DOI: https://doi.org/10.17816/MAJ34959

PERSONALIZED TOXICOLOGY: PHENOMENOLOGY, RELEVANCE, DEVELOPMENT PROSPECTS

V.R. Rembovsky, L.A. Mogilenkova

Scientific Research Institute of Hygiene, Occupational Pathology and Human Ecology Federal State Unitary Enterprise under Federal Medical Biological Agency, Leningrad Region

For citation: Rembovsky VR, Mogilenkova LA. Personalized toxicology: Phenomenology, relevance, development prospects. *Medical Academic Journal.* 2020;20(3):61-73. https://doi.org/10.17816/MAJ34959

Received: July 7, 2020 Revised: August 11, 2020 Accepted: September 7, 2020

Personalized toxicology is a research area that studies the individual toxicity of hazardous chemical compounds by experimental and clinical toxicology based on new molecular medicine approaches, including genetics and epigenomics, for prevention, diagnosis, and treatment of chemically induced diseases.

Goal of Research. To study individual genetically and epigenetically induced mechanisms of body's response to exposure to chemical substances, and their effect on preclinical and reversible changes, development of intoxications, and long-term effects, as well as assessment of the individual health risk of exposure to a chemical factor.

Keywords: chemical; toxicity; genotype; epigenome; health; individual.

ПЕРСОНАЛИЗИРОВАННАЯ ТОКСИКОЛОГИЯ. ФЕНОМЕНОЛОГИЯ. АКТУАЛЬНОСТЬ. ПЕРСПЕКТИВЫ РАЗВИТИЯ

В.Р. Рембовский, Л.А. Могиленкова

Федеральное государственное унитарное предприятие «Научно-исследовательский институт гигиены, профпатологии и экологии человека» Федерального медико-биологического агентства России, Ленинградская область

Для цитирования: Рембовский В.Р., Могиленкова Л.А. Персонализированная токсикология. Феноменология. Актуальность. Перспективы развития // Медицинский академический журнал. – 2020. – Т. 20. – № 3. – С. 61–73. https://doi.org/10.17816/MAJ34959

Поступила: 07.07.2020 Одобрена: 11.08.2020 Принята: 07.09.2020

Исследуемое направление — персонализированная токсикология — перспективно для изучения индивидуальной токсичности опасных химических соединений в рамках экспериментальной и клинической токсикологии на основе новых подходов молекулярной медицины с использованием генетических, эпигеномных методов в профилактике, диагностике, лечении химически обусловленных заболеваний.

Цель исследования — изучение индивидуальных генетически и эпигенетически обусловленных механизмов реагирования организма на действие химических веществ, их влияния на доклинические, обратимые изменения, развитие интоксикаций и отдаленных эффектов, оценка индивидуального риска для здоровья воздействия химического фактора.

Ключевые слова: химическое вещество; токсичность; генотип; эпигеном; здоровье; индивидуум.

The preservation of human health when exposed to a chemical factor is an urgent problem in ensuring chemical safety. According to the charter of the World Health Organization, health is a state of complete physical, mental, and social well-being and not just the absence of diseases or physical defects. Human health protection is one of the most important functions of the state [1]. At the same time, the probability of the negative impact of hazardous chemicals (Cs) on humans and the environment poses a conscious danger to ensuring the normal life activities and the health of people in the present times.

When assessing the real risk of developing chemically induced diseases, the primary tasks at present are the identification and quantitative determination of chemical agents and the diagnostics of characteristic manifestations of its toxic effects, considering both the general patterns and individual characteristics of the responses, including the mental response and consciousness of a person in contact with a chemical agent.

List of abbreviations

Cs — chemicals; AhR — aromatic hydrocarbon receptor; BCHE — butyrylcholin esterase; CYP — cytochrome P450; GST — glutathione S-transferase; NAT — N-acetyltransferase; SULT — sulfotransferase; UGT — UDP-glucuronyl transferase.

The major problem with modern toxicology involves proving the existence of pre-nosological and initial individual reactions to long-term exposure to Cs at the threshold level and below, especially for toxicants that are characterized by a wide range of hereditary clinical manifestations, including carcinogens and co-carcinogens. Our experience has proven that the standard determination of toxicometry parameters and other indicators of C toxicity are based on the fact that statistically significant average values of the noted effects does not reflect individual sensitivity, depending on gene polymorphisms and epigenetic and other hereditary factors, or reflects them indirectly (such as coefficients of variation, variance of values of median characteristics, and the time of the onset of the main symptoms of intoxication).

Variants of the effects due to C action, including small doses, are presented in Figure.

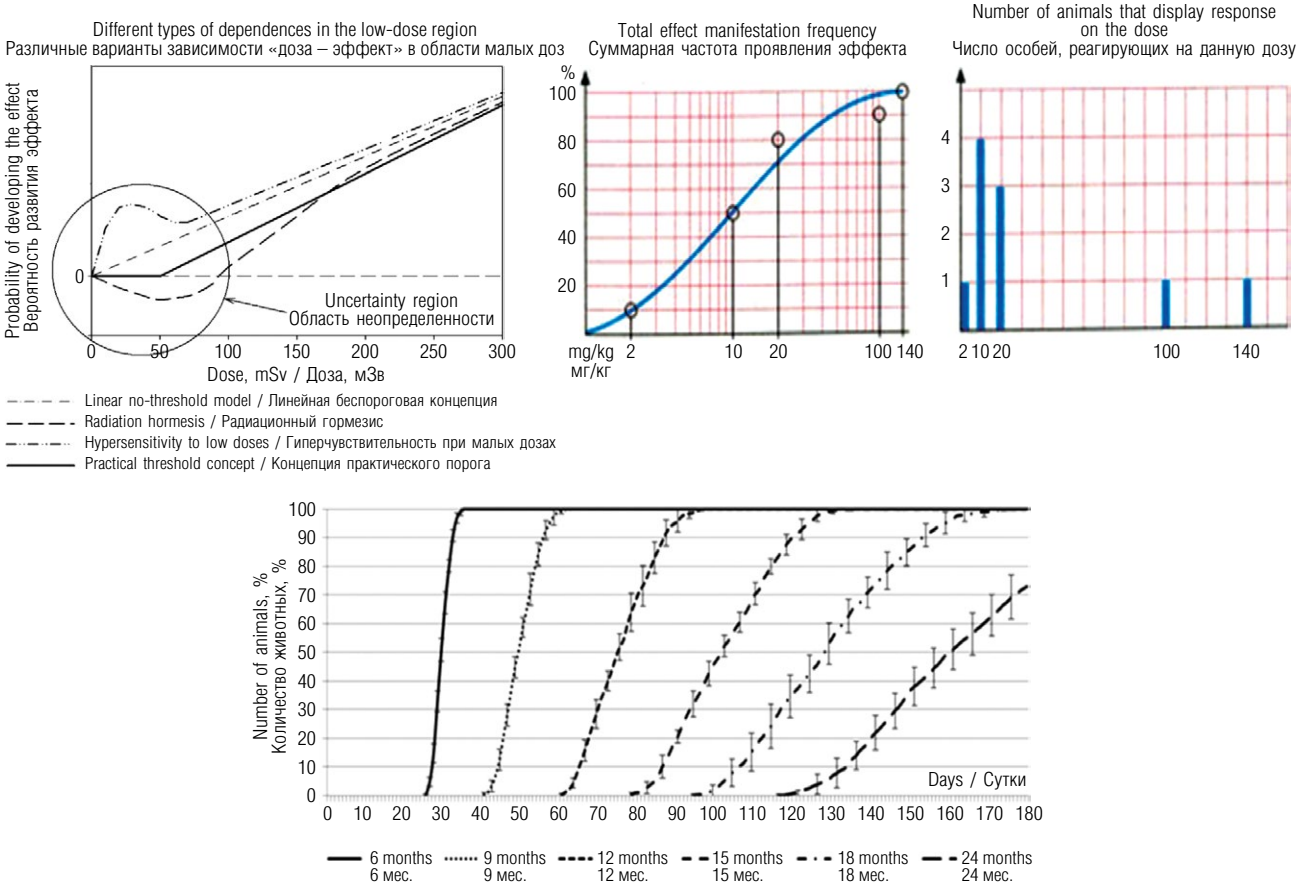
Numerous studies have indicated that a personalized approach is promising when selecting methods for early diagnostics and the means of therapeutic and prophylactic health maintenance (homeostasis management) [2–10] under the conditions of an individual's adaptation to adverse effects, including from chemicals.

It is believed that an individualized approach, which is actively developing in the field of clinical medicine and pharmacology, based on molecular diagnostics, can form the basis in experimental and clinical toxicology.

The term "personalized medicine" was first used by Kewal K. Jain in 1998 in connection with the development of innovative technologies based on genetic, bimolecular methods of diagnostics, and the methods of prevention, treatment, and rehabilitation of patients [6].

In Russia, V.S. Baranov was the first to formulate the concept of individual predictive medicine, which was developed on the basis of molecular genetic studies, that substantiated the creation of a "genetic passport" of a person [7].

The main aims of our proposed interdisciplinary field, namely personalized toxicology, are the study of individual genetic and epigenetic mechanisms of subjects' responses to the action of Cs, their influence on preclinical and reversible



"Dose – effect" dependences of the action of CV in the dynamics of observation

Зависимости «доза – эффект» действия химических веществ в динамике наблюдения

changes, the development of intoxications, and the long-term effects for assessing individual risks for health when exposed to a chemical factor, the development of individual treatment, and the preventive measures and rehabilitation programs for patients [4, 5].

The development of personalized toxicology in the system of modern medical sciences is associated with experimental preventive toxicology (assessment of toxicity, hazard of Cs, the study of the mechanism of action, toxicokinetics, toxicodynamics, and hygienic rating), its section, analytical toxicology (including the determination of Cs, their adducts, metabolites, endogenous metabolites in biological media, the development of methods, and the implementation of sanitary and chemical control), and the clinical field of toxicology (clinical forms of acute and chronic pathology, diagnostics, treatment, and correction of lesions), including molecular toxicology (molecular mechanisms of acute and chronic poisoning with Cs and prenosological changes in relation to genetic and epigenetic factors) using personalized medicine approaches.

Within the framework of the formation of this field of toxicology, there are some classic aspects of the systemic approach, namely, the prevention of a pathological condition, its diagnostics, and treatment (in the event of a disease due to the action of a chemical factor and the associated causes), and the rehabilitation of patients.

Personalized prevention, together with the conventional measures, enables the development of specific recommendations for the prevention of occupational and other diseases associated with chemical exposure such as the measures for labor protection and environmental protection, vocational guidance methods, lifestyle rules, principles of regular medical checkup and early registration of prenosological changes in health, determination of the appropriate non-drug and drug prevention means, including the study of the genotype and epigenetic characteristics of personnel and other persons in contact with Cs.

Personalized diagnostics implies the selection of biomarkers and their quantification to indicate the presence of a specific disorder or possible predisposition to it. Molecular diagnostics plays an important role in personalized medicine and includes genome determination (such as the complete characterization of the DNA of chromosomes and mitochondrial DNA of an individual), haplotypes, the study of gene expression, and other epigenetic factors as well as "multiomix" interventions (metabonomics, metabolomics, proteomics, and lipidomics). Large-scale international genomic studies under the programs "Human Genome," "Haploid Genome," "New Generation Sequencing" (NGS), genomic (GWAS), and epigenomic (EWAS) associations serve as the grounds for studying the hereditary factor in the pathogenesis of chemically induced pathology.

For effective personalized treatment and the rehabilitation of persons with occupational diseases, adequate pharmacological and nutritional support must be developed, which are aimed at normalizing the homeostasis under the conditions of the body adaptation to adverse effects [4, 8, 11].

The development of treatment and preventive measures both for a specific person and for a professional group and the population as a whole aims at making a prognosis of possible health disorders based on predictive medicine, toxicogenomics, and gene therapy.

The creation of an individual treatment and preventive program should be based on the choice of marker genes and the study of the interaction "environment – epigenome – gene," "gene – gene" according to the epigenomic regulation and the intergenic mutual influence toward maintaining the homeostasis of the body [4, 8, 11–24].

The reasons for individual differences in sensitivity to the action of a chemical factor can be as follows:

- the state of the environment and the level of contamination of food products with xenobiotics, including small doses of certain toxicants such as carcinogens and co-carcinogens;
- mutations of genes encoding biotransformation enzymes, components of the immune system, antioxidant defense and other detoxification systems, and a combination of their polymorphisms;
- polymorphisms of genes that predisposes to the development of pathology of target organs of Cs, namely the neurodegenerative processes, diseases of the cardiovascular and respiratory systems, and malignant neoplasms;
- the effect of epistasis, namely the interaction of non-allelic genes, in which the action of

one gene (epistatic) suppresses the action of another (hypostatic);
- epigenetic changes that cause genome modification and gene expression (DNA methylation and chromatin remodeling), which can manifest themselves over several generations;
- gender;
- age;
- physiological state and other internal factors;
- deterioration of the lifestyle, including indulgence in "bad habits" (smoking, alcohol consumption, and drug abuse);
- and the combinations of the above factors, which can lead to a significant change in the body's response to the action of Cs.

The tasks of an individual approach in assessing the health of persons in contact with Cs include the following:
- the search for individual and group differences in the structure of genes involved in the biotransformation of xenobiotics and characterization based on the presence of polymorphisms;
- selection of genetic markers that determine individual and group sensitivities to the action of a chemical factor;
- search for new markers of exposure, namely direct adducts with DNA, RNA, serum albumin and others, as well as markers of sensitivity, namely gene polymorphisms and epigenomic changes;
- selection of biomarkers of individual effects due to genetic characterization;
- creation of new experimental models of personalized studies using humanized animals on the cultures of human cells with different genetic characteristics;
- assessment of the relationship between the presence of genetic markers and sensitivity to a chemical factor in the dynamics of observation of effects (from the background level to assessing the effects of exposure);
- development of methodological approaches to assessing the risk of developing increased individual sensitivity to the action of Cs;
- population genetic analysis, prognosis, and preventive measures for high-risk groups (such as personnel of enterprises and people living near hazardous chemical facilities).

When conducting an individual assessment of the Cs toxicity in an experiment or on animals, it is necessary to take into account the following:
- the species of animals most sensitive to the possible toxic effects;
- age and gender of the experimental animals;
- physiological state of the animals;
- method of Cs administration, dose, the route of administration, and dosage regimen;
- and the stability of the test material under the conditions of the study.

The creation of new experimental models of personalized studies on the effect of Cs on animals in *in vivo* and *in vitro* experiments, as well as on tissue cultures of people with different pheno- and genotypes, genders, ages, and ethnic groups, among other such variables is of great importance, depending on the tasks set. The studies should be aimed both at searching for patterns of toxic effect by the conventional methods and at identifying the relationship of hereditarily determined mechanisms of individual response of multilevel systems for maintaining the homeostasis through molecular biology and mathematical modeling methods.

The selection and development of new models of laboratory animals for the assessment of chemically determined pathology similar to occupational diseases in humans [5, 12] should be performed individually for each animal during the entire follow-up period (during the preexposure, exposure, and recovery period), while considering the species sensitivity and the individual parameters of indicators of direct exposure of Cs to the target organs and the biomarkers of detoxification of these xenobiotics for extrapolation of data obtained in experiments on animals to humans.

The models of transgenic (knockout-gene) animals are considered promising, as they enable simulation of health disorders similar to diseases in humans, which are associated with individual genetic aspects [12]. Whenever possible, these studies should include studies on toxicokinetics.

Notably, substantiation of individual (group by genotypes) hygienic standards of Cs using contemporary methods of hygienic standardization is problematic due to the uncertainties involved in the choice of pathogenetically significant toxicity parameters calculated for each experimental animal during the entire follow-up period (from the baseline values to the level in the recovery period).

Table 1 / Таблица 1

General and distinctive approaches to toxicity assessment of hazardous chemicals in personalized and clinical toxicology studies

Общие и отличительные подходы к оценке токсичности опасных химических веществ в персонализированной и клинической токсикологии

Indicator	Clinical toxicology	Personalized toxicology
Gender	+	+
Age	+	+
Phenotype	±	+
Genotype	–	+
Epigenetic effects	–	+
Lifestyle	±	+
Health status	+	+
Individual approach to sanitary and chemical control of the condition of production and the environment		
Chemical factor	±	+
Habitat of the individual	–	+
Personal monitoring of toxicity (physiological, biochemical, immunological, genetic, pathomorphological, and other biological indicators)		
Background levels	+	+
In the dynamics of exposure	±	+
In the long-term	±	+
Cell culture genotypes	±	+
Therapy using genotyping materials	±	+
Factor analysis (principal component analysis, etc.)	±	+
Toxicity assessment results		
Average group indicators, including population ones	+	±
Individual (group by genotypes) data	–	+

N o t e. + — used in the experiment; – — not applicable; ± — not always.

With an individual assessment of the effect of a toxicant or a complex of Cs on the human health, the question arises regarding the selection of adequate physicochemical and biological indicators, primarily molecular biology. Table 1 presents the main differences between the studies on the effect of hazardous Cs on the body using personalized toxicology from the approaches used within the conventional clinical toxicology.

To understand the nature of the toxic dynamic effect, information is required on the behavior of Cs, their metabolites, and adducts with nucleic acids and proteins in the biological fluids (for example, in the plasma, blood serum, and urine). It has been reported that the degree and nature of toxic effects largely depend on the rate of formation as well as elimination of the toxic metabolites of xenobiotics:

— polar metabolites formed in the phase 1 of biotransformation with the involvement of oxidoreductases (CYP450) and hydrolases (cholinesterase and carboxylesterase);
— conjugation products formed in the phase 2 of biotransformation with the involvement of N-acetyltransferases, UDP-glucuronyl transferases, glutathione-S-transferases, and sulfotransferases.

The processes of the transport of metabolic products, characterized by the different activities of transport proteins, have a significant effect on the rate of elimination. Isoforms of transport proteins (such as P-gp, OATP, OAT, and MRP) with low activity aggravate the course of intoxication.

Currently, the role of polymorphism of genes that regulate the activity of enzymes of phase 1

Table 2 / Таблица 2

Some "unfavorable" allelic variants of xenobiotic detoxification system genes (4)
Некоторые «неблагоприятные» аллельные варианты генов системы детоксикации ксенобиотиков (4)

Gene	Allelic variants	Gene	Allelic variants
Biotransformation phase 1		Biotransformation phase 2	
CYP2D6	2D6*3, CYP2D6*4 etc.	*UGT1A1*	A1*1B, A1*28, 1A1*60
CYP2C9	2C9*2, 2C9*3	*NAT2*	NAT 2*5, NAT 2*в, NAT 2*7, NAT2*14 etc.
CYP2B6	2B6*5, 2B6*6	*TPMT*	TPMT*2, TPMT*3, TPMT*8
CYP3A4	A290G, 3A4*4	*GSTT1*	Null alleles (0/0)
NQO1	609 C>T	*GSTM1*	Null alleles (0/0)
BCHE	A209G etc.	*GSTP1*	GSTP1*B; GSTP1*C
Cytokines		Pro- and antioxidant systems	
IFNγ	+874A/T	*SOD2*	C (T/C and C/C)
TNFα	−308G>A, −238G>A	*CAT*	T (T/T and C/T); G (G/G)
IL4	−589T, −590T, −590C	*GPX4*	T (C/T and T/T)
IL6	−174C>T	*GCLC*	T (T/T)
IL10	−592C>A, −1082A>G, −2849A>G, −575T>A	*CYBA*	T (T/T) (640AA)
IL17	*G197A*	*NQO1 (NAD(P)H*	T (C/T)

(CYP and BCHE) and phase 2 (*GST*, *UGT1A1*, and *NAT2*) of biotransformation of xenobiotics, neurohumoral activity (*SLC6A*, *5-HTA*, *5-HTT*, *MAOA*, *DRD4*, and *COMT*), immune (genes *STAT4*, *STAT6*, encoding immunoglobulins, cytokines, mutations of genes *FOXP3*, and *UNC13D*), cardiovascular (*APOE*, *CETP*, *PON*, *FV*, *eNO*, and *ADRB*), and other systems in the development of multifactorial and chemically determined diseases has been actively studied [4, 13, 16, 20–22]. The role of genetic and environmental factors in the development of polygenic diseases is diverse and unique for each patient, including those being exposed to chemical pollutants.

High sensitivity to the action of toxic Cs can be due to both high and low activities of individual biotransformation enzymes and other systems associated with polymorphisms of the corresponding genes. A relationship exists between the processes of biotransformation and the immune system during the neutralization of Cs, while free radicals are formed with high reactivity to activate antioxidant protection, the lack of which induces oxidative stress.

To prove the individual toxicity of Cs, the genetically determined criteria must be selected, namely the polymorphisms of genes encoding the enzymes of the phases 1 and 2 of biotransformation of xenobiotics that regulate immune responses, the function of antioxidants and other detoxification systems; epigenetic disorders; and their complexes, which significantly affect the nature of pathological processes in the body. Table 2 presents some allelic variants of genes that regulate the processes of detoxification of xenobiotics associated with "unfavorable" consequences of exposure to Cs.

There is often a cascade effect of the homeostasis impairment when exposed to Cs. For example, the transcription of genes containing sites sensitive to polyaromatic hydrocarbons, dioxins, and other xenobiotics is associated with the aromatic hydrocarbon receptor gene. *AhR* activates the expression of genes that regulate the processes of phases 1 and 2 of biotransformation, oxidative stress, intracellular transport, metabolism, immune response, and pro-inflammatory signaling, among others. The activation of the nuclear transcription factor NF-κB during the interaction of its subunits (such as RELA, RELB, and c-Rel) with AhR increases the expression of genes-receptors of immunocompetent cells, reagents of the acute phase of inflammation, cell adhesion molecules, growth factors, proliferation, metastasis of tu-

mor cells, viral replication, transcription factors, regulators of the cell cycle, and apoptosis [24]. For genes encoding isoenzymes CYP, NAT, and GST, polymorphisms are characteristic, manifested phenotypically by the presence in the population of "fast," "slow," or intermediate metabolizers. The greatest deterioration in health is more common with a combination of a high level of enzyme activity of phase 1 and low activity of enzymes of phase 2 in biotransformation. Particularly high sensitivity is registered in individuals with a combination of gene mutations *CYP1A1* C/C and *GSTM1* "0/0," *GSTT1* "0/0"; the combinations of genotypes *GSTT1*+ and *GSTM1* (0/0), *GSTM1* 0/0 and *CYP2E1* T/A, *GSTP1* and *CYP2C19*.

The control of the activity of various subpopulations of immunocompetent cells provide an immune response to antigens, which is associated with the HLA complex for humans [13]. It has been proven that the same antigen causes an immune response of different levels in individuals with different genotypes; meanwhile, the body can be reactive to different antigens to different degrees. The influence of polymorphisms of cytokine genes regulate immune and other processes in maintaining the homeostasis in the development of various pathologies has been most studied. The inhibitory effect on cytochrome P450-dependent monooxygenases has been reported in cytokines, namely IFNα, IFNβ, IFNγ, and IL-1 and TNF, IL-6, IL-11, and IL-2.

Under the conditions of the human habitat, hereditary factors that determine the physical, mental, and spiritual welfare are implemented.

The increased sensitivity to chemical exposure may be associated with personality traits. Conversely, chemical agents, primarily those with a neurotropic effect, and high neuropsychic stress during work with Cs as a situation requiring constant adaptive stress with the involvement of epigenetic mechanisms, can become the primary factor provoking not only several disorders of neuropsychic functions but also the development of psychosomatic diseases registered in the personnel of chemically hazardous industries [25–27]. It is therefore necessary to study genetic and epigenetic markers of predisposition to these health disorders due to exposure to a certain chemical factor.

The polymorphisms of genes involved in the regulation of mental functions (such as dopaminergic and serotonergic, GABA-ergic, hypothalamic-pituitary and adrenergic systems, and neurotrophins), which play a major role in social orientation, memory, behavior, and social functions, have been most studied [15–23]. The genes of the neurotropic factor of the brain and its receptor and the metabolism of polyamines, glial cells, and metabolism are also the genetic markers of stress response in humans.

It has been experimentally demonstrated in laboratory animals that genes for the receptors of dopamine, serotonin, norepinephrine, nuclear factor NF-κB, mitogen-activated protein kinase, neurotrophic factors, transducers, and transcriptional activators that control the transmission of nerve impulses as well as the characteristics of the immune system, affect the nature of the stress response and the recovery of the body after stress [28].

Table 3 presents some allelic variants of genes that determine the negative forms of mental functions in humans. The selection of these genotypes for use as biomarkers of sensitivity to specific Cs is important when conducting professional selection and in ensuring adequate performance of personnel in chemically hazardous industries.

Table 3 / Таблица 3

Polymorphisms of genes that determine negative forms of behavior and other mental functions in humans
Полиморфизмы генов, определяющих негативные формы поведения и другие психические функции человека

Gene	Allele, polymorphic locus	Mental disorders
SLC6A3 (dopamine transporter)	9R	Violent behavior and aggressiveness, tendency to schizophrenia, alcoholic psychosis, decreased attention; depression in patients with cerebral atherosclerosis
SLC6A3 (dopamine transporter)	10R	Risk behavior
DAT1 (dopamine transporter)	9R, 10R	Predisposition to depression, drug addiction and other mental disorders

End of table 3 / Окончание табл. 3

Gene	Allele, polymorphic locus	Mental disorders
DRD2 (type 2 dopamine receptors)	A1A1(T), A1A2(CC)	Tendency to schizophrenia, addictive behavior (alcoholism, drug addiction); acceleration of mental fatigue during cognitive load
DRD4 (type 4 dopamine receptors)	7R, 4R	Tendency to seek thrills, especially when exposed to negative psychosocial factors, to depressive psychosis, instability to stress
SLC6A4 (serotonin transporter)	5-HTTLPR, SS, rs1042173	Tendency to depression, anxiety, violence, instability to stress
5-HTR2A (serotonin transporter)	A1438G, T102C, A2A2	Tendency to schizophrenia, depression, aggressive behavior
HTR2A (serotonin transporter)	102T>C, 1438G<A, rs 7997012, rs17069218 (T/T), A1A1	Tendency to schizophrenia, depression, addictive behavior (alcoholism, drug addiction); aggressiveness, susceptibility to cardiovascular diseases
TPH1 (catalyst for the oxidation of tryptophan to 5-HT)	A218C (A/A)	Depressive and suicidal affective disorders
MAOA (monoamine oxidase A; degradation of the neurotransmitters of adrenaline, noradrenaline, serotonin, and histamine)	5R, 4R, 3R, 2R, low-active gene variant (LPR)	Men who survived parental violence are most prone to aggressiveness and antisocial behavior;
TPH1 (tryptophan hydroxylase, serotonin synthesis)	A218C (A)	the risk of aggressive and hostile behavior at a young age
TPH2 (tryptophan hydroxylase, serotonin synthesis)	G703T (T)	Aggressiveness, anxiety, impulsivity, suicidal behavior
NET (noradrenaline transporter)	A1287G (A/A), T182C (T/T)	Aggressiveness, anxiety
COMT (catechol-O-methyltransferase: degradation of catecholamines)	G472A (A/AA/AA/A), G472A, G472AG472A, G472Ars4680A>G	Schizophrenia, bipolar disorders, aggressiveness, antisocial behavior
AVPR1A (vasopressin hormone receptor)	rs1042615 (T)	Aggressive behavior
AVPR1B (arginine-vasopressin hormone receptor)	rs28632197 (A), rs33911258 (A/A)	Mental disorders, aggressive behavior
OXT (oxytocin)	rs6133010(A/A)	Aggressiveness
OXTR (oxytocin receptor)	Deletion, rs53576A/G (A) and rs4564970(G), rs7632287 (T) and rs11720238 (T)	Autism, decreased empathy, prosocial behavior, aggression, decreased stress resistance, development of mental disorders.
GAD1 (synthesis of GABA isoforms by glutamate decarboxylase)	rs3749034	Tendency to schizophrenia
GABBR2 (metabotropic GABA receptors)	rs35400353	Tendency to schizophrenia
BDNF (brain-derived neurotropic factor)	rs6265 (196G>A)	Depression under stress, aggressive behavior

The combination of unfavorable polymorphisms of genes regulating neuropsychiatric functions and human developmental conditions increases the risk of behavioral problems and the degree of predisposition to depressive and other disorders; for example, the interaction of polymorphic loci of genes for vasopressin hormones (*AVPR1A, AVPR1A*) and oxytocin genes with genes of the serotonergic system increases the risk of aggressive behavior. Moreover, the combination of some alleles of catechol-O-methyltransferase with inactive methylenetetrahydrofolate reductase affects the risk of development and the course of schizophrenia. However, an individual's predisposition to impaired behavioral reactions such as work and social activity may not manifest itself throughout his life if he has developed and lives in a favorable environment.

The phenotype of a behavior, other mental functions, as well as physiological, morphological, and functional characteristics of an individual is determined not only by the genotype (DNA sequence) but also by the epigenetic mechanisms [4, 29].

The components of the cascade of neuro-endocrine-immune responses regulate the activity of genes in the brain cells and peripheral tissues through epigenetic changes. In case of epigenetic inheritance, the DNA sequence does not change, while other genetic factors regulate the activity of genes and the processes of adaptation to the effects of the internal and external environment. Genome modifications and gene expression are associated with the processes of DNA methylation, compaction, and decompaction of chromatin, as well as the regulation of non-coding and other RNAs, particularly microRNA biogenesis at the stage of microRNA precursor processing, with protein prionization and X-chromosome inactivation [4, 28, 30].

Epigenetic mechanisms provide dynamic and long-term regulation of neurons, the maintenance of neurons and neural networks, and the neuropsychic status. An inverse relationship between DNA methylation and histone acetylation has been reported [28]. Methylation of H3K4, H3K9, and H3K27 is significant in various behavioral responses to stress; these epigenetic modifications are regulated by histone methyltransferases. The genes for the serotonin transporter *SLC6A4* [31], corticotropin-releasing hormone *CRH* [32], glucocorticoid receptor *NR3C1* [33], brain-derived neurotropic factor *BDNF* [34, 35], and ankyrin family ank3 have been most thoroughly investigated in relation to epigenetic changes during the formation of stress reactions and post-stress conditions [36]. The molecular cascades of cellular responses to stress have been described, including the mobilization of transposones [37] and the changes in the functioning of mitochondria such as ATP synthesis and the regulation of protein synthesis [38].

Epigenetic changes can induce pathological conditions, including the acceleration of aging and the development of neurodegenerative, cardiovascular diseases, diabetes, neoplasms, and other multifactorial diseases [4, 24, 39, 40]. The epigenetically dependent development of diseases can be influenced by gender, age, hormonal status, unhealthy diet, social interactions, environmental problems, and other reasons. When Cs influence the phenotype or expression of genes in the initial stages, these changes are reversible.

DNA hypomethylation (demethylation) and the resulting chromosomal instability with age has been studied [40]. In fact, with aging, some promoter regions have been reported to be hypermethylated, including certain tumor suppressor genes. Increased epigenetic age is associated with the activation of pro-inflammatory and interferon pathways and a decrease in the activation of transcription/translation mechanisms, the response to DNA damage and mitochondrial signatures, which should be considered when assessing the effect of a chemical factor on human health. Thus, the acceleration of the "epigenetic age" in comparison with the chronological one by 5 years increased the risk of mortality in humans, as determined by the Horvath method by 22% and by the Hannuman method by 16%, as well as the development of carcinogenesis and other pathologies.

Thus, to characterize the individual predisposition to the action of Cs and to compile a multifactorial database for each employee (citizen), it is important to integrate information about the hereditary biological and psychosocial properties, constitutional, behavioral, morphophysiological, metabolic characteristics, as well as research data on environmental and other factors.

The differential diagnostics of diseases is based on an assessment of the clinical presentation of a patient with chemically determined diseases, which involves the results of an analysis several systems of the body homeostasis, including hereditary predisposition.

The emergence of the clinical field of personalized medicine, associated with customization (i.e., selection for individual characteristics) of drugs implies a promising transition from traditional pharmacotherapy, with a focus on the entire population, to a new group model (ideally an individual model, which is molecular-targeted therapy, to its new stage, targeted medicine) [41]. The development of this field can ensure greater efficiency and safety of treatment, and then, based on the evidence and approaches of systemic genetics, it will enable proceeding with the development of the translational (precise) medicine.

Taking into account the current development of medicine, the urgent problem of the clinical section of personalized toxicology is the improvement of predictive, preventive, personalized, and participatory fields of health management, as adopted in Russian and other international practice [4, 9, 41–45]. Predictivity is the determination of the probability of diseases occurrence in order to comply with the chemical safety measures and adjust to the employee's lifestyle in order to prolong the life and improve its overall quality. The preventive field is aimed to prevent the onset of disease development. The personalized field represents an approach to the provision of health care with a preventive focus and treatment based on the individual characteristics of workers (i.e., patients). The participatory field implies the active participation of the person himself/herself in the process of making specific medical decisions and in defining a general strategy for monitoring his/her health.

The introduction of the methodology for personalized assessment of the toxicity of Cs into the clinical practice of medical institutions of chemically hazardous industries will enable the following:

- the development of an algorithm enabling individual assessment of the potential hazards of highly, extremely toxic chemicals (contamination with Cs of the working area air, equipment surfaces, building structures, environmental objects, presence of Cs and their metabolites, and adducts in biological media), including data from personal dosimeters, questionnaires for recording the employee's stay in the hazardous areas;
- the creation of a material, technical and laboratory base for clinical, genetic and experimental studies on individual toxicity;
- the improvement of the conduct of comprehensive environmental-hygienic and clinical-epidemiological studies of personnel and the general population, including an assessment of the potential and real risks and the identification of a risk group when working with Cs through a personalized approach;
- the determination of the internal dose (exposure marker) of hazardous Cs that entered the body during the shift (i.e., day, year, total contact time);
- detection of markers of early detection of prenosological, clinical manifestations of intoxication, and the possible long-term effects, including "omix" (genomics, epigenomics, lipidomics, toxicometabolomics) indicators characterizing individual reactivity;
- the selection of markers of the mechanism of action of drugs and the effectiveness of treatment;
- the establishment of predictors of the clinical outcome of a disease;
- introduction into practice of new genetic express methods for diagnosing the state of health of the examined persons in the follow-up studies;
- the development of individual (group) approaches to the hygienic regulation of Cs based on genotypes (epigenomes) that affect the degree of their toxicity (hazard) in persons in contact with these compounds;
- improvement of the database of personal data of health registers, considering the genetic characteristics in groups of populations under consideration for maintaining the medical and sanitary passports of enterprises and territories of the zone of protective measures;
- introduction of a set of effective measures for individual health protection of workers and the population in contact with chemical pollutants and their future generations, including the selection of food products based on nutrigenetics and nutrigenomics

Thus, personalized toxicology is a promising field of comprehensive research aimed at assessing the hereditary reserve capacities of an organism, its response to chemical exposure, and other related factors. For effective prevention, including the treatment and rehabilitation of patients, it is necessary to create a database of individual data characterizing genetically determined a priori (potential) and absolute risks (in terms of markers of exposure, susceptibility, and effect) with the priority of high social responsibility of specialists with access to personal biometric data.

Additional information

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

Author contributions. The literary sources were collected and analyzed in equal shares, the concept of a personalized field of toxicological studies was jointly developed, and proposals were made for the implementation of an individual approach to experimental and clinical toxicology. The article was formatted by L.A. Mogilenkova in accordance with the rules of the journal.

References

1. Устав (Конституция) Всемирной организации здравоохранения. Нью-Йорк, 22 июля 1946 г. [Charter (Constitution) of the World Health Organization. New York, 1946 July 22. (In Russ.)]. Доступно по: http://docs.cntd.ru/document/901977493. Ссылка активна на 16.07.2020.
2. Уйба В.В. Современные технологии охраны здоровья при воздействии особо опасных факторов. Персонифицированный подход // Белушкина Н.Н., Чабан Е.А. Научные основы эффективности и безопасности лекарственных средств / под ред. М.А. Пальцева, Н.Н. Белушкиной. – М.: РАН, 2015. – С. 30–44. [Uiba VV. Sovremennye tekhnologii okhrany zdorov'ya pri vozdeistvii osobo opasnykh faktorov. Personifitsirovannyi podkhod. In: Belushkina NN, Chaban EA. Nauchnye osnovy ehffektivnosti i bezopasnosti lekarstvennykh sredstv. Ed. by M.A. Pal'tsev, N.N. Belushkina. Moscow: RAN; 2015. P. 30-44. (In Russ.)]
3. Баранов В.С., Баранова Е.В., Иващенко Т.Э., Асеев М.В. Геном человека и гены «предрасположенности». Введение в предиктивную медицину. – СПб.: Интермедика, 2000. – 270 с. [Baranov VS, Baranova EV, Ivashchenko TE, Aseev MV. Genom cheloveka i geny "predraspolozhennosti". Vvedenie v prediktivnuyu meditsinu. Saint Petersburg: Intermedika; 2000. 270 p. (In Russ.)]
4. Рембовский В.Р., Могиленкова Л.А. Процессы детоксикации при воздействии химических веществ на организм. – СПб.: Изд-во Политехнического ун-та, 2017. – 383 с. [Rembovskiy VR, Mogilenkova LA. Protsessy detoksikatsii pri vozdeystvii khimicheskikh veshchestv na organizm. Saint Petersburg: Izdatelstvo Politekhnicheskogo universiteta; 2017. 383 p. (In Russ.)]
5. Рембовский В.Р., Могиленкова Л.А. Перспективы развития персонализированной токсикологии // Medline.ru. – 2019. – № 20. – С. 244–249. [Rembovsky VR, Mogilenkova LA. Prospects for the development of personalized toxicology. *Medline.ru*. 2019;(20):244-249. (In Russ.)]
6. Jain KK. Textbook of Personalized Medicine. New York: Springer; 2015.
7. Баранов В.С., Асеев М.В., Баранова Е.В. «Гены предрасположенности» и генетический паспорт // Природа. – 1999. – № 3. – С. 17–27. [Baranov VS, Aseev MV, Baranova EV. "Geny predraspolozhennosti" i geneticheskii passport. Priroda. 1999;(3):17-27. (In Russ.)]
8. Hale VG, Woo K, Lipton HL. Oxymoron no more: The potential of nonprofit drug companies to deliver on the promise of medicines for the developing world. *Health Affairs.* 2005;24(4)1057-1063. https://doi.org/10.1377/hlthaff.24.4.1057.
9. Hood L, Friend SH. Predictive, personalized, preventive, participatory (P4) cancer medicine. *Nat Rev Clin Oncol.* 2011;8(3):184-187. https://doi.org/10.1038/nrclinonc.2010.227.
10. Киселев В.И., Пальцев М.А. Регуляция активности генов и новые лекарственные вещества // Белушкина Н.Н., Чабан Е.А. Научные основы эффективности и безопасности лекарственных средств / под ред. М.А. Пальцева, Н.Н. Белушкиной. – М.: РАН, 2015. – С. 93–106. [Kiselev VI, Pal'tsev MA. Regulyatsiya aktivnosti genov i novye lekarstvennye veshchestva. In: Belushkina NN, Chaban EA. Nauchnye osnovy ehffektivnosti i bezopasnosti lekarstvennykh sredstv. Ed. by M.A. Pal'tsev, N.N. Belushkina. Moscow: RAN; 2015. P. 93-106. (In Russ.)]
11. Мартинчик А.Н., Маева И.В., Янушевич О.О. Общая нутрициология: учебное пособие. – М.: Медпрес-информ, 2005. – 392 с. [Martinchik AN, Maeva IV, Yanushevich OO. Obshchaya nutritsiologiya: uchebnoe posobie. Moscow: Medpres-inform; 2005. 392 p. (In Russ.)]
12. Рембовский В.Р., Могиленкова Л.А., Бельтюков П.П. Персонализированный подход в экспериментальной токсикологии // Medline.ru. – 2020. – № 21. – С. 442–451. [Rembovskiy VR, Mogilenkova LA, Beltyukov PP. Personalized approach in experimental toxicology. *Medline.ru*. 2020;(21):442-451. (In Russ.)]
13. Хаитов Р.М. Иммунология: учебник. – М.: ГЭОТАР-Медиа, 2016. – 255 с. [Haitov RM. Immunologiya: uchebnik. Moscow: GEOTAR-Media; 2016. 255 p. (In Russ.)]
14. Меньщикова Е.Б., Ланкин В.З. Окислительный стресс. Прооксиданты и антиоксиданты. – М.: Слово, 2006. – 553 с. [Men'shchikova EB, Lankin VZ. Okislitel'nyi stress. Prooksidanty i antioksidanty. Moscow: Slovo; 2006. 553 p. (In Russ.)]
15. Фукс Б.Б. Факторы транскрипции программируют гены нейронов, участвующих в запрограммированном поведении // Бюллетень сибирской медицины. – 2013. – Т. 12. – № 2. – С. 275–283. [Fuks BB. Programming genes in brain and problem of social behavior of man. *Bulletin of Siberian medicine*. 2013;12(2):275-283. (In Russ.)]
16. Заботина А.М., Белинская М.А., Журавлев А.С., и др. Влияние полиморфных вариантов rs6311 и rs6313 гена рецептора серотонина 2A (HTR2A) на уровень его мРНК и белка в лейкоцитах периферической крови при терапии антипсихотиками // Цитология. – 2018. – Т. 60. – № 5. – С. 381–389. [Zabotina AM, Belinskaya MA, Zhuravlev AS, et al. The influence of rs6311 and rs6313 polymorphisms of serotonin 2A receptor gene (HTR2A) on its mRNA and protein levels in peripheral blood leukocytes in treatment with antipsychotics. *Tsitologiya*. 2018;60(5):381-389. (In Russ.)]. https://doi.org/10.31116/tsitol.2018.05.08.
17. Heinz A, Goldman D, Jones D, et al. Genotype influences *in vivo* dopamine transporter availability in human striatum.

Neuropsychopharmacology. 2000;22(2):133-139. https://doi.org/10.1016/S0893–133X(99)00099-8.

18. Ness S, Owens M, Kilts C. The variable number of tandem repeats element in DAT1 regulates *in vitro* dopamine transporter density. *BMC Gene*. 2005;6:55-66. https://doi.org/10.1186/1471-2156-6-55.
19. Голимбет В.Е., Алфимова М.В., Митюшина Н.Г. Полиморфизм гена рецептора серотонина (5HTR2A) и особенности личности // Молекулярная биология. – 2004. – Т. 38. – № 3. – С. 404–412. [Golimbet VE, Alfimova MV, Mitjushina NG. Polymorphism of the serotonin 2A receptor gene (5HTR2A) and personality traits. *Molecular biology*. 2004;38(3):404-412. (In Russ.)]
20. Поликанова И.С., Коршунов А.В., Леонов С.В., Веракса А.Н. Ассоциация рецептора к дофамину второго типа (DRD2) с развитием утомления в результате длительной когнитивной нагрузки // Национальный психологический журнал. – 2016. – Т. 38. – № 3. – С. 115–126. [Polikanova IS, Korshunov AV, Leonov SV, Veraksa AN. Type II dopamine receptor (DRD2) association with the development of fatigue as a result of prolonged cognitive load. *National psychological journal*. 2016;38(3):115-126. (In Russ.)]. https://doi.org/10.11621/npj.2016.0314.
21. Lucht MJ, Barnow S, Sonnenfeld C, et al. Associations between the oxytocin receptor gene (OXTR) and affect, loneliness and intelligence in normal subjectsand affect. *Prog Neuropsychopharmacol Biol Psych*. 2009;33(5):860-866. https://doi.org/10.1016/j.pnpbp.2009.04.004.
22. Валиуллина А.Р. Изучение роли генов нейропептидов и нейротрансмиттерных систем в развитии агрессивного поведения человека: автореф. дис. … канд. биол. наук. – Уфа, 2013. – 20 с. [Valiullina AR. Izuchenie roli genov neiropeptidov i neirotransmitternykh sistem v razvitii agressivnogo povedeniya cheloveka. [dissertation abstract] Ufa; 2013. 20 p. (In Russ.)]
23. Платонкина Т.В., Боговин Л.В., Наумов Д.Е., Овсянкин А.И. Генетические исследования депрессивных расстройств: обзор литературы // Бюллетень физиологии и патологии дыхания. – 2018. – № 68. – С. 96–106. [Platonkina TV, Bogovin LV, Naumov DE, Ovsjankin AI. Genetic researches of depressive disorders: literature review. *Bulletin of physiology and respiratory pathology*. 2018;(68):96-106. (In Russ.)]. https://doi.org/10.12737/article_5b19ee7411be17.38016141.
24. Софронов Г.А., Рембовский В.Р., Радилов А.С., Могиленкова Л.А. Современные взгляды на механизм токсического действия диоксинов и их санитарно-гигиеническое нормирование // Медицинский академический журнал. – 2019. – Т. 19. – № 1. – С. 17–28. [Sofronov GA, Rembovskij VR, Radilov AS, Mogilenkova LA. Modern views on the mechanism of the toxic action of dioxins and their hygienic rationing. *Medical academic journal*. 2019;19(1):17-28. (In Russ.)]. https://doi.org /10.17816/MAJ19117-28.
25. Рембовский В.Р., Филиппов В.Л., Филиппова Ю.В. Влияние химического фактора на психосоматическое здоровье персонала химически опасных объектов // Экология и развитие общества. – 2015. – № 2. – С. 31–37. [Rembovsky VR, Filippov VL, Filippova YuV. Influence of the chemical factor on the psychosomatic health of personnel of chemically hazardous facilities. *Ecology and development of society*. 2015;(2):31-37. (In Russ.)]
26. Рембовский В.Р., Могиленкова Л.А., Олейникова Е.В. Анализ риска в системе мониторинга воздействия химического фактора. – СПб.: ЭЛБИ-СПб, 2014. – 304 с. [Rembovskii VR, Mogilenkova LA, Oleinikova EV. Analiz riska v sisteme monitoringa vozdeistviya khimicheskogo faktora. Saint Petersburg: ELBI-SPb; 2014. 304 p. (In Russ.)]
27. Филиппов В.Л., Филиппова Ю.В. Химическая психосоматическая болезнь. Медико-гигиенические аспекты обеспечения работ с особо опасными химическими веществами // Труды научно-практ. конф., посв. 40-летию НИИ ГПЭЧ ФУ «Медбиоэкстрем» МЗ России. – СПб., 2002. – С. 106–116. [Filippov VL, Filippova YuV. Khimicheskaya psikhosomaticheskaya bolezn'. Mediko-gigienicheskie aspekty obespecheniya rabot s osobo opasnymi khimicheskimi veshchestvami. (Conference proceedings) Trudy nauchno-prakt. konf., posv. 40-letiyu NII GPEHCH FU "Medbioehkstrem" MZ Rossii. Saint Petersburg; 2002. P. 106-116. (In Russ.)]
28. Дюжикова Н.А., Даев Е.В. Геном и стресс-реакция у животных и человека // Экологическая генетика. – 2018. – Т. 16. – № 1. – С. 4–26. [Dyuzhikova NA, Daev EV. Genome and stress-reaction in animals and humans. *Ecological genetics*. 2018;16(1):4-26. (In Russ.)]. https://doi.org/10.17816/ecogen1614-26.
29. Закиян С.М., Власов В.В., Дементьева Е.В. Эпигенетика. – Новосибирск: Изд-во СО РАН, 2012. – 592 с. [Zakiyan SM, Vlasov VV, Dement'eva EV. Ehpigenetika. Novosibirsk: Izd-vo SO RAN; 2012. 592 p. (In Russ.)]
30. Graff J, Kim D, Dobbin MM, Tsai LH. Epigenetic regulation of gene expression in physiological and pathological brain processes. *Physiol Rev*. 2011;91(2):603-649. https://doi.org/10.1152/physrev.00012.2010.
31. Tsuji M, Miyagawa K, Takeda H. Epigenetic regulation of resistance to emotional stress: Possible involvement of 5-HT1A receptor-mediated histone acetylation. *J Pharmacol Sci*. 2014;125(4):347-354. https://doi.org/10.1254/jphs.14r07cp.
32. Xu L, Sun Y, Gao L, et al. Prenatal restraint stress is associated with demethylation of corticotrophin releasing hormone (CRH) promoter and enhances CRH transcriptional responses to stress in adolescent rats. *Neurochem Res*. 2014;39(7):1193-1198. https://doi.org/10.1007/s11064-014-1296-0.
33. Murgatroyd C, Spengler D. Epigenetic programming of the HPA axis: Early life decides. *Stress*. 2011;14(6):581-589. https://doi.org/10.3109/10253890.2011.602146.
34. Tsankova NM, Berton O, Renthal W, et al. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nat Neurosci*. 2006;9(4):519-525. https://doi.org/10.1038/nn1659.
35. Tsankova NM, Kumar A, Nestler EJ. Histone modifications at gene promoter regions in rat hippocampus after acute and chronic electroconvulsive seizures. *J Neurosci*. 2004;24(24):5603-5610. https://doi.org/10.1523/JNEUROSCI.0589-04.2004.

36. Ferreira MA, O'Donovan MC, Meng YA, et al. Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. *Nat Genet*. 2008;40(9):1056-1058. https://doi.org/10.1038/ng.209. PMID 18711365.
37. McGowan PO, Hope TA, Meck WH, et al. Impaired social recognition memory in recombination activating gene 1-deficient mice. *Brain Res*. 2011;1383:187-195. https://doi.org/10.1016/j.brainres.2011.02.054.
38. Misiewicz Z, Iurato S, Kulesskaya N, et al. Multi-omics analysis identifies mitochondrial pathways associated with anxiety-related behavior. *PLoS Genetics*. 2019;15(9):e1008358. https://doi.org/10.1371/journal.pgen.1008358.
39. Паткин Е.Л., Софронов Г.А. Эпигенетика популяций, экотоксикогенетика и болезни человека // Экологическая генетика. – 2012. – Т. 10. – № 4. – С. 14–28. [Patkin EL, Sofronov GA. Population epigenetics, ecotoxicology and human diseases. *Ecological genetics*. 2012;10(4):14-28. (In Russ.)]
40. Horvath S, Garagnani P, Bacalini MG, et al. Accelerated epigenetic aging in Down syndrome. *Aging Cell*. 2015;14(3):491-495. https://doi.org/10.1111/acel.12325.
41. Баранов В.С., Баранова Е.В. Эволюция молекулярной медицины: от электронного «генетического паспорта» до геномной электронной карты здоровья // Молекулярно-биологические технологии в медицинской практике: сб. статей. Вып. 24. – Новосибирск: Академиздат, 2016. – С. 3–17. [Baranov VS, Baranova E V Evolution of molecular medicine: from electronic genetic passport to genomic electronic health records. In: Molekulyarno-biologicheskie tekhnologii v meditsinskoy praktike: sb. statei. Vypusk 24. Novosibirsk: Akademizdat; 2016. P. 3-17. (In Russ.)]
42. Баранов В.С. Программа «Геном человека» как научная основа профилактической медицины // Вестник РАМН. – 2000. – № 10. – С. 27–37. [Baranov VS. Program "Human Genome" as a scientific basis for preventive medicine. *Annals of the Russian Academy of medical sciences.* 2000;(10):27-37. (In Russ.)]
43. Щербо С.Н., Щербо Д.С. Лабораторная медицина как основа персонализированной медицины. Применение биочипов в медицине // Клиническая лабораторная диагностика. – 2014. – Т. 59. – № 5. – С. 4–11. [Scherbo SN, Scherbo DS. Laboratory medicine as the basis of personalized medicine. The use of biochips in medicine. *Russian clinical laboratory diagnostics*. 2014;59(5):4-11. (In Russ.)]. https://doi.org/10.1186/1878-5085-4-7.
44. Perna L, Zhang Y, Mons U, et al. Epigenetic age acceleration predicts cancer, cardiovascular, and all-cause mortality in a German case cohort. *Clin Epigenetics*. 2016;8:64. https://doi.org/10.1186/s13148-016-0228-z.
45. Levine ME, Lu AT, Quach A, et al. An epigenetic biomarker of aging for lifespan and healthspan. *Aging (Albany NY)*. 2018;10(4):573-591. https://doi.org/10.18632/aging.101414.

Information about the authors / Сведения об авторах

Vladimir R. Rembovskiy — Doctor of Medical Sciences, Professor, Scientific Director. Scientific Research Institute of Hygiene, Occupational Pathology and Human Ecology Federal State Unitary Enterprise under Federal Medical Biological Agency, Leningrad Region, Russia. https://orcid.org/0000-0001-9636-3807; SPIN-code: 7427-7395. E-mail: niigpech@rihophe.ru.

Владимир Романович Рембовский — д-р мед. наук, профессор, заслуженный деятель науки и техники РФ, научный руководитель. ФГУП «НИИ гигиены, профпатологии и экологии человека» ФМБА России, Ленинградская область. https://orcid.org/0000-0001-9636-3807. SPIN-код: 7427-7395. E-mail: niigpech@rihophe.ru.

Lyubov A. Mogilenkova — Doctor of Medical Sciences, Leading Researcher. Scientific Research Institute of Hygiene, Occupational Pathology and Human Ecology Federal State Unitary Enterprise under Federal Medical Biological Agency, Leningrad Region, Russia. https://orcid.org/0000-0001-9033-0537. SPIN-code: 7427-7395. E-mail: gpech@fmbamail.ru; matveeva@fmbamail.ru.

Любовь Абрамовна Могиленкова — д-р мед. наук, ведущий научный сотрудник научно-организационного отдела. ФГУП «НИИ ГПЭЧ» ФМБА России, Ленинградская область. https://orcid.org/0000-0001-9033-0537. SPIN-код: 7427-7395. E-mail: gpech@fmbamail.ru; matveeva@fmbamail.ru.

✉ Corresponding author / Контактное лицо

Lyubov A. Mogilenkova / Любовь Абрамовна Могиленкова
E-mail: gpech@fmbamail.ru; matveeva@fmbamail.ru