N.A. Solovieva, O.N. Kolosova

GENETIC ASPECTS OF THE REGULATION OF CIRCADIAN RHYTHMS AFFECTING STRESS RESISTANCE

DOI 10.25789/YMJ.2020.72.27

The article presents the results of the analysis of the literature data on the molecular genetic mechanisms of control and regulation of circadian rhythms that determine the chronotype of a person.

It has been established that disturbance of circadian rhythms arising as a result of psychoemotional and physical stress expressed in degree and / or duration, can lead to a decrease in the body's resistance to stress factors with the subsequent development of maladjustment processes, which in turn can be a trigger mechanism for the onset of the development of such pathological conditions as diseases of the cardiovascular system, gastrointestinal tract, autoimmune, mental, neurodegenerative, oncological and other diseases.

According to the results of numerous studies, the molecular genetic control of circadian rhythms consists of interacting positive and negative feedbacks of regulatory loops of clock genes, such as *genes Bmal1, Clock, Per1, Per2, Per3, TIM, Npas2, Cry1 and Cry2, Csnk1d, Csnk1e, Rev-erba, Rora, Bhlhe40, Bhlhe41*, as well as genes *FBXL3, FTO, MADD, CYP2A6, ARNTL, Mel1a, Mel1b and GPR50*. The transcription factors encoded by these genes, enzymes, transporters, prohormones, signaling and other proteins are involved in regulation of daily frequency.

Despite the fact that the main components of the molecular genetic mechanisms of circadian rhythms are already known, the issue of regulating their work remains relevant today. The results of studies carried out on different populations with respect to individual polymorphic variants of genes are not always unambiguous and require a more detailed study, since it is the result of the interaction of genes that can determine their phenotypic effect.

Thus, understanding the molecular mechanisms and identifying genetic markers that cause disturbances in circadian rhythms is an important step in the development of methods aimed at preventing and correcting pathological conditions caused by maladjustment processes.

Keywords: adaptation, stress factors, circadian rhythm, clock genes.

Reforms of the socio-economic system, actively taking place in the world in recent decades, lead to the renewal of conditions and principles of organizing human life. Life in conditions of a huge flow of information and fierce competition has become the norm, a modern person lives and works in a "round-the-clock readiness" mode, which requires intense and well-functioning work from the internal systems of the body, the failure of which can cause a violation of adaptation processes and, as a result, the development of stress. In this regard, the problem of resistance to stress is currently considered one of the most serious and increasingly important for public health.

According to G. Selye's definition "stress or general adaptation syndrome is a set of nonspecific adaptive neurohumoral reactions that arise in response to exposure to adverse factors (stressors) that are significant in strength and duration, and body systems that counteract extreme stimuli causing stress are aimed at maintaining constancy the internal environment of the body - homeostasis" [16]. Today it is already known that the biological meaning of these processes at the early stages of the development of a stress reaction is aimed at maintaining the functions of vital organs and systems by increasing the availability of energy resources, regulating regional blood flow, activating enzymes of cellular metabolism and other factors of biological adaptation. In other words, the cascade of neurohumoral and metabolic events arising in response to the action of stressors is designed to provide an urgent and then long-term adaptation to new environmental requirements. At the same time, the same adaptive reactions, reaching a certain intensity, can acquire a damaging character and be included in almost any pathological process. According to the results of numerous studies, it has been shown that stress caused by excessive exposure to irritating factors can be a triggering mechanism in the development of such pathological conditions as diseases of the cardiovascular system, gastrointestinal tract, autoimmune, mental, neurodegenerative, oncological and other diseases [9, 11, 18]. That is why, modern biomedical science pays more and more attention to the pathogenesis mechanisms of the development of diseases, namely, the study of the possibilities of adaptive potential. Studies have shown that nonspecific characteristics of influences are of decisive importance in the manifestation of the body's response to a particular stimulus: the relative strength or intensity of the acting stimulus; relative amplitude-time dynamic characteristics of the stimulus (duration of exposure, rate of rise, reaching a "plateau", rate of decline, total dose); preferential localization of the application of the impact (central nervous system, respiratory tract, gastrointestinal tract, skin and others). Depending on these characteristics of the impacts, a systemic response of the organism is formed, which is imprinted by its individual characteristics caused by genetic factors [3]. According to the concept of systemic (neuroendocrine) regulation of genetic processes and the implementation of genetic information, it is the nervous system that triggers and connects the components of the stress response at all levels, up to the genome of nerve cells and cells of peripheral organs and tissues "according to the feedback principle in accordance with the requirements of the environment, current the needs of the body and its individual experience" [2]. The genetic component of the organismic stress response includes both regulatory changes within the normal range of the target cell genotype response and structural changes outside of it. The study of the stress response in humans and animals has shown that in addition to the changes that occur in the body during acute stress exposure, there are delayed effects of stress caused by long-term changes in the functioning of the neuro-endocrine-immune system, suggesting long-term modification of gene activity. The continuous extreme action of the stressor can lead to depletion of the reserves of responding cells and induce the restructuring of the genetic material, up to its partial or complete disintegration in case of impossibility of adaptation to external conditions, it is this mechanism that underlies the formation of stress-de-

SOLOVIEVA Natalya Alekseevna - candidate of medical sciences, senior researcher of the Institute for Biological Problems of Cryolithozone, Federal Research Center of YSC SB RAS, sonata608@yandex.ru, **KOLOSOVA Olga Nikolaevna** - Doctor of Biological Sciences, Professor, Chief Researcher of the Institute for Biological Problems of Cryolithozone, Federal Research Center of YSC SB RAS

pendent pathology [15]. Thus, taking into account the rhythm of work of a modern person in conditions of high psychoemotional and physical stress, due to the frequent change of time zones when flying on airplanes, the leveling of time frames associated with the need and ability to work via the Internet at any time of the day, the problem of violation of circadian rhythms as the risk factor for the development of pathological conditions is most relevant today.

According to the definition of the British neurobiologist, specialist in circadian rhythms Russell Foster, "circadian rhythms" are internal biological rhythms of the body with a period of about 24 hours. They adjust all physiological processes of the body in accordance with the daily rotation of the Earth and are present in almost all living organisms on the planet, including bacteria. In humans, the main circadian rhythm is the cycle of sleep and wakefulness, but at the same time, the influence of circadian rhythms on the body is not limited only to sleep and waking up, they affect the work of hormones, heart, digestion, immunity, and even body temperature and much more. The regulation of circadian rhythms is carried out by means of a "biological clock" consisting of a large number (about 20 thousand) of nerve cells located in the hypothalamic part of the brain, called the suprachiasmatic nucleus. From the cells of the retina, the suprachiasmatic nucleus receives information about the light, adjusts the neurons in it, which send signals that coordinate the work of all other processes in the body. In other words, the work of the circadian rhythms must coincide with the work of the biological clock, and they, in turn, with the signals of the environment. However, this system does not work well for all people, many are faced with such a phenomenon as "jetlag" which occurs as a result of a person's rhythm mismatch with the daytime rhythm, due to night work or a quick change of time zones. To a large extent, the individual variability of adaptive capabilities is associated with genetic characteristics that form the chorotypes of a person [5, 14, 19].

The first assumption about the existence of biological clock genes was made by the english biorhythmologist Colin Pittendrigh. Guided by the results of studies carried out in the 1960s, he formulated the main provisions of biorhythmology, according to which circadian rhythms are independent oscillations of endogenous origin and have autonomy [12]. Several years later, in 1971, Ron Konopka and Seymour Benzer's experiments with the fruit fly Drozophila malanogaster provided convincing evidence of the genetic nature of circadian rhythms. In their experiments, they found 3 different mutations in the X chromosome region associated with deviations in the periodicity of circadian rhythms and designated the gene responsible for this as *Per* (from the engl. *period*) encoding the Per protein [8]. *Clork* - circadian rhythm gene was discovered later in 1990. A little later, Jeffrey Hall and Michael Rosbash suggested that the protein of the same name encoded by the PER gene blocks the work of its own gene, and such a feedback loop allows the protein to prevent its own synthesis and cyclically, continuously regulate its level in cells, but for this the protein needs to get into the cell nucleus. where the genetic material is stored (Fig. 1). In their experiments, they showed that the PER protein accumulates in the nucleus overnight, but how it gets there remained a mystery until in 1994 Michael Young discovered another "clock gene" of the circadian rhythm, *Timeless*, encoding the TIM protein necessary for normal circadian rhythm. Michael Young showed that when the TIM protein is bound to the *PER* protein, both proteins can enter the cell nucleus, where they block the activity of the Per gene, thus closing an inhibitory feedback loop (Figure 2). After some time, he identified another gene and named it *Doubletime*, his eponymous protein DBT, was able to delay the accumulation of the PER protein. Subsequently, these results were confirmed by other scientists, it was found that the molecular clockwork consists of not one, but at least nine interacting positive and negative feedbacks of the regulating loops of circadian clock genes. These include the *Bmal1* and *Clock* genes, which form heterodimers and trigger transcription; period transcription factor genes (*Per1, Per2, Per3); Timeless* gene (*TIM*); the *Npas2* gene; genes of proteins of cryptochromes 1 and 2 (*Cry1 and Cry2*) involved in the process of light capture; casein kinase genes (*Csnk1d, Csnk1e*), as well as *Rev-erbα, Rora, Bhlhe40 and Bhlhe41* genes. Transcription factors encoded by these genes, enzymes, transporters, prohormones, signaling and other proteins are involved in the regulation of the diurnal periodicity [7,10]. The key role of the regulator of the circadian mechanism today is assigned to genes associated with melatonin metabolism. Two of them encode the enzymes arylalkylamine-N-acetyltransferase (AANAT) and hydroxyindole-o-methyltransferase (ASMT), which are responsible for the formation of melatonin from serotonin. The genes *Mel 1a, Mel 1b* and *GPR50* provide the synthesis of melatonin receptor proteins located on the surface of the cell membranes of the suprachiasmatic nucleus of the hypothalamus, hippocampus, cerebral cortex and cerebellum. The interaction of melatonin with these receptors activates the signaling systems of the cell and the synthesis of secondary messengers of cyclic adenosine monophosphate (cAMP), a change in the concentration of calcium ions [19]. The expression of genes *Mel 1* is found in the coronary arteries, *Mel 2* - in the aorta, left ventricle, coronary arteries of healthy people and patients with coronary artery disease [6]. It is assumed that these receptors provide the vasodilating effect of melatonin and the circadian rhythm of hemodynamics, making the connection between the melatoninergic system and the suprachiasmatic nucleus of the hypothalamus. Melatonin is also able to bind to receptor proteins on the surface of the nucleus and act at the chromatin level, directly affecting protein synthesis. The genes *Ror α, Ror β, Ror γ*, found in various organs and tissues, including the suprachiasmatic nucleus of the hypothalamus, the retina and the pineal gland, encode proteins of nuclear receptors (the so-called orphan nuclear retinoid receptors Ror / Rzr), in relation to which melatonin acts in the role of the ligand [13]. In addition, the effect of melatonin on the expression of some mitochondrial genes, as well as genes that control the cell cycle, adhesion and transport, cell proliferation and apoptosis, was noted, and a direct link between melatonin and genes related to oncogenesis was revealed [1]. Given the cyclical nature of gene expression due to the synchronization of the central regulator of the circadian rhythm of the suparchiasmatic nucleus with light information, the negative effect of artificial lighting cannot be underestimated as lamps, TV screens, computer monitors and telephones, which are essentially light “pollutants”, significantly increasing the proportion of people experiencing chronic lack of sleep. In experiments on rats, it was found that constant illumination increases the threshold of sensitivity of the hypothalamus to the inhibitory effect of estrogens, and this is a key mechanism in the aging of the reproductive system in female rats. Similar results have been obtained for women, it has been proven that the influence of light at night leads to the development of dysmenorrhea [4, 17].

In this regard, today no one doubts that the regulation of circadian rhythms is carried out at a well-systematized and

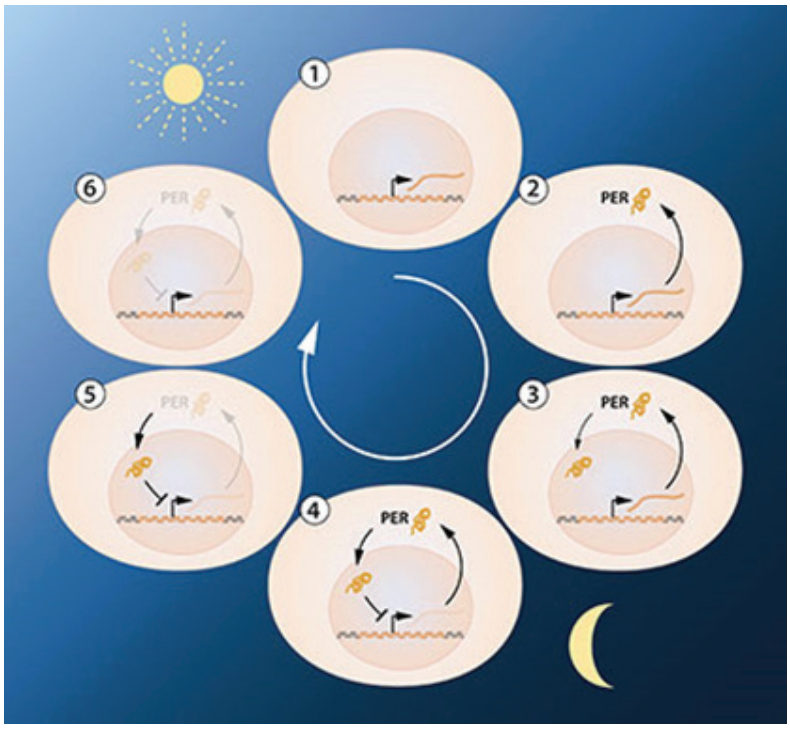

Fig. 1. Scheme of the PER gene according to the principle of "feedback" showing the sequence of events in 24 hours
Note. 1. The PER gene is active, its mRNA is produced; 2, 3. mRNA of the PER gene leaves the cell nucleus into the cytoplasm, becoming a matrix for the production of the PER protein; 4. PER protein accumulates in the cell nucleus; 5. The activity of the PER gene decreases; 6. The work of the PER gene is blocked, a feedback loop is closed.

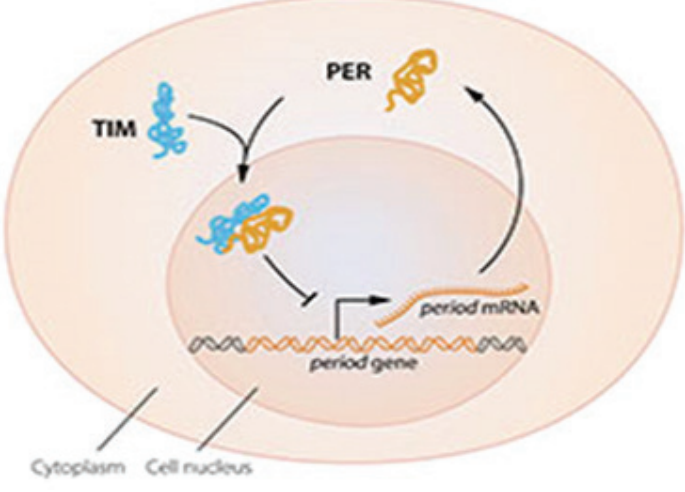

Fig. 2. Molecular mechanism of circadian rhythms by means of communication between PER and TIM proteins.

ordered molecular genetic level, and its violation entails negative consequences. Insufficient level of wakefulness, drowsiness and accompanying attention deficit, rapid fatigue and chronic fatigue are important risk factors for the development of disorders of the body's adaptation, which in turn can become a trigger mechanism of the disease.

Thus, understanding the molecular mechanisms and determining the genetic markers associated with the chronotype of individuals is an important step for the development of methods aimed at preventing and correcting pathological conditions caused by maladjustment processes.

Analysis of literature data was carried out within the framework of project VI.62.1.8. "Development of biological products from tissues of plants and animals of Yakutia on the basis of studying the peculiarities of their biochemical composition and mechanisms of adaptation to the conditions of the North" (No. 0376-2019-0005 registration number AAAA-A17-117020110055-3) of the Institute for Biological of Cryolithozone of the Siberian Brach of the RAS – Division of Federal Centre "The Yakut Scientific Centre of the Siberian Brach of the Russian Academy of Sciences".

References

1. Анисимов В.Н. Эпифиз, биоритмы и старение организма / В.Н.Анисимов // Успехи физиол. наук. - 2010. - Т. 39 (4). - С. 40–65 [Anisimov V.N. Epiphysis, biorhythms and aging of the body / V.N. Anisimov // Advances fiziol. sciences. – 2010. - T. 39 (4). - P. 40–65].

2. Лопатина Н.Г. Гипотеза нервной регуляции процесса реализации наследственной информации / Н.Г. Лопатина, Г.П. Смирнова, В.В. Пономаренко // Проблемы высшей нервной деятельности и нейрофизиологии. Под ред. Н.Ф. Суворова. - Л., 1975. - С. 107–121 [Lopatina N.G. Hypothesis of nervous regulation of the process of realization of hereditary information / N.G. Lopatina, G.P. Smirnova, V.V. Ponomarenko // Problems of higher nervous activity and neurophysiology. Ed. N.F. Suvorov. - L., 1975. - P. 107-121]

3. Ушаков И. Б. Адаптационный потенциал человека. / И. Б. Ушаков // Вестник РАМН. - 2004. - № 3. - С. 8-13 [Ushakov I.B. Human adaptive potential / I.B. Ushakov // Bulletin of the Russian Academy of Medical Sciences. - 2004. - No. 3.- P. 8-13]

4. Bedrosian T. Endocrine effects of circadian disruption / T. Bedrosian, L. Fonken, R. Annu Nelson // Rev. Physiol. - 2017. - Vol. 78.- P.109-131. DOI: 10.1146/annurev-physiol-021115-105102

5. Breakpoints of time in bed, midpoint of sleep, and social jetlag from infancy to early adulthood / C. Randler, C. Vollmer, N. Kalb et al. // Sleep Med. - 2019. - Vol. 57(80). - P. 86. DOI:10.1016/j.sleep.2019.01.023

6. Ekmekcioglu C. The melatonin receptor subtype MT2 is present in the human cardiovascular system / C. Ekmekcioglu, T. Thalhammer, S. Humpeler // J. Pineal. Res. - 2003. - Vol. 35 (1) :40-4.

7. Genome-wide association analyses of chronotype in 697,828 individuals provides insights into circadian rhythms / E. Samuel, M. Jacqueline, Andrew R Wood et al. // Nature Communications. – 2019. - Vol. 10. – P. 343. DOI: 10.1038/s41467-018-08259-7.

8. Konopka R. Clock mutants in Drozophila melanogaster // R.Konopka, S. Benzer // Proc. Natl. Acad. Sci. U.S.A. - 1971. - Vol. 68. - P.2112-2116.

9. Longitude position in a time zone and cancer risk in the United States / F.Gu, S. Xu, S. Devesa et al. // Cancer Epidemiol Prev Biomark. - 2017. - Vol. 26. - P.1306–1311. DOI: 10.1158/1055-9965. EPI-16-1029.

10. Martha H. Genetics of Circadian Rhythms / H. Martha, S. Kazuhiro, J.Peng // Neurol Clin. - 2019. - Vol. 37(3). - P.487-504. DOI: 10.1016/j.ncl.2019.05.002.

11. Musiek E. Circadian clock disruption in neurodegenerative diseases: cause and effect? / E. Musiek // Front. Pharmacol. - 2015. - Vol. 6 (29). - P. 40–44.

12. Pittendrigh C. Temporal organization: reflections of a Darwinian clock-watcher / C. Pit-

tendrigh // Ann. Rev. Physiol. - 1993. - Vol. 55(1). - P.17-54.

13. Rijo-Ferreira F. Genomics of circadian rhythms in health and disease / F. Rijo-Ferreira, J. Takahashi // Genome Med.- 2019.- №11(1). - Vol.82. DOI: 10.1186/s13073-019-0704-0.

14. Rönnlund M. Time perspective biases are associated with poor sleep quality, daytime sleepiness, and lower levels of subjective well-being among older adults / M. Rönnlund, M. Carelli // Front Psychol. - 2018. - Vol. 9. DOI:10.3389/fpsyg.2018.01356.

15. Savvateeva-Popova E. Stress and genome lability: Drosophyla and Rat genetic models. In: Proceedings of the International Norway-Russian Startup PHAsE / E. Savvateeva-Popova, N. Dyuzhikova // Seminar "Physiological mechanisms of humans and animals in the processes of adaptation to environmental changes". Saint Petersburg. - 2017. - P. 18-19.

16. Selye H. Conditioning by corticoids for the production of cardiac lesions with noradrenaline / H. Selye, E. Bajusz // Acta Endocrinol. - 1959. - Vol. 30. - P. 183–194.

17. Social jetlag and menstrual symptoms among female university students / Y. Komada, M. Ikeda Sato et al. // Chronobiol Int. - 2019. - Vol.36(2). - P.258–264. DOI: 10.1080/07420528.2018.1533561.

18. The association between social jetlag, the metabolic syndrome, and type 2 diabetes mellitus in the general population: the new hoorn study / A. Koopman, S. Rauh, E. Van't Riet et al. // J. Biol. Rhythms. - 2017. - Vol. 32(4). - P.359–368. DOI: 10.1177/0748730417713572.

19. The genetics of circadian rhythms, sleep and health / A. Jagannath, L. Taylor, Z. Wakaf et al. // Human Molecular Genetics. - 2017. - Vol. 26. - P.128 –138. DOI: 10.1093/hmg/ddx240

POINT OF VIEW

Zaykova Z.A.

ANALYSIS OF LIFE EXPECTANCY OF POPULATION OF THE IRKUTSK REGION

DOI 10.25789/YMJ.2020.72.28

The purpose of the research is to analyze life expectancy (LE) of the population of the Irkutsk region and to identify factors affecting the indicator at the municipal level.

Materials and methods of research. The data were used for LE of the Irkutsk region and the Russian Federation for 1990-2019, municipalities of the region for 2018; methods of descriptive statistics, correlation and regression analysis, criterion *W* of the Shapiro – Wilk test to check the normal distribution of 42 indicators.

Results and discussion. In the Irkutsk region, LE of the population increased from 66.5 years in 1990 to 69.60 years in 2019. The difference in LE in the region was lower than the national average by 3.8 years, for men and women - by 4.2 and 2.9 years. In 2018, the following characteristics of LE were recorded for the municipalities of the region: 1) maximum - 75.8 years; minimum - 58.3; 2) 18 municipalities with LE of men below 60 years old; 3) the amplitude of LE of men was 20.3 years, women - 14.1 years; 4) the maximum gender difference is 18.1 years, the minimum is 6.6 years. Due to the uneven development of the territories of the Irkutsk region, the indicators had high variability. This made it difficult to select them to study the influence of factors on LE at the municipal level. The resulting multiple regression models include: general mortality rate (LE of both sexes, men, women); mortality from diseases of the circulatory system (LE of both sexes and men), total fertility rate (LE of women); provision of hospital beds (LE of both sexes, men), provision of paramedical personnel (LE of women).

Conclusion: Irkutsk region in terms of LE is one of the last places among the subjects of the Russian Federation. 70% of the main measures to increase LE are included in state programs for the development of the region, but unsolved problems of socio-economic development impede their effective implementation. According to the results of the correlation and regression analysis, the links between LE at the municipal level and the general indicators of fertility and mortality, mortality from diseases of the circulatory system, provision of hospital beds and paramedical personnel were established. To achieve LE of 80 years in 2030, a differentiated socio-demographic policy is required for individual municipalities of the region.

Keywords: life expectancy, region, municipal level, socio-economic indicators, correlation and regression analysis

Introduction. Life expectancy (LE) of the population is an integral indicator of the state of health, quality of life of the population, an assessment of the level of socio-economic well-being of the state, and is used to calculate the human development index [3, 10, 13]. Despite the gradual growth, LE in the Russian Federation remains quite low, as well as lagging behind developed countries, including by gender gap, interregional variation, difference for urban and rural population [3, 6, 8-10, 13, 15, 23]. Efforts of all levels of government are required to increase LE with significant geographical differences [17, 19, 20]. Due to the special significance of the indicator, it is important to monitor trends and find out the reasons for the decline and stagnation [21, 25].

The purpose of the research is to analyze LE of the population of the Irkutsk region and to identify factors affecting the indicator at the municipal level.

Materials and methods of research. The Rosstat data on life expectancy of the population of the Irkutsk region and the Russian Federation for 1990-2019 have been applied; morbidity, mortality, socio-economic indicators for 42 municipalities for 2018. Life expectancy indicators for medical organizations for 2018 were calculated on the basis of the age and sex composition of the resident population of the Irkutsk region as of 01.01.2019 and the number of deaths from tables C51 «Distribution of deaths by sex, age groups and causes of death». The ranking of the subjects of the Russian Federation to determine the rating was carried out in descending order of the indicator.

Statistical analysis of the data was carried out using Microsoft Excel 10 and the Shapiro-Wilk Test calculator (https://www.statskingdom.com/320ShapiroWilk.html). Checking the correspondence of the distribution of variables to the law of normal distribution was carried out using the Shapiro-Wilk test (W). Descriptive statistics were calculated, an analysis of the variability of variables by coefficients of variation (Cv), Pearson correlation analysis, multiple regression analysis using the method of successive exclusion of variables was carried out. Before building regression models, the applicability of the multiple regression method was tested. The statistical significance of the constructed model was assessed using Fisher's F-test. The quality of fitting a linear function was assessed by the multiple determination coefficient (R2). The

ZAYKOVA Zoya Aleksandrovna – Associate Professor, Department of General Hygiene, the Federal State Budgetary Educational Establishment of Higher Education, the Irkutsk State Medical University of the Ministry of Health of Russia, Ph.D., e-mail: zaikovazoya@mail.ru.