

**SABIROV ZHANBOL BAYZHANOVICH**

**SUBSTANTIATION OF CRITERIA FOR PRENOSOLOGICAL  
CONDITIONS IN PERSONS LIVING IN AN ECOLOGICALLY  
UNFAVORABLE REGION**

**ABSTRACT**

**of the dissertation for the degree of Doctor of Philosophy (PhD) in the  
specialty 6D060700-Biology**

**The relevance of research.** At present, one of the most important tasks of science in the field of fundamental research in the natural sciences is to study the influence of adverse environmental factors on the health of the population. Most of the major cities in the modern world are in environmentally unfavorable conditions. The state of environmental objects is an important indicator, that determines the living conditions of people and all living beings in the biosphere.

In Kazakhstan, there is a very difficult environmental situation in many regions: in the south, the drying up of the Aral Sea, in the northeast, the consequences of nuclear tests at the world's largest nuclear test site, in the center of the chemical industry.

The deteriorating ecological situation leads to the accumulation of various chemicals in environmental objects, due to which the majority of xenobiotics enter the human body, which can have a genotoxic, cytotoxic effect. Currently, among the factors that pollute the air that deserve special attention are suspended particles, which are dust, where the chemical elements may significantly exceed the maximum permissible concentration (MPC) and therefore considered as a risk factor for human health. One of the main components of dust are metals, the accumulation of metals increases with prolonged exposure in an unfavorable hygienic environment. Heavy metals are one of the most widespread factors of environmental pollution. The accumulation of metals in the environment is a consequence of environmental disasters, the activities of industrial enterprises, the impact of vehicle emissions and other anthropogenic impacts. One of the proofs of the influence of chemical factors on genetic information is a statement of accomplished facts, such as an increase in cases of congenital pathology, genetic and hereditary syndromes, and an increase in the number of neoplasms.

Based on the foregoing, it can be concluded that understanding the initial stages of pathogenetic processes and detecting predictors of early physiological disorders in a population living in an unfavorable environmental environment is very relevant. For many years, studies have been conducted on the degree of genotoxic, cytotoxic and metabolic hazards of chemicals, which include heavy metal ions, but the mechanisms of such an effect on the human body have not yet been elucidated. Various studies show the toxic and mutagenic properties of chemicals, although it is not possible to come to a general concept of pathogenesis, since the physiological role of metals and their significance in the life of the organism are not fully known. It is known that the concentration of many toxicants

in the environmental objects of industrial regions and territories of the ecological crisis significantly exceeds similar concentrations in the environmental objects of the compared regions and MPC values for these elements. In this regard, there is a need to study the features of the development of adverse effects at the molecular, cellular, genomic levels.

**The purpose of the study.** Identification of bioindicators of early changes in the body in living conditions in an environmentally unfavorable region.

**Research objectives:**

1. To identify the level of trace element status in the blood of the population living in environmentally unfavorable conditions.
2. To determine the nature of changes in hematological and biochemical parameters that occur in the population living in environmentally unfavorable conditions.
3. To give a cytomorphological assessment of the state of epithelial cells in the population living in environmentally unfavorable conditions.
4. To substantiate the influence of chemical factors on the occurrence of induced mutagenesis based on the frequency and spectrum of chromosomal aberrations.

**The object of the study.** databases, biological substrates, chromosome preparations, cell cultures, slides of epithelial smears, serum and whole blood.

**Research methods.** To solve this goal, the level of chromosomal aberrations was evaluated, cytomorphological evaluation of epithelial cells was given, microelement, biochemical and hematological analyses were conducted. The following research methods were used: «cultivation of lymphocytes in peripheral blood», «method of accounting for chromosomal aberration », «method of karyotyping», «method of counting of micronuclei», «spectral analysis for content of chemical elements by atomic emission method» Studies of buccal epithelium of the cheek (BES), biochemical and hematological analysis of blood, statistical analysis.

**The obtained results, their novelty, scientific and practical significance.**

**The scientific novelty of the study** lies in determining the features of early changes in cellular homeostasis and the nature of the shift in the processes of cellular regulation (apoptosis, repair, regeneration processes), to the manifestation of physiological disorders at the level of organs and body systems.

Cytogenetic, cytomorphological and metabolic abnormalities have been identified that can act as prenosological predictors, indicating the risk of developing a disorder.

It has been shown that in the pathogenesis of the formation of chromosomal mutations under the influence of chemical agents, in particular heavy metals, one of the features of the influence is cytomorphological changes in the cell, where the leading factor is the violation of its barrier function.

The distinguishing features of this work in comparison with the previous ones are:

Firstly, in the development of the design of the study, which includes strict inclusion and exclusion criteria, according to which the sample consisted of

relatively healthy individuals of reproductive age, without chronic and acute diseases. In previous works, the main criterion was interaction with the impact factor (highly trained production workers, with harmful production factors or people living in nearby areas to the source of pollution, with various somatic diseases and age-related changes, due to which the results in different work were multidirectional, sometimes even contradictory).

Secondly, in order to obtain a more complete picture of the accumulation of harmful substances and their effect on cellular physiological processes, toxic trace elements in the blood were identified as the main factor of influence, and not in environmental objects, as in previous works. Since chemicals can enter the body with different intensity and under different conditions, pollution of environmental objects can show different concentrations depending on the time of year, wind direction, temperature, the surrounding landscape and many other factors, in addition, in the body of an individual, work metabolic processes of transformation, detoxification mechanisms, binding, excretion and other processes due to hereditary phylogenetic and epigenetic factors, which cannot be fully taken into account. Also, the determination of the accumulation of heavy metals in the body makes it possible to understand their role in the formation of early changes at the cellular and subcellular levels;

Thirdly, previous works informatively show the features of pathology, long-term consequences and changes in the state of health at the level of organs and systems, aimed at searching for environmentally dependent diseases. This research work, unlike the previous ones, is aimed at searching for primary shifts in cellular homeostasis and the processes of its provision, as well as searching for the initial stages of changes at the cellular and subcellular levels, manifested in laboratory parameters in healthy individuals living in environmentally unfavorable regions of Kazakhstan.

**The theoretical and practical significance of the results** lies in the construction of a pathogenesis scheme at the cellular and subcellular levels, where it was shown that one of the features of the effect is cytomorphological changes in the cell, where the leading factor is the violation of its barrier function. As a result of membrane denaturation, intracellular enzymes (ASAT) are released into the intercellular space, capable of transporting some of its monomeric components; when the membranes of erythrocytes are disturbed, various substances (water and sodium) penetrate into the cytoplasm, as a result of which they increase in volume; violation of the integrity of cells makes it possible for xenobiotics of various nature to penetrate into them, capable of exerting mutagenic properties (heavy metals, viruses and bacteria).

An imbalance of microelements was revealed: the level of cytotoxic metals in the body (lead, nickel, manganese) were increased relative to the comparison group, while the level of vital microelements (selenium, zinc and iodine) was significantly reduced, as a result, inhibition of intracellular biochemical processes at the stage of inclusion of essential elements into enzymes, against the background of a decrease in barrier and protective functions.

A hypothesis of the mechanism for the formation of chromosomal aberrations has been developed and various paths of pathogenesis during chemical mutagenesis have been considered, from the direct effect of a chemical agent on hereditary structures to the role in the disruption of the cell barrier function and, thereby, in increasing the cell permeability to mutagens of various nature. Based on the correlation analysis and regression model, the nature of the pathological activity of heavy metals was established and their role in the pathogenesis of the formation of cytomorphological and cytogenetic changes was shown. One of the mechanisms for the formation of chromosomal aberrations under the action of a chemical factor can be newly formed atomic bonds between chemical elements and the DNA molecule, as a result of competition for an unshared pair of electrons of donor atoms of the DNA molecule.

Degenerative cytomorphological changes in cells (vacuolar dystrophy of cells and contamination with microflora) acts as a sign of toxic damage to the cell and an intermediate link in the pathogenesis of the formation of chromosomal aberrations through a decrease in primary barrier and protective functions.

Biochemical and hematological studies showed significantly significant differences with the control group, with an increase in the average volume of erythrocytes (MCV), characterizing anisocytosis, in the predominant percentage of individuals in regions with increased environmental load. There is a general mass trend in the change in the morphological structure of blood cells (the spread of a sign of a borderline state), with a normal state of the main blood parameters. As biochemical criteria for prenosological conditions, indicators of increased ASAT and GGT are recommended.

As a practical significance, indicators are proposed that can act as biomarkers of prenosological changes in people living in unfavorable environmental conditions:

- the level of chromosomal aberrations with a frequency above 1.5%;
- increased level of chromatid type aberrations;
- cytomorphological changes in the form of vacuolar dystrophy, karyorrhexis, phagocytosed apoptosis (residual bodies);
- epithelial cells with signs of damage;
- increased content of toxic microelements, such as (Ni, Pb, Mn);
- reduced content of essential trace elements (I, Zn, Se);
- erythrocyte anisocytosis, increased MCV values;
- increase in ASAT and GGT.

A spontaneous level of CA rearrangements of chromosomes not exceeding 1.5% is recommended, including 0.85% of chromatid type mutations and 0.65% of chromosomal type.

A cytogenetic risk scale is given, which includes 4 categories: acceptable, elevated, high, and ultrahigh.

### **Results presented to the defense.**

1. The peculiarities of differences in laboratory parameters during cytogenetic, cytomorphological, trace element, biochemical and hematological studies in healthy individuals living in an ecologically unfavorable region were revealed.

2. Early changes in cellular homeostasis, the nature of the shift in cellular regulation processes and laboratory indicators reflecting these changes were determined before the manifestation of physiological disorders at the level of organs and body systems.

3. The mechanism of pathogenesis is presented, reflecting how an increase in the level of toxic trace elements causes destructive processes in epithelial cells, cytomorphologically manifested in the form of vacuole cell dystrophy and destruction of the cell membrane.

4. A model of the formation of chromosomal mutations is presented, showing the dependence and causal relationship of the frequency of chromosomal aberrations with chemical trace elements in the body and an increase in microflora. Cytomorphological changes in cells have an effect on the formation of chromosomal aberrations and act as an intermediate stage in the process of mutagenesis.

5. In contrast to earlier works, laboratory indicators are proposed as bioindicators of prenosological conditions.

#### **Implementation of the results of work.**

Currently, the results of the work have been implemented in the "Scientific Research Sanitary and Hygienic Laboratory" of the Institute of Public Health and Occupational Health of the NCJS "KMU" and in the research park of Biotechnology and Ecomonitoring of the Faculty of Biology and Geography of the NCJS "Karaganda Buketov University" for research in biomedical research (Appendix A).

#### **Declaration of personal participation of the author.**

The author personally developed the design of the study, carried out cytogenetic, cytomorphological and hematological studies, made preparations, microscopy analysis, statistical data processing. The author participated in the collection of biomaterial for biochemical and trace element studies, conducted a statistical analysis of the results of these types of research and analysis of the results obtained. The main provisions, conclusions and dissertation work are formulated. The text of scientific publications was written independently. The personal contribution of the author was 89%.

**The volume and structure of the dissertation.** The dissertation consists of an introduction, three sections, a conclusion, conclusions and a list of references. The dissertation contains 150 pages.

**The number of illustrations, tables, list of references.** The dissertation contains 12 figures, 44 tables and 1 formula. The number of literary references is 270, including 120 foreign sources.

**The list of keywords:** biomarkers, ecology, cell, cellular homeostasis, mutagenesis, chromosomal aberrations, trace elements, heavy metals, buccal epithelium of the cheeks, micronucleus test, biochemistry, hematology, disruption of cellular adaptation.

#### **Approbation of the dissertation results.**

The results of the research and the main provisions of the work were presented at the following conferences and congresses:

- Actual problems of biology and ecology: materials of the international scientific conference (Karaganda, 2018);
- Integration of science, education and production: International Scientific and Practical Conference (Karaganda, 2018);
- Profession and health: Materials of the II International Youth Forum (Yalta, 2018);
- Ecology. Radiation. Health: materials of the XIV International Scientific and Practical Conference (Semey, 2019);
- 15th Russian National Congress with international participation "Profession and Health" (Samara, 2019);
- Health protection of medical workers: Materials of the scientific and practical conference (Karaganda, 2020);
- Science and Health: Materials of the Republican Scientific and Practical Conference of Young Scientists with international participation (Semey, 2021);
- Preservation of the health of the working population. medical examinations, problems and opportunities: Materials of the scientific and practical conference (Karaganda, 2021);

The results are published in the journals of the Scopus database "Open Access Macedonian Journal of Medical Sciences" (Macedonia), "Israel Journal of Ecology and Evolution" (United Kingdom), "Occupational Medicine and Industrial Ecology" (Russia), and in journals recommended by the Committee for Quality Assurance in Education and Science of the Ministry of Science and Higher education of the Republic of Kazakhstan "Bulletin of Karaganda University. Series: Biology. Medicine. Geography" and "Astana medical journals".

#### **Information about publications.**

1. Sabirov, Z., Namazbaeva, Z., Battakova, S., Otarbayeva, M., Mukasheva, M., & Eshmagambetova, A. (2020). Chemical Mutagenesis and Cytogenetic Chromosomal Abnormalities in a Population Living in the Aral Sea region. Open Access Macedonian Journal of Medical Sciences, 8(E), 544-550.
2. Namazbaeva, Z., Battakova, S., Ibrayeva, L., & Sabirov, Z. (2018). Change in metabolic and cognitive state among people of the Aral zone of ecological disaster. Israel Journal of Ecology and Evolution, 64(1-4), 44-55.
3. Sabirov, Z. B., Eshmagambetova, A. B., Turlybekova, G. K., Duzbayeva, N. M., Mukasheva, M. A., & Onoshko, I. A. (2020). Biochemical parameters of blood plasma of the male population living on the territory of the Aral Sea. Вестник Карагандинского университета Серия «Биология. Медицина. География». № 4(100), 100-105.
4. Саби́ров, Ж. Б., Мукашева, М. А., & Ешмагамбетова, А. Б. Изучение роли цинка в образовании хромосомных aberrаций с помощью расчетного метода оценивания. (2020) Вестник Карагандинского университета Серия «Биология. Медицина. География». № 3(99), 155-160.
5. Саби́ров, Ж. Б., Намазбаева, З. И., Бакбергенов, М. Б., Жарылкасын, Ж. Ж., Мукашева, М. А., Картбаева, Г. Т., ... & Жалмаханов, М. Ш. (2020). Цитоморфологическая оценка эпителия щек у лиц, проживающих в условиях

экологически неблагоприятного региона. Серия «Биология. Медицина. География». № 1(97), 68-72.

6. Сабиров, Ж. Б., Намазбаева, З. И., Жанбасинова, Н. М., Цветкова, Е. В., & Киспаева, Т. Т. (2018). Оценка гематологических показателей женского населения Приаралья. Медицина труда и промышленная экология, (8), 47-52.

7. Намазбаева, З. И., Цветкова, Е. В., Сабиров, Ж. Б., Почевалов, А. М., & Жумашкин, Е. Т. (2018). Метаболический профиль населения Приаралья (зона экологического кризиса). Медицина труда и экология человека, (3 (15))

8. Намазбаева, З. И., Цветкова, Е. В., Сабиров, Ж. Б., & Сембаев, Ж. Х. (2018). Оценка гормонального профиля у лиц третьего поколения, проживающего вблизи Семипалатинского полигона. Медицина труда и промышленная экология, (8), 58-62.