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#### COMPARATIVE CLINICAL-GENETIC HEALTH ANALYSIS OF CHILDREN LIVING IN VARIOUS ECOLOGICALLY UNFAVORABLE AREAS

*The analysis of clinical-genetic parameters of health in children living in regions with various ecological trouble for optimum methods elaboration of forecast of combined chronic pathology and chromosomal damages development.*

**Keywords:** children, ecological trouble, chronic diseases, small anomalies of development (SAD), chromosomal aberrations.

Not only biological determinants defines formation of individual health but also external environmental factors such as physical environment, social and economic circumstances, housing conditions [1]. Influence of physical and chemical factors (radiation, carcinogenic substances, cloudy) on the human population even in small doses can cause morbidity growth, embryogenesis infringement, various mutation and gene pool change during several generations [2]. This problem has the special importance for Kazakhstan, territory of which characterizes by high level of environmental pollution. The Semipalatinsk nuclear ex-range and Aral Sea regions were officially announced by the zones of ecological catastrophe because of ecological processes of these territories although there are environmental pollution of different nature [3,4,5]. The experts of the National Nuclear Center of Republic of Kazakhstan, Nuclear Centers of Science of USA, France and experts of the International Committee on Atomic Energy continue study of radioactive pollution in the Semipalatinsk nuclear range areas now. According to preliminary data the level of Cs - 137 and Sr - 90 of ex-range pollution is within the limits of acceptable values, except of some sites about 2160 sq. km. from the total square of 18 thousand sq. km. However, situation with the pollution level of Pu - 239 and others transuranium elements remains poorly investigated [6]. Thus, the population living on the territories nears the Semipalatinsk nuclear ex-range is exposed to influence of small doses of radiation from 0 up to 1 Гр [7, 8]. The radioisotopes are present practically in all components of natural systems and are involved in geochemical and biological cycles of migration. It causes a plenty ways of external and internal irradiation for the population and creates risk for his health. At the same time researches of radioecological situation in the Semipalatinsk nuclear ex-range region has revealed the following features: long influence (40 years) of large and small doses of ionizing radiation as a result of air, ground and underground nuclear explosions; practically total pollution of three areas of Kazakhstan by radioactive products; repeated acute and chronic influence on million population's health in conditions of poor social economic situation; absence of the injured population rehabilitation [9].

Region of the Aral Sea is the region of ecological trouble with other nature of pollution. These territories are characterized by prevalence of chemical toxic substances influence. External unfavorable environmental factors of the Aral Sea region determine character of influence on health:

The droughty and hot climate (more than 4 months per a year). Since 1960 the level of the Aral sea has decreased on 15 meters, its area has decreased twice (from 66.5 to 34,0 thousand sq.m.), and volume has decreased three times, salt quantity has increased from 9,94 % to 28,4 %. Saline dust mounts in atmosphere from the sea bottom and increase atmosphere pollution more than on 5 %.

- Lack of fresh drinking water;

- The high contents of stable toxic substances in the soil (salts of heavy metals and microelements (Cd, Zn, Cr, Pb etc.)) 2,5- 3,0 times is higher than normal level. It is established as a result of more than 2500 soil tests analysis which have been carried out by the laboratory of the Institute of soil of National academy of Sciences of Republic of Kazakhstan.

- Pollution of superficial pools by minerals, chemical substances (DDT), salts of heavy metals, bacteria, in exceeding marginal concentration from 3 to 250 times [10,11].

Therefore, problem of children's health living in various ecologically unfavorable regions is important for Republic of Kazakhstan. Objective rating of level and degree of physical development harmonicity, functional status of basic organs and systems condition, quantitative and qualitative distribution of small anomalies of development (SAD), congenital malformations of development, cytogenetic parameters is necessary for elaboration of optimum methods of forecast of combined chronic pathology and chromosomal damages development. The complex analysis of clinical and genetic changes of children's health has increasing value for diagnostics of external reasons influence consequences according to the International statistical classification of illnesses and problems connected to health of the tenth revision, WHO, 1995 [12].

Materials and methods. 423 children aged 7 -15 y. were examined in the department "Ecology and children" of Republican Children's Clinical Hospital since 1999 and until 2002. Selection of children was carried out by the random repetition-free sampling method. All surveyed children were conditionally divided into three groups, according to the research objectives.

The first group consist of 120 children constantly living in the area near the Semipalatinsk nuclear ex-range concerning to the zone of maximal radiating risk (The Law of Republics of Kazakhstan from December 16, 1992 "About social protection of citizens living near the Semipalatinsk nuclear range").

The second group consists of 203 children living from birth in the Aral Sea region - zone of ecological accident (The Law of Republic of Kazakhstan from January 18, 1992 "About urgent measures on radical transformation of living conditions of the Aral Sea region population").

The control group consisted of 100 children constantly living in the region of ecologically clean region of Kazakhstan (The report of the Ministry of Natural Resources and Environment Preservation, 1996 [13]). Group of comparison were selected by the principle of "pair-copy" (sex, age, nationality, social status and etc.).

Children are divided according to age and sex. There was identical quantity of girls and boys in all surveyed groups. Children of the senior school age a little bit prevailed (the application A).

Practically all surveyed children (94,8 %) were Kazakh.

Complex examination included general clinical and special methods of examination (table 1).

Table 1 - Health examination volume

Researches	Quantity of surveyed children
Complex clinical examination	423
Account of SAD	423
Cytogenetic investigation	250

Physical development of children was estimated by the method of percentiles, which most strictly and objectively reflects distribution of attributes among children [14].

Clinical, functional and laboratory examination was carried out to all children. Complaints and anamnesis (history of illness development) were specified during conversation with children and on the basis individual medical card of children's development data. The absence of anamnesis data about such diagnoses as alcoholic, diabetes and infectious embryo-, fetopathy in the newborn period and hereditary diseases were specified. Data about parents' health and age, professional harmfulness, pregnancy course and delivery, nutrition character were obligatory taken into account. It is necessary to note, that according to analysis of individual medical cards of development the information about pathology of any system were registered only in 16,0 % of surveyed children before the present hospitalization.

Ultrasound examination (USE) of peritoneal cavity organs, oesophagogastroduodenoscopy (OGD), Echoencefalography, electroencefalography (EEG), radiography methods, electrocardiography (ECG), echocardiography, laboratory analysis: common analysis of blood (CAB), common analysis of urine (CAU), biochemical analysis of blood (BAB) coprology analysis, consultations of neurologist, oculist, gastroenterologist, nephrologist, cardiologist, genetics specialist, pulmonologist, otorhinolaryngologist, endocrinologist, allergologist, dermatologist children's gynecologist were carried out to all children in accordance with the regulations of the Ethical protocol.

The received data after clinical and functional examination of children were registered in the numbered individual medical genetic cards developed on pediatric department of the Kazakh National Medical University. Account of SAD was carried out according to the unified spectrum of attributes recommended by the Conference of Medical Genetics at Minsk in 1982.

100 children from the Semipalatinsk nuclear ex-range, 100 children from the Aral Sea region and 50 children of control group are studied by cytogenetic method. Control cytogenetic parameters recommended by the WHO are used [15]. Cytogenetic investigation included cultivation of lymphocytes by macro method according to the standard technique in the experimental mutagenesis laboratory of the Institute of Common Genetics and Cytology of Ministry of Education and Science of Republic Kazakhstan [16].

Statistical processing of research results was carried out by the standard methods in variation statistics.

Results. As a result of profound clinical laboratory and functional examination the structure of chronic pathology in all age groups of surveyed children is revealed. The basic pathology in compared groups of children is disease of gastrointestinal tract: 100 % - region of Semipalatinsk nuclear ex-range, 99%- the Aral Sea region. The most frequent pathology of gastrointestinal tract among children from the basic groups are diseases of stomach and duodenum: 93,3 %- region of Semipalatinsk nuclear ex-range, 79,8% - the Aral Sea region.

Chronic diseases of otorhinolaryngological organs have the second place among somatic pathology of children from the surveyed group: Semipalatinsk nuclear range - 72,5 % and the Aral Sea region- 80,3 %.

Pathology of central nervous system is on the third place in both basic groups: region of Semipalatinsk nuclear ex-range – 56,7 % and the Aral Sea region – 58,6 %.

Diseases of urinary system in the structure of children's pathology of the Aral Sea region are on the fourth place - 50,7 %, and on sixth place in group of children from the region of Semipalatinsk nuclear ex-range - 16,7 % ( $p < 0,001$ ).

Pathology of cardiovascular system is found in 38,3 % of children from the region of Semipalatinsk nuclear ex-range (fourth place) and in 49,3 % of children from the Aral Sea region , that corresponds to the fifth place.

Endocrine pathology is registered in identical percent as in children from the region of Semipalatinsk nuclear ex-range (22,5 % - fifth place), and in children of the Aral Sea region (22,2 % - sixth place), basically, and characterized by various infringements of thyroid gland functions.

Pathology of respiratory system takes the seventh place in the structure of chronic pathology in the region of Semipalatinsk nuclear ex-range (9,2 %) and sixth place (47,8 %) ( $p < 0,001$ ) in the Aral Sea region. It is represented by chronic bronchitis in both studied groups.

The high frequency of tubercular infection is registered in children from the Aral Sea region - 39,9 %, in comparison with children from the Semipalatinsk region - 1,7 % ( $p < 0,001$ ).

Congenital malformations of development (CMD) are registered with equal frequency in children from the Semipalatinsk nuclear ex-range (16,7 %) and in children from the Aral Sea (12,8 %) region and this parameter is authentically higher than similar parameter of the comparison group (6,0 %) (Fig.1).

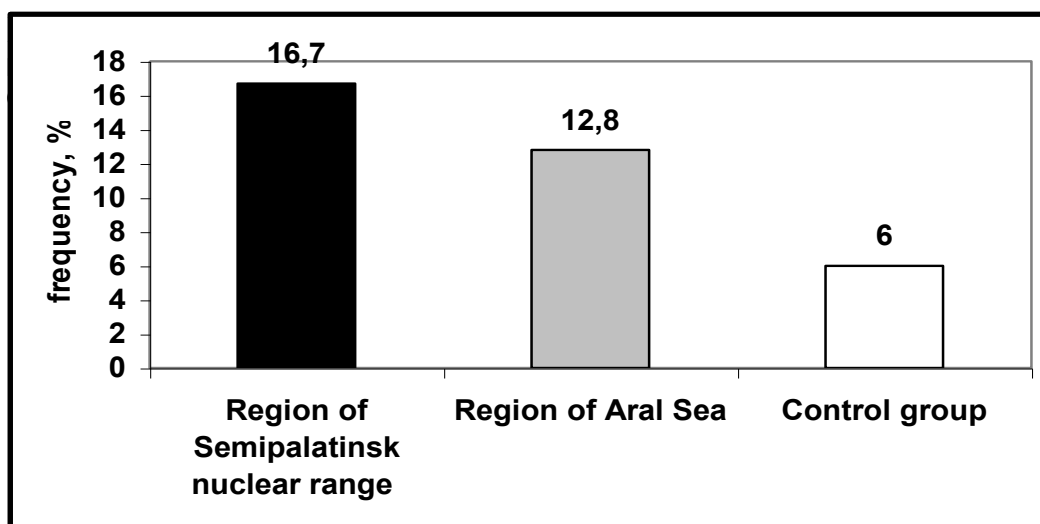


Figure 1 - The frequency of congenital malformations of development in surveyed children

Malformations of mesenchymal genesis prevail in the structure of CMD of children from both basic groups. At the same time malformations of urinary system prevail in children of Semipalatinsk nuclear ex-range region (35,0 %), and congenital malformations of heart in children of the Aral Sea region (76,9 %). CMD of locomotorium apparatus authentically are more often ( $p < 0,05$ ) registered in children living in the Semipalatinsk nuclear ex-range region (35,0 %) in comparison with group from the Aral Sea region (7,7 %). 15,0 % of children living on territories polluted by radiating factors have combined CMD. Children from the Aral Sea region have not combined CMD.

Three and more chronic diseases are revealed authentically more often in children from the Semipalatinsk nuclear ex-range region (66,7 %) and from the Aral Sea region (61,6 %) than in group of comparison (46,0 %).

The average value of SAD children living in the Aral sea region ( $11,98 \pm 0,24$ ) is higher than average value of SAD in children from the Semipalatinsk nuclear ex-range region ( $8,94 \pm 0,27$ ). The similar parameter of children from comparison group is  $4,05 \pm 0,17$  ( Fig. 2).

The following list of SAD most frequently is registered in children of the Semipalatinsk nuclear ex-range region and in children from the Aral Sea region: SAD of skin (83,3% и 91,6%); SAD of palate (75,8% и 94,6%); limbs and joints; SAD of hair (64,5 % and 50,0 %); SAD of skull (64,5 % and 40,8 %); SAD of ears (70,4 % and 30,8 %); SAD of teeth (78,8 % and 44,2 %). Thus, SAD of connective tissue prevail in children from both regions.

Frequency of "internal" SAD considerably does not differ in children of the basic groups (Semipalatinsk nuclear ex-range region (16,7%) and the Aral Sea region (16,3%)), but exceeds the similar parameter in children of control group (6,0 %) ( $p < 0,02$  and  $p < 0,01$ ).

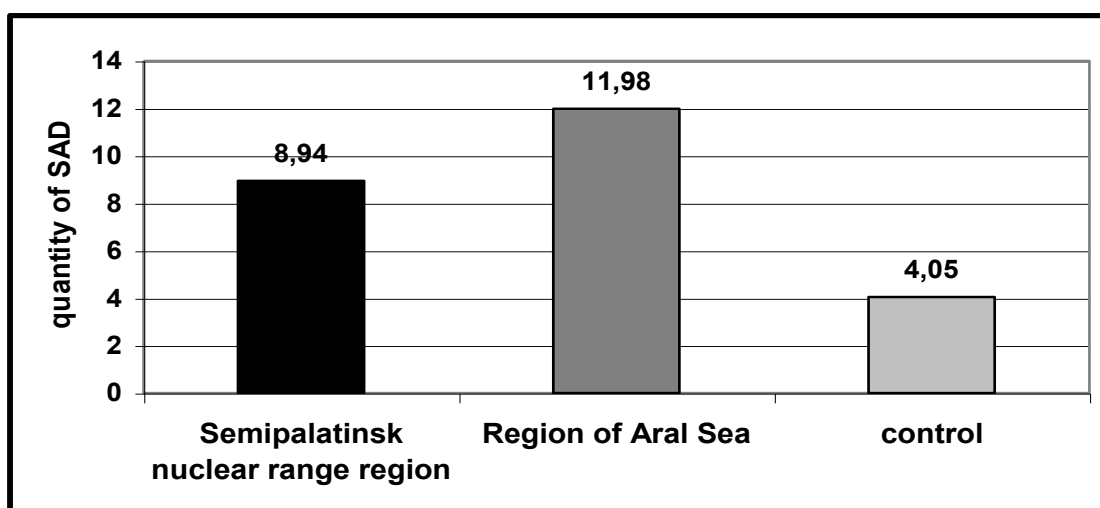


Figure 2 - The average quantity of SAD in children of surveyed groups

SAD of heart more often registered in the SAD structure of internal organs of the basic groups children: Semipalatinsk nuclear range ex-region (70,0%) and the Aral Sea region (78,8 %). They are represented by: additional chord of left ventricle and prolapse of the mitral valve. SAD of gall bladder such as strangulations in the field of the gall bladder body and isthmus, change of the gall bladder form are diagnosed less often in children living near Semipalatinsk nuclear ex-range region (50,0%) and in children from the Aral Sea region (15,1%) ( $p < 0,01$ ). 20,0 % of children of Semipalatinsk nuclear ex-range region have combination of several "internal"

SAD. Children of the Aral Sea region have not combinations of SAD. Combination of internal organs SAD is determined only in 20,0 % of children living in the Semipalatinsk nuclear ex-range region and in 6,1 % of children living in the Aral Sea region. The increased level of SAD, especially in combination with increased frequency of CMD in children living in ecologically unfavorable regions can testify not only about teratogenic or damaging effect of chemical combination and radiation of fetus development, but also about mutagenic effect, that is ability to cause mutations in somatic cells. Cytogenetic investigation has determined presence of chromosomal aberrations in more than in half of children living in the Semipalatinsk nuclear range region (61,0%) and in the Aral Sea region (66,0%). Whereas this infringement is registered only in 34,0 % of children from control group ( $p < 0,01$  and  $p < 0,001$  accordingly). Distribution of children with chromosomal aberrations in accordance with sex has not revealed authentic distinctions. Spectrum chromosomal aberrations are submitted in the table 2.

Table 2 - Spectrum chromosomal aberrations in children of the surveyed groups

Category of aberrations	Frequency of aberrations (% , $M \pm m$ ) in children			
	Semipalatinsk nuclear range region	Aral Sea region	Control group	WOH
Common frequency of aberrations	1,86 ± 0,09	1,90 ± 0,09	0,62 ± 0,07	0,90 ± 0,09
Aberrations of a chromosomal type:	0,47 ± 0,04	0,30 ± 0,03	0,10 ± 0,03	0,34 ± 0,06
Pair acentric fragments	0,32 ± 0,03	0,22 ± 0,03	0,10 ± 0,03	0,34 ± 0,06
Acentric rings	0,01 ± 0,01	0	0	0
Dicentrics	0,12 ± 0,02	0,06 ± 0,01	0	0
Translocations	0,02 ± 0,01	0,02 ± 0,01	0	0
Aberrations of chromatide type:	1,39 ± 0,08	1,60 ± 0,08	0,52 ± 0,07	0,57 ± 0,07
Single fragments	1,31 ± 0,08	1,51 ± 0,08	0,52 ± 0,07	0,57 ± 0,07
Exchanges	0,03 ± 0,01	0,03 ± 0,01	0	0
Deletions	0,05 ± 0,01	0,06 ± 0,01	0	0

Study of interrelation between chronic diseases, CMD, SAD and chromosomal instability was the obligatory condition for development of optimum methods of forecast of health status of children living in various ecologically unfavorable regions. The more high level of SAD is revealed in children having three and more chronic diseases from both unfavorable regions: Semipalatinsk nuclear ex-range region ( $r=0,86-0,96$ ) and the Aral Sea region ( $r=0,91-0,96$ ).

Children living near Semipalatinsk nuclear ex-range region have direct strong connection between quantity of SAD and pathology of central nervous system ( $r=0,92$ ) and pathology of cardiovascular system ( $r=0,94$ ). Children of Aral Sea region have direct strong connection between quantity of SAD and pathology of urinary system ( $r=0,76$ ). That possibly testifies to distinction of pollution nature.

There is correlative dependence between the level of chromosomal aberrations and quantity of chronic diseases ( $r=0,99$  and  $r=0,99$  accordingly) (Fig.3).

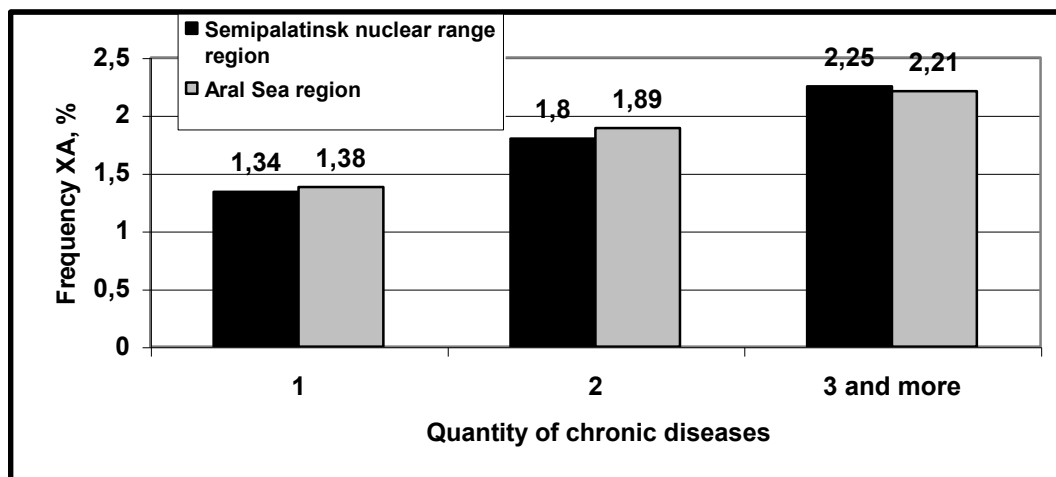


Figure 3 - Frequency of chromosomal aberrations in children's groups with different quantity of chronic diseases.

Changes in genetic apparatus are the one of the reasons not only of CMD formation, but also of SAD development. The established interrelation between SAD quantity and chromosomal aberrations frequency has shown, that children living in Semipalatinsk nuclear ex-range region have high level of chromosomal aberrations frequency (2,18%) - 7-9 SAD, whereas among children living in Aral Sea region (2,21%) this parameter is 10-12 SAD (Fig. 4).

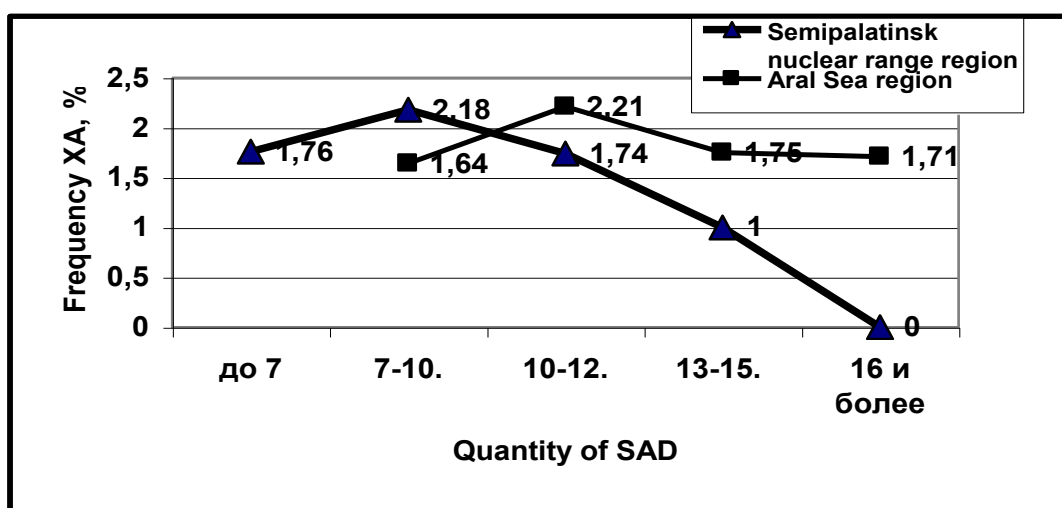


Figure 4 - Frequency of chromosomal aberrations in surveyed children with different quantity of SAD.

Discussion. Results of the carried out combined clinical genetic examination of children living in various ecologically unfavorable regions of Republic of Kazakhstan, have determined presence of essential changes in the health status such as chronic diseases, CMD, increased level of SAD and increased quantity of common frequency of chromosomal aberrations.

Pathology of intestinal tract organs and otorhinolaryngological diseases prevails in the structure of chronic diseases of both basic groups children. Children of the Aral Sea region have prevalence of urinary tract and respiratory system diseases. Three and more chronic diseases are revealed authentically more often-in children from the Semipalatinsk nuclear ex-range region and from the Aral Sea region than in children of control group.

SAD average value of children living in the Aral Sea region exceeds in 1,3 times of SAD average value of children living in Semipalatinsk nuclear ex-range region.

Method of combined clinical laboratory and cytogenetic examination has allowed estimating status of genetic health of children living in Semipalatinsk and in the Aral Sea regions. The general frequency of chromosomal aberrations practically does not differ in children from ecologically unfavorable regions, and three times higher than similar parameter in control group children. Children living in various ecologically unfavorable regions have distinctions in the spectrum of chromosomal damages and aberrations of stable type. In addition to that, they have cells with multiple chromosomal damages, which were not registered in the control group.

Children living in various ecologically unfavorable regions have interrelation between of chronic diseases quantity, SAD and cytogenetic parameters. The more high level of small anomalies of development is revealed in children having three and more chronic diseases from both ecologically unfavorable regions.

Thus combined clinical-genetic analysis including estimation of organs and systems functional condition, quantitative and qualitative characteristics of small anomalies of development and frequency of chromosomal aberrations is an optimum method of forecast of combined chronic pathology development and chromosomal damages in children living in various ecologically unfavorable regions.

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#### С.В.ЧОЙ

#### ЭКОЛОГИЯЛЫҚ АПАТ АЙМАҚТАРЫНДА ТҰРАТЫН БАЛАЛАР ДЕНСАУЛЫҒЫНЫҢ САЛЫСТЫРМАЛЫ КЛИНИКАЛЫҚ-ГЕНЕТИКАЛЫҚ АНАЛИЗИ

**Түйін:** Экологиялық апат аймақтарында тұратын балалар денсаулығының салыстырмалы клиникалық-генетикалық көрсеткіштерін анализден өткізу арқылы, көптеген созылмалы патологиялар мен хромосомды зақымдануларды болжаудың ең оптимальды тәсілдерін тауып жүзеге асыру.

**Кілт сөздер:** балалар, экологиялық апат аймақтары, көптеген созылмалы патологиялар, хромосомды зақымданулар, шағын аномалиялардың анықталуы

#### С.В.ЧОЙ

#### СРАВНИТЕЛЬНЫЙ КЛИНИКО-ГЕНЕТИЧЕСКИЙ АНАЛИЗ ЗДОРОВЬЯ ДЕТЕЙ, ПРОЖИВАЮЩИХ В РАЗЛИЧНЫХ ЭКОЛОГИЧЕСКИ НЕБЛАГОПОЛУЧНЫХ РЕГИОНАХ

**Резюме:** Проведен анализ клинико-генетических показателей здоровья детей, проживающих в регионах с различной характеристикой экологического неблагополучия, для разработки оптимальных методов прогноза развития хронической сочетанной патологии и хромосомных повреждений.

**Ключевые слова:** дети, экологическое неблагополучие, хронические болезни, малые аномалии развития (МАР), хромосомные aberrации.