabolite in biological media, as well as the values of some biochemical parameters that are determined in practically healthy persons who have professional contact with a chemical substance at the level of hygienic regulations (TLV, TWA, MAK) [20, 21]. When analyzing the advantages and disadvantages of various approaches to assessing the risk of exposure to chemicals on the body, indicators such as exposure biomarker and BEI are used. The difference between these terms lies in the fact that the exposure biomarker characterizes the content of a chemical in the body of a worker as a result of professional contact with a toxicant. BEI or MPBC is the safe content of a toxicant in the human body under the external action of the same toxicant at an acceptable level ($MAC_{w.z.}$, TLV, TWA) [20]. BEI recommended in the USA, in France were called Tentative maximum permissible concentration (TMPC), in Germany – biological tolerance values (Biologische Arbeitstoftoleranzwerte – BAT), in Russia – biological maximum permissible concentrations (MPBC). Confirmation of the need to compare BEI with the obtained exposure biomarker values and threshold limit values (TLV, TWA) is that ACGIH has included threshold limit values (TLV, TWA) in its lists, thus emphasizing the importance of comparing the external effects of a toxicant with acceptable levels of TLV, TWA and BEI, especially when preparing expert opinions [7, 8, 20]. ACGIH materials are regularly published and constantly updated.

Another characteristic necessary to identify high-risk groups is the identification of biomarkers of the effect in persons subjected to chemical exposure. The difficulties in substantiating biomarkers of the effect or damage are due to the need to study the metabolism and mechanism of the damaging effect, compare the clinical symptoms of poisoning with changes in biochemical, physiological, immunological and many other indicators with concentrations or doses of chemical exposure to the toxicant at an acceptable and/or effective level. The study of the mechanism of the damaging effect of the chemical and a thorough analysis of the clinical picture of intoxication, identification of the most characteristic symptoms of poisoning, allows us to substantiate them as biomarkers of the effect. For example, a decrease in the level of reduced glutathione and an increase in its oxidized form during mercury poisoning, the detection of an increased amount of mercury in biological media, which is accompanied by the manifestation of characteristic clinical signs of poisoning, makes it possible to diagnose mercury intoxication [22, 23]. It would be a mistake to assume, like the opinion of some authors, that the diagnosis of occupational disease and the determination of aptitude can be established only according to biomonitoring data, based on the detection of a toxicant or its metabolites in biological media [10, 11]. The results of the performed biological control on the content of toxicants in biological media are an additional objective characteristic of the professional effects of chemicals on the body. According to I.M. Trachtenberg, who repeatedly drew the attention of researchers to the fact that the determination of even an elevated mercury content in blood or urine without symptoms of poisoning cannot be the basis for a diagnosis – mercury intoxication [24, 25].

Biomarkers of the effect or damage as the body's response to chemical exposure depends on many factors including individual genetic characteristics, the activity of biotransformation enzymes, the nature of nutrition, social conditions, and bad habits. A personalized approach to substantiating biomarkers of the effect based on genetic methods makes it possible to identify the predisposition and development of the most common and socially significant diseases. First of all, this concerns the polymorphism of such genes as: *CYP1A2*, *CYP2A6*, *CYP2D6*, *NAT2*, which allow predicting the development of oncological diseases. It is these categories of people who need more frequent medical examinations, especially when in contact with chemical oncogenes. The determination of the activity of biotransformation enzymes involved in the detoxification of foreign compounds, the expression of metallothioneine synthesis genes

(*MT2A* and *MT3*), which play an important role in the detoxification of heavy metals, make it possible to identify the most vulnerable persons among personnel with a high degree of reliability during regular medical examinations [26, 27]. The substantiation of biomarkers of the effect or damage, taking into account genetic characteristics in different population groups, makes it possible to carry out the prevention and diagnosis of occupational and professionally caused diseases of chemical etiology at a qualitatively new level [27].

There are proposals on the use of indicators of the immune system in persons exposed to allergens, for example, beryllium, which can be considered as biomarkers of the effect during periodic medical examinations [8, 28].

It is not convincing enough to assert that when justifying biomarkers of the effect for workers who come into contact with solvents during the production process, only a micronuclear test on lymphocytes can be used to avoid the need to determine a whole range of chemical compounds in the blood of personnel [12]. Without denying the importance and possibility of using a micronuclear test as an additional characteristic in substantiating the biomarker effect, for an expert opinion on the professional effect of chemicals on the health of personnel, first of all, detailed information is needed on the active concentrations determined in the air of the work area and the identification of a priority pollutant or its metabolite in biological media, after which biomarkers can be justified exposure, and in the presence of symptoms of intoxication, biomarkers of the effect [12].

In the Russian Federation, according to Sanitary Regulations and Norms 1.2.3685-21, 2484 hygienic regulations for the air of the working area have been approved, but MPBC, as is known, have not been developed for the absolute majority of standardized chemicals. First of all, biological exposure indices, or, as is customary in the Russian Federation, MPBC, are necessary for substances entering the body not only by inhalation, but also penetrating through the skin. Their number is quite large and accounts for about one third of all substances used in industry. The following groups of substances, for which the development of MPBC is mandatory, represent industrial poisons that cause serious violations and consequences for human health, for example, damage to the hematopoietic system with substances such as benzene, aniline, nitrotoluene, chemicals widely used in industry, with which significant contingents of workers come into contact, as well as substances that affect reproductive function and toxicants that have a pronounced specific effect: carcinogens, allergens, teratogens [8, 29].

Informativeness of various biosubstrates for determination inorganic substances [22]

Name of the chemical	The biological environment of the body					
	Blood	Urine	Hair	Nails	Teeth	Saliva
Lead	++	+	++	+	++	–
Mercury	+	+	+	+	–	–
Cadmium	x	++	+	+	+ ?	–
Arsenic	x	+	++	+	–	–
Fluorine	–	++	++	+	++	++
Chrome	+	+	+	+	+	–
Nickel	x	+ ?	x	–	–	–
Cobalt	+	–	x	+	–	–
Manganese	+	+ ?	+	–	–	–
Zinc	–	+	x	+	+	–
Antimony	–	–	+	–	–	–
Selenium	–	+	+	+	–	–
Copper	x	+	x	x	+	+

Notation:

+ the content of the element in the biosubstrate varies;
 ++ the element content in this biosubstrate is detected earlier than in others;
 x The content of the element is detected only at high levels of exposure;
 ? data on the detection of an element in biological media are contradictory/missing.

When performing biomonitoring studies, it should be taken into account that not all biological media are equally informative enough to detect and quantify the incoming chemical in the body. The table shows that the reliability and informativeness of the results of the analysis of various biological media depends on the toxicokinetic and toxicodynamic properties of chemicals [22]. It is known that each chemical has its own characteristics of intake, distribution, accumulation and excretion, which are the main characteristics of the toxicant when choosing a biological medium for analysis and justification of the time of selection of biomaterial. Most often, biomonitoring uses such biological media as urine, blood, exhaled air, intestinal contents, for special studies, the determination of toxicants is carried out in saliva, breast milk, hair, nails, teeth, adipose tissue, sweat and cerebrospinal fluids. It is no coincidence that the values of the BEIs recommended by the ACGIH are presented with mandatory indication of the biological environment of the study and the sampling time [20, 21].

In the documents of the Ministry of Health of the USSR, the problem of biological monitoring was first presented in the Methodological Recommendations “Biological control of industrial exposure to harmful substances” (Moscow, 1990, No. 5205-90 approved on 12/07/1990), which set out the basic principles

of performing biological control of the effects of hazard chemicals in production conditions. Using the example of the justification of the MPBC of toluene, the determination of hippuric acid and o-cresol in the urine of workers at the end of a shift is proposed. The determination of toluene metabolites showed that at the level of $MAC_{w.z.}$ toluene, hippuric acid (HA) and o-cresol content correspond to the physiological level of these metabolites: HA – 0.74 ± 0.05 g/L; o-cresol – 0.12 ± 0.07 mg/L. The authors of the document draw attention to the difficulties of substantiating MPBC as a result of the dispersion of individual data on the amount of HA and o-cresol in the urine of workers. Unfortunately, the cited methodological recommendations provide only one example (definition of toluene MPBC) and the proposed toluene MPBC has not been approved.

In 2012, the Federal State Budgetary Institution of Science “Institute of Toxicology of the Federal Medical and Biological Agency” developed methodological recommendations “Identification of high-risk groups among the professionally employed population in contact with the most hazardous metals” (MR 2.2.5.059–2012), which generally sets out an algorithm for identifying high-risk groups among people exposed to metals, provides characteristics of biological media for analysis, and methods for determining certain metals in the biological environment of the body. The proposed methodological techniques for identifying high-risk groups among people exposed to metals, as set out in MR 2.2.5.059–2012, require addition and further improvement. The characteristics of biological media for analysis, methods for determining certain metals in the biological environment of the body are presented. The proposed methodological techniques for identifying high-risk groups among people exposed to metals, as set out in MR 2.2.5.059–2012, require addition and further improvement.

In general, the algorithm for identifying high-risk groups based on biomonitoring represents the sequential execution of certain stages.

At the first stage, the level of external exposure to chemicals in the air of the working area is determined, if necessary, using individual samplers and flushing from the surfaces of the equipment. Based on the results of the analysis of the results of chemical monitoring, the identified toxicants are ranked according to the degree of toxicity and danger to humans and a priority pollutant is allocated.

At the second stage, the priority pollutant or its metabolites are determined in the most informative biological substrates of the body, taking into account the toxicodynamic and toxicokinetic characteristics of the toxicant. The nature of the toxic effect of the

substance and its toxicokinetics makes it possible to substantiate the most informative biological environments of exposure, to substantiate the time of sampling for research, to establish a quantitative characteristic of the effects of industrial poison, to determine the biomarker of exposure.

The third stage consists in a clinical examination of the staff, taking into account the information received about the nature of the toxic effect of priority chemical pollutants, the quantitative content of the toxicant in environmental objects and in the biological environment of the body. The results of chemical and biological monitoring, the value of the exposure biomarker, are compared with the data of a clinical examination, which allows us to objectively substantiate the biomarker of the effect.

Conclusion

Summing up the above, it is necessary to emphasize the undoubted advantages of including biomonitoring, as an obligatory element of evidence-

based medicine, in the algorithm for examining personnel of chemically hazardous facilities to improve the prevention, diagnosis and treatment of diseases of chemical etiology. However, there are a number of unresolved problems in the development of methodological approaches to risk assessment based on biomonitoring:

1. Maximum permissible biological concentrations (MPBC) are practically not being developed. The research is mainly aimed at determining biomarkers of exposure and substantiating sensitive methods for the determination of toxicants or their metabolites in biological media.

2. Due attention is not paid to the justification of the choice of informative biological media and the time of analysis for the determination of toxicants in biological substrates.

3. The most difficult situation seems to be the proof of biomarkers of effect / damage, since it requires the combined efforts of specialists in various fields: hygienists, chemists, toxicologists, occupational pathologists.

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