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Contact Information:
82 Monastyrskaya St.,
Perm, 614045, Russia
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PREVENTIVE MEDICINE: URGENT ASPECTS OF RISK ANALYSIS

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REGULATORY-LEGAL AND METHODICAL ASPECTS OF SOCIAL-HYGIENIC MONITORING AND RISK-ORIENTED SURVEILLANCE MODEL INTEGRATION

A.Yu. Popova[1], N.V. Zaitseva[2], I.V. May[2], D.A. Kiryanov [2]

[1] Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing, 18 Vadkovskiy lane, build 5 and 7, Moscow, 127994, Russian Federation
[2] Federal Scientific Center for Medical and Preventive Health Risk Management Technologies, 82 Monastyrskaya Str., Perm, 614045, Russian Federation

The authors stress in the paper that at a moment when a large-scale administrative reform of control-surveillance activities in the Russian Federation took place there was an efficient tool greatly compatible with control and surveillance activities, a so called social-hygienic monitoring system. When control and surveillance activities and social and hygienic monitoring are brought together, it is a process when mutual integration of both systems takes place; results obtained in one of them give grounds for planning in another. Control and surveillance activities should give precise and targeted recommendations for the social social-hygienic monitoring system for those objects which are to be observed systematically. Both systems accumulate data on which obligatory requirement this or that surveillance object is likely to violate. The monitoring systems allows to make scientifically grounded choice on observation points and monitoring programs development taking all zones influenced by risk sources into account.

Measurement results are aimed at validated and precise determination of unacceptable health risk occurrence or threats to human life or health as well as an object causing such threats. But still each systems continues to solve each own tasks attributable only to it.

Both systems, social-hygienic monitoring and control and surveillance activates, are becoming dynamic. Monitoring points and observations programs are changing in accordance with surveillance authorities actions and economic entities reactions to such actions. Control and surveillance authorities get another tool which helps to further validate their efficiency over the previous time periods.

System management processes are cyclic and have time gaps between specific stages during a year; it causes substantial time expenses which are necessary to obtain optimal parameters. The overall management cycle for one system is equal to 4 years, and for combined systems, 8 years.

Key words: *social-hygienic monitoring, control and surveillance activities, combination, risk-oriented model, management.*

Surveillance and control activities are now being reformed in the Russian Federation and risk-oriented approaches are being implemented in the sphere. These changes are to make overall administrative burden for businesses lower but in no way should

Anna Yu. Popova – Doctor of Medicine, Professor, Head (e-mail: depart@gsen.ru; tel.: +7 (499) 458-95-63).

Nina V. Zaitseva – Member of the Russian Academy of Sciences, Doctor of Medical Sciences, Professor, Research Supervisor (e-mail: znv@fcrisk.ru; tel.: +7 (342) 237-25-34).

Irina V. May – Doctor of Biological Sciences, Professor, Deputy Director for Scientific Work (e-mail: may@fcrisk.ru; tel.: +7 (342) 236-32-64).

Dmitry A. Kiryanov – Candidate of Technical Sciences, Head of the Department of Mathematical Modeling of Systems and Processes (e-mail: kda@fcrisk.ru; tel.: +7 (342) 237-18-04).

they result in loss of the state control over the situation. It is especially true for these spheres under surveillance where the state protects such values as life and health of the country citizens.

Authorities which are responsible for sanitary surveillance in the RF were created almost 100 years ago and they have been improving procedures and forms of hygienic and epidemiologic assessments aimed at detecting hazards for citizens' health ever since [1]. So, they now possess a wide range of instruments for providing sanitary-epidemiologic welfare in the country as an addition to control and surveillance mechanisms which are now being administratively restructured. Social-hygienic monitoring (SHM) is one of such instruments (and we must say, the most efficient one) [1–3]. "Regulations on social-hygienic monitoring procedures"[1], approved by the RF Governmental Order on February 2, 2006, No. 60 and being in force at the moment set forth the following basic SHM tasks:

- to perform hygienic assessment of the environment and population health;
- to reveal cause-and-effect relations between population health and impacts exerted by environmental factors basing on the systemic analysis and health risks assessment;
- to detect causes and conditions which made for occurrence and spread of infections and mass non-infectious diseases (intoxications);
- to work out propositions how to eliminate detected hazardous impacts exerted by environmental factors.

Social-hygienic monitoring was initially implemented to accumulate information which could help to reveal cause-and-effect relations between the RF population health and factors influencing it. It was also to provide informational support for managerial decisions at various levels of public administration. As a result, social and hygienic monitoring is now a complicated open system which for many years has been accumulating and processing heterogeneous data on environmental factors, social and economic parameters of people's life in the country regions, medical and demographic peculiarities of the society in general and specific population groups [3, 4].

Any complicated system which integrates data flow from various sources has its drawbacks; the same is the case with SHM, and these drawbacks are to be eliminated. However, there is no other state monitoring system in the RF which involves comprehensive interdepartmental interaction and collects such diverse data as SHM. The system has accumulated results of instrumental environmental quality measuring in all the RF subjects over the years of its functioning. In 2017 Rospotrebnadzor's authorities and offices acting within SHM frameworks took and analyzed more than 1.1 million atmospheric air samples; assessed drinking water quality taken from centralized water supply systems at more than 11,000 monitoring points; analyzed soils samples taken at more than 8,000 points located in settlements [5]. The federal information fund created due to such activities is practically inexhaustible from the analytical point of view and allows

[1] On approval of Regulations on social-hygienic monitoring procedures: The RF Governmental Order signed on February 2, 2006. No. 60. Available at: http://www.ohranatruda.ru/ot_biblio/normativ/data_normativ/46/46812/ (20.01.2018).

[2] On making alterations into the Federal Law «On protection of juridical persons and sole proprietors when the state and municipal control (surveillance) procedures are performed: Federal Law passed on July 03, 2016 No, 277-FL». Available at: http://www.consultant.ru/document/cons_doc_LAW_200571/3d0cac60971a511280cbba229d9b6329c07731f7/#dst100049 (12.02.2018).

to perform scientifically intense data processing to solve various tasks, including those set in the sphere of surveillance and control improvement [6, 7].

We should note that the system was created in such a way that its functional development was quite possible. When a new methodology of health risk assessment under exposure to hazardous environmental factors was introduced into the system, it has become the most significant progressive change in SHM since the moment it was created. Results obtained via health risk assessment enabled detection of regional and local priority factors, determination of zones where health risks were high, or, on the contrary, territories which were sanitary and epidemiologically safe [8, 9].

A new concept, "control activities performed without interaction with juridical persons or sole proprietors", was fixed in the Federal Law passed on July 03, 2016 N 277-FL [2]; this concept was fundamentally new, and it gave an additional impulse for the social and hygienic monitoring development. The clause 8.3, added to the Law, states that "... examining and measuring parameters of environmental objects (atmospheric air, water, soils, and planetary interior) within performance of the state ... social and hygienic monitoring according to procedures fixed in the RF legislation" belong, among others, to such control activities the performance of which does not require any interaction between a public authority and juridical persons or sole proprietors.

So, the legislation fixes a direct correlation between two most important Rospotrebnadzor's functions, performance of control and surveillance activities and social and hygienic monitoring. This combination of two basic functions is quite harmonious and well justified. As SHM most significant task, from its very beginning, was to examine correlations within "environment - health" system, it has always focused on objects which could cause hazards and risks for human health. A new model of surveillance and control activities, in its turn, is aimed at stricter surveillance at objects which cause the greatest risks for protected values, first of all, people's life and health [10–13]. Here control and surveillance involve prevention, detection, and elimination of sanitary legislation violations, including those which cause environmental contamination [14].

Given such conditions, the combination of control and surveillance activities and social and hygienic monitoring is a process when two systems become mutually integrated, and the results obtained in one of them, give grounds for planning in another. But still, each system continues to solve independent tasks which are only its responsibility (Figure 1).

But at the same time, mutual penetration of the systems requires new tasks being set and solved in each of them. Control and surveillance activities are to give clear and targeted recommendations for social and hygienic monitoring concerning objects which require systemic observations in zones influenced by them. If we wish to optimize SHM exactly as per control and surveillance activities results, we are to understand, which obligatory requirements are most likely to be violated by this or that object under surveillance. Social and hygienic monitoring has to give scientific grounds for the selection of monitoring points and programs which are to be closely connected with a zone influenced by an object which causes health risks. Consequently, measurement results are to validate occurrence and level of intolerable health risks or threat of damage to people's life and health as well as to give clear evidence on an object which causes such risks or threats.

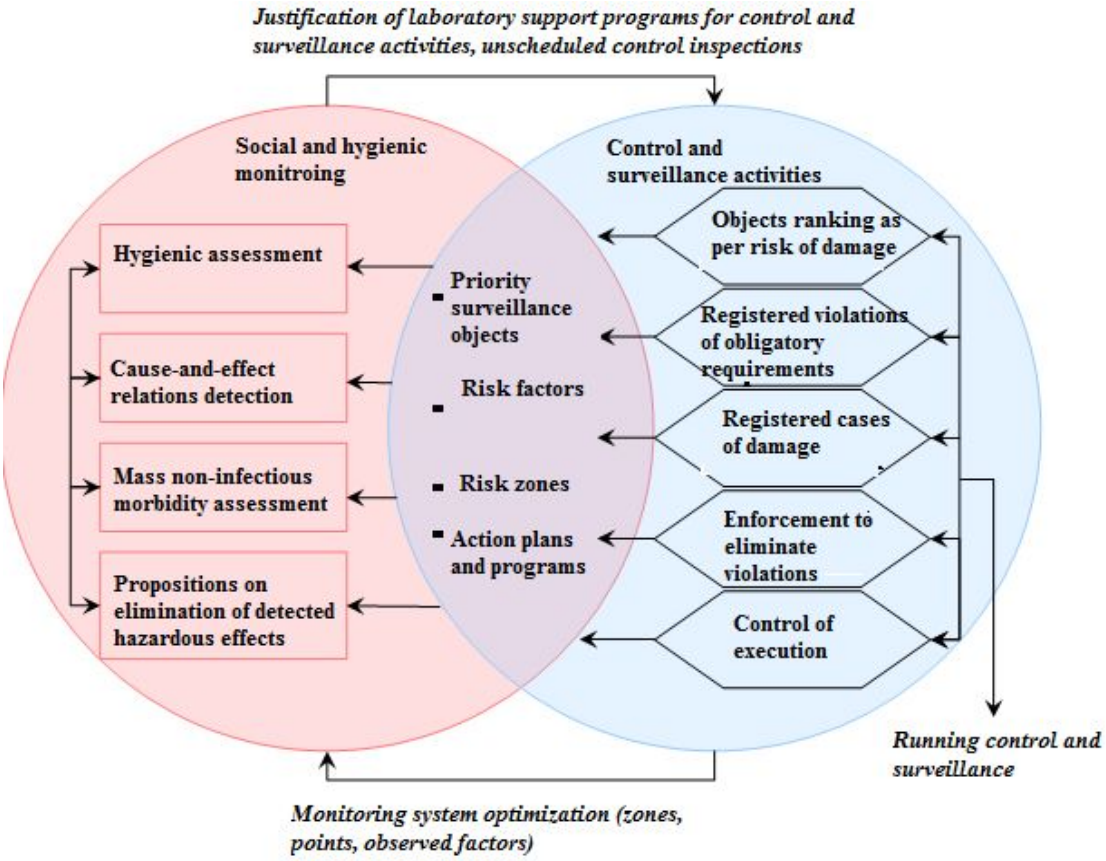

Figure1. The general scheme for combination of social and hygienic monitoring and control and surveillance activities by Rospotrebnadzor

The results of two systems being combined is their mutual enrichment:

- instrumental examinations programs are created allowing for objects being ranked as per potential health risks and they can be based on more informative data;

- research results obtained via correct and targeted programs can, in their turn, give informational grounds for control activities performed without any interaction with juridical persons or sole proprietors.

Such mutual enrichment makes both systems, social and hygienic monitoring and control and surveillance activities, become dynamic and cyclic. Monitoring points and programs are changed relevantly to activities performed by controlling authorities and to response measures taken in relation to actions by economic entities.

Control and surveillance authorities get an instrument which additionally confirms efficiency of their own activities performed in previous time periods. They can also monitor whether their responses to economic entities' actions were efficient or not.

There is a dynamic planning concept created in management theory; this concept is known as Deming cycle. It means that quality of all the results obtained in any activities is constantly regulated via consequent steps which are usually denominated as follows: Plan - Do - Check - Act (PDCA). Deming cycle, when it is applied in Rospoternadzor functioning, is in its essence a process of consequent increase in the efficiency of the performed activities (their optimization) due to surveillance activities being planned and organized allowing for social and hygienic monitoring re-

sults, and monitoring, in its turn, being planned and organized allowing for the results of inspections conducted at industrial objects.

Separate stages are divided into different time periods, and it is a peculiarity of Rospotrebnadzor surveillance and control activities optimization. In other words, if we perform planning during a time period t, then surveillance is conducted during t+1, results are checked during t+2, they are analyzed and activities are optimized during t+3. The process is a helix-like one, and if we allow for specific features of surveillance and control activities planning, organization, and performance within Rospotrebnadzor system, we can state that a time interval between the steps (time lag) amounts to 1 year.

An increase in control and surveillance activities efficiency is closely related to the same process in social and hygienic monitoring.

Although optimization processes for control and surveillance activities and social and hygienic monitoring are quite similar, the latter has a peculiarity as its cycle has a reverse direction. But at the same time the cycles have common elements and two helix-like processes interact. Figure 2 shows a three-dimensional image of interaction between the cycles where blue arrows show control and surveillance activities management, and red ones, SHM system management.

Cyclic processes of the systems management with time lags between separate steps being equal to 1 year leads to substantial time costs which are necessary for obtaining optimal parameters. As we can see from the schemes given in Figure 2, the full managerial cycle for each separate system is equal to 3-4 years, and for their combination, to 6–8 years.

We should also note that although time lags lead to greater time required for finding optimal solutions, the management process is continuous. Moreover, as social-economic, sanitary-epidemiological, and medical and demographic situation is constantly changing, any optimal solution can only be temporary. Consequently, the basic managerial task in the combined "control and surveillance activities - social and hygienic monitoring" system is to form such managerial decisions which are as efficient as possible in terms of its improvement.

Implementation of theoretical ap-

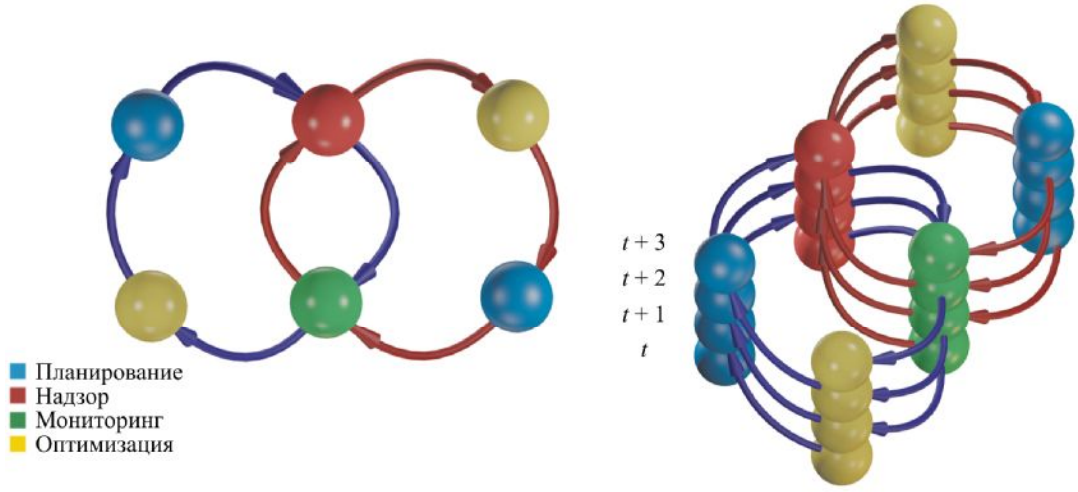

Figure 2. Three-dimensional image of interaction between managerial cycles for surveillance and control activities (blue arrows) and SHM system (red arrows).

proaches to optimization of control and surveillance activities performed by Rospotrebnadzor on a regional level requires developing and implementing new techniques for complex planning; such planning should be based on interactions between Rospotrebnadzor subdivisions in the spheres of information exchange and systemic analysis of data taken from the departmental statistic reports and SHM regional information funds.

Necessary conditions for the systems integration are:

– keeping up a register of juridical persons and sole proprietors which are subjects to surveillance;

– calculating potential health risks which can be caused by each object under surveillance: it is necessary for objects ranking and surveillance activities planning[3];

– spotting out objects which cause extremely high and high health risks for regional population;

– spatial binding of all such objects to territories;

– justifying "risk profiles" for objects under surveillance as a system of parameters which characterizes priority factors causing the overall risk level of an object and their internal relations;

– conjugating risk levels of an object with medical and demographic situation on a territory and spotting out territories with the highest mortality and morbidity shares associated with risks caused by an object under surveillance as a results of sanitary legislation being violated;

– creating SHM programs allowing for the following requirements: a monitoring point should be located on a territory where the highest potential health risk can be caused by an object under surveillance should sanitary legislation be violated and where the highest morbidity associated with a hazardous factor can occur; a monitoring program is aimed at measuring factors which cause the highest health risks; a monitoring program includes minimum sufficient number of observations which are required for the consequent analytical treatment.

Social and hygienic monitoring results should be taken into account in further planning and assessing efficiency of control and surveillance activities. Should social and hygienic monitoring results reveal there is environmental contamination which is dangerous for people's health, then the most essential task is to adjust control and surveillance activities concerning objects which can be a source of such contamination.

This approach fully corresponds to control and surveillance activities orientation at their ultimate result, namely, population health preservation. However, new tasks set stricter requirements to each element in social and hygienic monitoring and a risk-oriented model implemented into surveillance and control activities.

Stricter requirements are also set for the quality of registers which comprise economic entities being subject to sanitary-epidemiologic surveillance, as well as for correctness and transparency of calcula-

[4] On application of risk-oriented approach when organizing specific activities in the sphere of the state control (surveillance) and making alterations into some Orders by the RF Government (together with "The Rules for attributing activities performed by juridical persons and sole proprietors and (or) industrial objects used by them to a specific risk category or to a specific hazard category): The RF Governmental Regulations dated August 17, 2016 No. 806. Available at: http://docs.cntd.ru/document/420372694 (12.02.2018)

tions related to an object ranking as per possible health risks.

There is a new task related to spotting out priority chemical, biological, and physical risk factors which are subject to measuring. Rospotrabnadzor's authorities and offices require a wider range of tools for situational modeling, including those based on GIS-platforms [14–16].

It is extremely vital to create a scientific-methodical foundation for accounting, evidencing, and registering cases in which damage was done to people's life or health as a result of sanitary legislation violation and when such violation was proved by SHM measuring results.

In accordance with item 4, clause 8.3 of the 294-FL, all the control activities (inspections) which are performed without any interaction with juridical persons or sole proprietors should be accomplished basing on a set of inspection tasks approved by a surveillance authority supervisor. Given the above-mentioned, it is extremely essential to work out principles for drawing up such sets of tasks, their layout, and a form in which inspections results are to be presented.

Rospotrebnadzor authorities and offices have accumulated experience in conducting control inspections without any interaction with juridical persons or sole proprietors (in the spheres not related to sanitary surveillance). This experience proves that an inspection task should contain clear description of its goals, state its date, list all the basic information on an inspection object (its location, address, whom it belongs to and according to what rights). All the procedures are to be strictly documented. Inspection results are to be presented as an inspection report which should contain the following: a type of an inspection; information about a task this inspection was based on; a date or a period during which it took place; a time when it started and finished; its participants; a short descriptions of actions performed by an official and other participants; data obtained during it including the results of examinations, measuring, and observations; information on technical means which were applied for technical measuring; fixation of the inspection course and its results; data on any appendices to a report as well as explanations, additions or remarks made by inspection participants.

Schemes, tables, and measuring reports as well as any other supporting technical documents designed according to a established procedures are supplements to a report.

To sum up, a task to combine social and hygienic monitoring and surveillance and control activities is a vital one and requires the following:

- to work out and approve on a new edition of the regulations on SHM in relation to the Federal Law issued on June 29, 2016 No. 277- FL "On making alterations into the Federal Law «On protection of juridical persons and sole proprietors when the state and municipal control (surveillance) procedures are performed" and the Federal Law "On strategic planning in the Russian Federation";

- to develop a scientific approach to creating "risk profiles" for objects under sanitary-epidemiologic surveillance due to violation of sanitary-epidemiologic legislation;

- to give scientific grounds for selection of monitoring points and creation of programs for instrumental research on atmospheric air, natural and drinking water and soils in zones influenced by economic entities which cause extremely high, high, or significant health risks due to violation of obligatory requirements to environmental objects quality;

- to create and document methodical approaches to specific research within SHM system which is control activities performed without interaction with juridical persons or sole proprietors in zones influenced by economic entities which cause extremely high, high, or significant health risks;

- to develop requirements to presentation of sampling and measuring results obtained during control inspections without interaction with juridical persons or sole proprietors and fix these requirements in regulatory documents;

- to work out scientific and organizational approaches to detecting, evidencing and registering cases in which damage was done to health due to violation of obligatory requirements by objects under sanitary-epidemiologic surveillance.

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SCIENTIFIC AND METHODICAL APPROACHES TO RISK ANALYSIS IN HYGIENE AND EPIDEMIOLOGY

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RISK-ORIENTED MODEL FOR PREDICTING EPIDEMIOLOGICAL SITUATION WITH CRIMEAN-CONGO HEMORRHAGIC FEVER (ON THE EXAMPLE OF STAVROPOL REGION)

V.M. Dubyanskiy, D.A. Prislegina, A.N. Kulichenko

Stavropol Anti-plague Institute, 13–15 Sovetskaya Str., Stavropol, 355035, Russian Federation

Our research object was a multi-factor prediction of risks related to even a single case of Crimean-Congo hemorrhagic fever (CCHF) on a territory of a particular administrative district in a RF subject (on the example of Stavropol region). Risk-oriented model aimed at yearly prediction of CCHF occurrence was created with heterogeneous sequential statistics clarification procedure. We considered monthly climatic parameters (air temperature, relative air humidity, precipitations quantity, snow mantle size, and air pressure) and epidemiologic data (number of CCHF cases last year and number of settlements where CCHF cases were registered) as predictors for new CCHF cases occurrence. To check our prediction model precision, we took data on risk factors from 2011 to 2015 for each administrative district in Stavropol region. Threshold level of a positive solution probability was set at 99 % (error probability was equal to 1 %).

We tested our prediction model as per retrospective data collected in 2013–2016. It allowed us to predict even a single patient with CCHF occurrence for each administrative district in Stavropol region in 2017. In the course of data analysis we detected high precision in potential prediction results. Totally we revealed six false-positive and two false-negative (actually erratic) results but they can result from objective factors, for example insufficient diagnostics of the disease, as well as imported cases. The obtained data can be applied in practical activities of Rospotrebnadzor offices aimed at planning and organizing CCHF prevention. The next stage in the prediction model development will be creation of a technique for calculating an expected number of CCHF cases for each administrative district where at least one case of the disease is predicted in the forthcoming year.

***Key words**: Crimean-Congo hemorrhagic fever, risk-oriented model, morbidity, risk factors, prediction, informative value coefficients.*

Southern territories in Russia are endemic in terms of Crimean hemorrhagic fever (CHF) which is an extremely dangerous natural-nidal infection. The disease cases were registered on the territory of almost each region in the Southern and North Caucasian Federal districts (except Krasnodar region, Adygei Republic, North Ossetia-Alania Republic, and Chechen Republic). Overall, from 1999 to 2016 2,047 patients with CHF were detected, 82 of them died (mortality amounted to 4%). As

Vladimir M. Dubyanskiy – Doctor of Biological Sciences; Head of Epizootologic Monitoring and Prediction Department (e-mail: snipchi@mail.stv.ru; tel.: +7 (865) 226-03-12).

Daria A. Prislegina – Junior Researcher at Epidemiology Laboratory (e-mail: daria775@ rambler.ru; tel.: +7 (865) 226-03-12).

Aleksandr N. Kulichenko – Corresponding Member of the Russian Academy of Sciences, Doctor of Medical Sciences, Professor; Director (e-mail: snipchi@mail.stv.ru; tel.: +7 (865) 226-03-12).

it is the case with many natural-nodal infections, CHF morbidity is cyclic. The first peak was detected in a period from 2005 to 2009. The next morbidity rise started in 2015/ 90 patients with CHF were registered in 2014; 138, in 2015; and 162, in 2016 [1, 2] (Figure 1).

In 2016 the disease cases were registered in 6 southern Russian regions, 37% of them occurred in Stavropol region where epidemiologic situation as regards Crimean hemorrhagic fever has remained unfavorable for the last five years with no morbidity falling trends [3–5]. Favorable landscape-geographic and climatic conditions, as well as a wide range of small mammals and birds which are hosts for Hyalomma-marginatum mites, basic infection carriers, make for evolvement and preservation of the infection natural focuses in the region [6,7]. At the same time, as we analyzed spatial distribution of morbidity with this infection on Stavropol region territory, we noted that there are administrative districts where the disease cases are multiple, but still there are some districts where no disease cases have been registered over the last five years or just single CHF cases occur there periodically [8] (Figure 2).

Given that there are no specific CHF prevention means at the moment, main focus is on general prophylaxis and anti-epidemic activities. The most important is to make sure that medical and prevention organizations are ready for laboratory diagnostics and providing timely and qualified medical aid to patients with CHF. So, to perform scientifically grounded and targeted planning of activities aimed at the disease prevention, it is necessary to make annual quantitative forecasts on morbidity cases risk in each administrative district of Stavropol region [9].

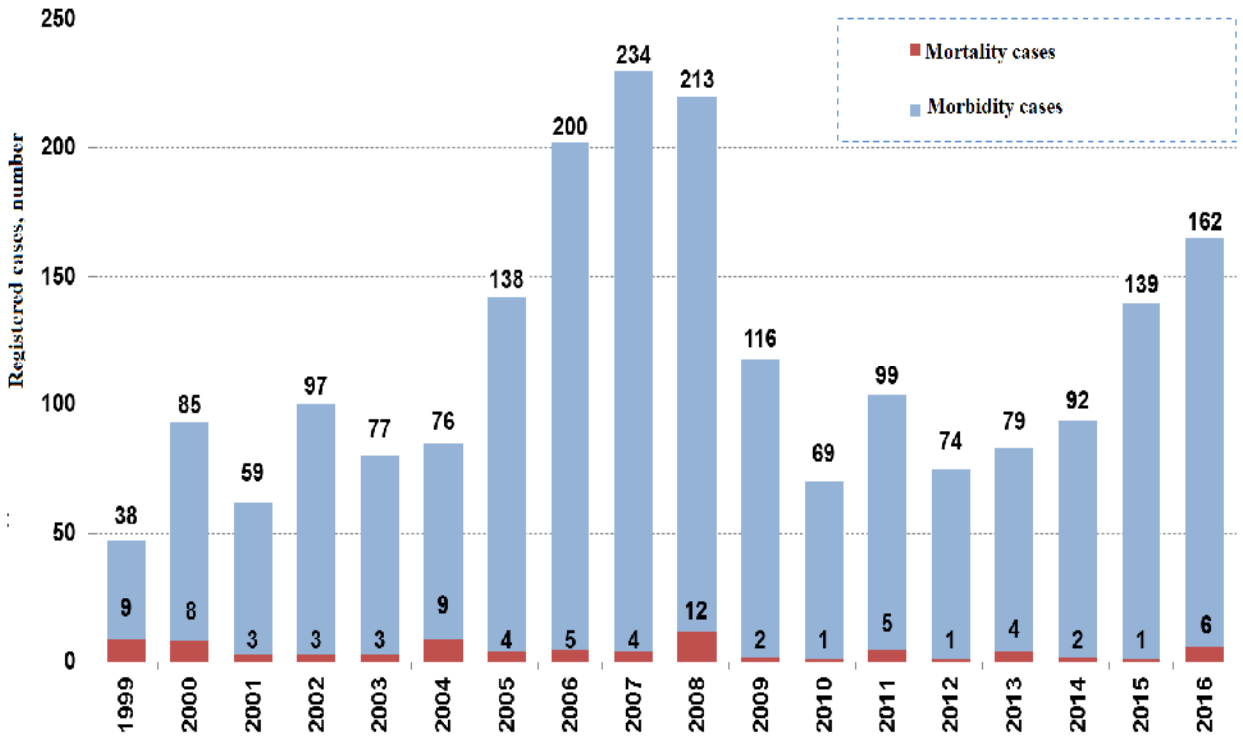

Figure 1. Crimean hemorrhagic fever morbidity dynamics in the Russian Federation over 1999–2016

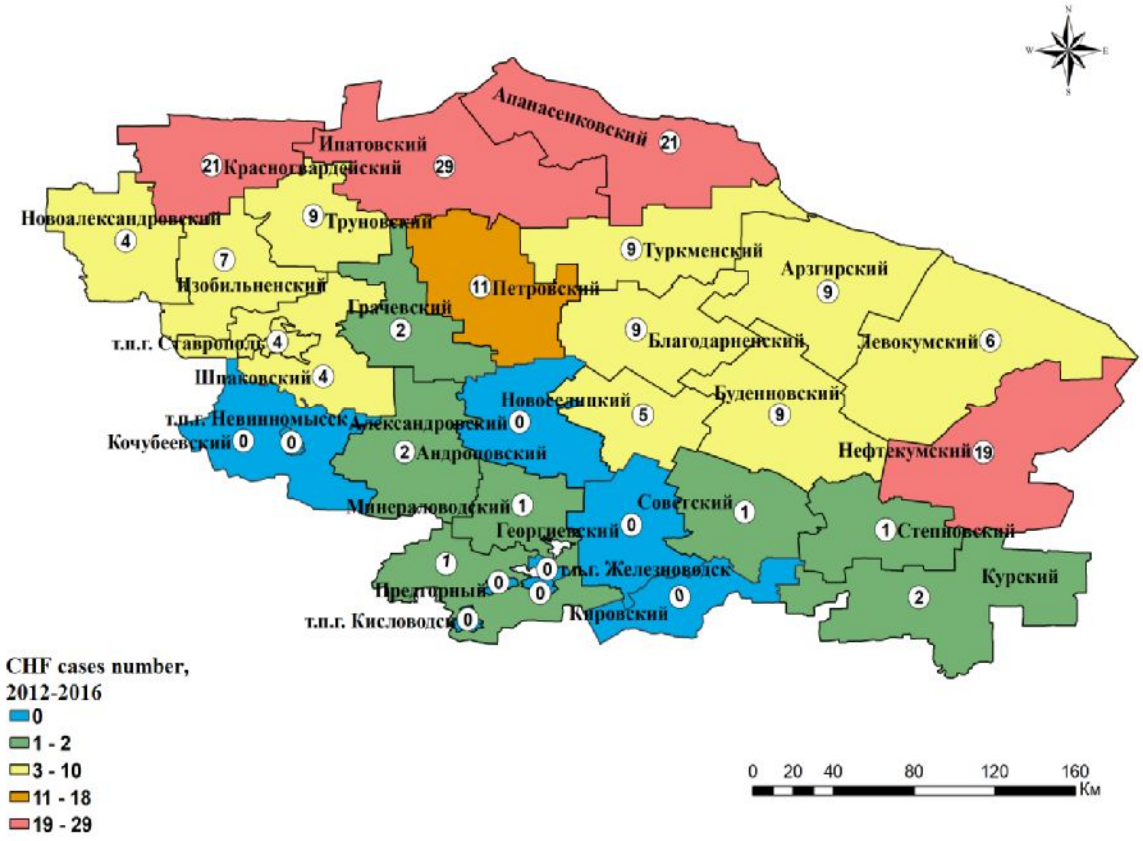

Figure 2. Distribution of the registered CHF morbidity cases in various administrative districts of Stavropol region (2012–2016)

The existing CHF morbidity prediction techniques are based only on epidemiologic or climatic data and don't allow for the whole set of factors influencing the infection epidemic process. Thus, a mathematic model applied for short-term prediction of CHF cases number which is based on "maximum stability" determination and regression analysis allows to determine an expected number of patients (annual parameter) in the current year as per morbidity parameters in a "key" month [10]. There is also another technique based on a SIR type agent model for a disease prevalence. This prediction technique involves dividing all individuals in an examined population into three groups: healthy susceptible ones (S); infected who are infectious agents sources (I); and recovered or individuals with specific immunity (R). This model functioning is based exceptionally on analyzing stages in infectious disease development and reflects only probabilistic nature of an epidemic process [11]. Other mathematical procedures make it possible to draw up forecasts for the general CHF mortality dynamics depending on climatic factors for the whole territory of an examined region [12–15]. So, at present we don't have a risk-oriented model based on multifactor analysis of predictors and applied for quantitative predicting whether CHF cases will occur next year on a territory of each administrative district in a region.

Our research goal was to create a risk-oriented model which would allow to predict whether at least one CHF case was likely to occur in each administrative district (on Stavropol region example) in the forthcoming year.

We tested the suggested technique (on the bases of retrospect data collected in 2012–2016) and made predictions for 2017; this paper contains the test results and the prediction.

Data and methods. We took final annual data on CHF morbidity collected by the Federal Service for Surveillance over Consumer Rights Protection and Human Well-being (Stavropol regional office), results of laboratory research performed on field materials by Rospotrebnadzor's Stavropol Scientific Research Anti-Plague Institute and Stavropol Regional Center for Hygiene and Epidemiology, demographic statistical parameters by Federal Statistics Service (ROSSTAT). Hydrometeorological data were obtained from Russian Scientific Research Institute for Hydrometeorological Information – World Data Center (http://www.meteo.ru), and from meteorological stations achieves which are stored on "Weather Schedule" LLC web-site (https://rp5.ru) and weather logs by Gismeteo (https://www.gismeteo.ru/diary).

To create our risk-oriented model, we applied a heterogeneous sequential clarification procedure (HSCP). This technique is widely used in various medical research to calculate pathological processes outcomes risks and is based on selecting most informative clinical and laboratory signs; it is also applied in epidemiologic and epizootologic predictions, in particular, in case of natural plague focuses [16–23]. Basic HSCP advantages are possibility to allow for multi-directional influences exerted by predictors values and presentation of results in an alternative form, that is, one of two possible prediction variants will be obtained for a year which follows after an initial one: "conditionally positive" (the disease cases occurrence), or "conditionally negative" (no disease cases). Intermediate results cases most frequently mean there is not enough information. Besides, the above mentioned technique is quite simple to apply, doesn't require use of complicated multi-dimensional statistic techniques and is relevant in case of any signs distribution.

We considered all the basic factor groups influencing CHF epidemic process as our risk predictors: biotic (basic CHF carriers contamination as per results of laboratory research performed on mites and aimed at CCHF viruses markers detection), abiotic (monthly climatic factors parameters: air temperature, relative air humidity, precipitations, snow mantle size, and air pressure), social (annual population density in various administrative districts per 1 square kilometer), and epidemiologic data (number of people who applied to medical-prevention organizations because of mites bites, number of patients with CHF, and number of settlements where CHF cases were registered in each administrative district in Stavropol region in 2011–2015). Anti-mites treatment of pasture lands, natural biotopes, and epidemiologically significant objects, as well as acaricide treatment of agricultural animals which took place during the examined period on territories of all the administrative districts in Stavropol region were quite sufficient, but they didn't exert any influence on CHF morbidity. In relation to that, we didn't allow for this factor in our research.

To select the most significant predictors, we calculated informative value coefficient for each of them; this coefficient showed significance of contribution made by this factor into approaching one of prediction variants. Predictors with low in-

formative value coefficient (<0.5) were excluded from the further research as their application was pointless since they didn't increase the overall informative value but instead made analysis procedures longer and could lead to more errors [16]. The remaining predictors were then ranked in their informative value coefficient descending order; thus we obtained an optimized risk factors list necessary for the further model construction.

Threshold level of positive solution probability for each administrative district was set at 99% (probability of error was equal to 1%). Accordingly, total diagnostic coefficient for each administrative district was equal to 20 («+» meant «positive results» or registration of even 1 CHF case; «-» meant «negative result» or CHF cases absence). A learning sample comprised data on registered patients number and risk predictors for all 32 administrative districts In Stavropol region over the previous year. A training sample comprised data on occurrence of at least 1 patient with CHF in the following year. We performed retrospect checking of at least 1 disease case risk in an administrative district of Stavropol region for the following pairs of years: 2013–2014, 2014–2015, 2015–2016 г. In January 2017 we presented our 2017 epidemiologic zones calculation based on 2016 data.

To automate risk-oriented model creation procedure, we developed a program in Microsoft Excel 2010.

Results and discussion. Table shows results of risk-oriented model testing (on retrospect data) and an operating prediction for 2017.

When we analyzed our model testing results, we detected that potential prediction results were highly precise. Total coincidence with actual parameters in all administrative districts was obtained for

Results of predicting CHF cases occurrence or absence for each of 32 administrative districts in Stavropol region over 2013–2017

Prediction results	Years									
	2013		2014		2015		2016		2017	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%
Correct	31	96,9	30	93,8	30	93,8	32	100	29	90,6
False positive*	1	3,1	2	6,2	0	0	0	0	3	9,4
False negative **	0	0	0	0	2	6,2	0	0	0	0

Note : * – false positive result means that at least one morbidity case was predicted but eventually didn't occur in reality.;

** – false negative result means we didn't predict any morbidity cases but actually a morbidity case was registered.

2016. When explaining three detected false positive results, we should allow for the following objective factor: the disease wasn't possibly diagnosed due to prevalence of CHF forms without any hemorrhagic syndrome in the recent years. Two false negative results which can be considered truly erratic were obtained only in 2015 and can be explained by imported disease cases when patients got infected during their staying in other administrative districts or even in another region. 2017 operating prediction results coincided with actual data in 29 out of 32 administrative districts, and we didn't obtain any false negative ("truly erratic") results. Air humidity and precipitations (in spring and summer), as well as snow mantle size in February-March, were the most informative and significant risk factors for prediction out of all the examined climatic parameters in the stated period. It can be explained by their direct influence on number and activity of Hyalommamarginatum mites and other mites which are the main

CCHF infectious agents; this influence was proved in some works [6,7,14]. Such factors as wind speed, population density in administrative districts, and results of laboratory tests performed on mites in order to detect CCHF virus markers, turned out to be not informative. The last factor's low informative value coefficient can be explained by materials sampling being not representative enough. Accordingly, territories in Stavropol region were divided as per predicted risks of at least one individual being infected with CCHF agent on the basis of climatic factors values (air temperature, relative air humidity, precipitations, snow mantle size, and air pressure) and epidemiologic data (number of patients with CHF in the previous year and a number of settlements where the disease cases were registered) obtained for each administrative district.

To sum up, after testing our risk-oriented model for predicting CHF cases occurrence we can state that it is quite relevant and can be applied in practice. The obtained results as self-sufficient data can be applied by Rospotrebnadzor offices for targeted planning of prevention activities in administrative districts with high risks of CHF cases occurrence (medications supplies for CHF treatment can be accumulated in advance, laboratory bases can be prepared for clinical materials examinations, and workshops on CHF epidemiological and clinical issues can be held for primary medical personnel thus raising their epidemiological awareness).

We should note that it was the first time when we applied HSCP to calculate predictors informative value in relatively great number of spatial points (32 administrative districts). Previously this technique was applied in epizootology and epidemiology of natural-nidal infections to calculate predictors informative value in time and relative to only one spatial point. The authors don't have any information about other existing techniques for spatial multifactor prediction of at least one CHF case occurrence in each administrative district. It is a very significant advantage of the developed model over other ones which were developed earlier.

We tested a possibility to predict a risk of at least one disease case occurrence in the year which followed the current one in administrative districts of Stavropol region. The next stage in our prediction model development will be an attempt to calculated an expected number of CHF disease cases for each administrative district where we predict at least one patient with CHF in the forthcoming year.

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ON SOME APPROACHES TO CALCULATION OF HEALTH RISKS CAUSED BY TEMPERATURE WAVES

D.A. Shaposhnikov, B.A. Revich

National Economic Prediction Institute of the Russian Academy of Sciences, 47 Nakhimovsky Prospect, Moscow, 117418, Russian Federation

The paper dwells on techniques applied for assessing impacts exerted by environmental factors on population health which have become conventional all over the world over recent years. The greatest attention is paid to up-to-date approaches to calculating risks of additional mortality which occurs in big population groups during cold and hot temperature waves. The authors consider basic stages in direct epidemiologic research: temperature waves definition; statistics hypotheses formulation; models specification; statistical criteria sensitivity, and statistical validity of the obtained results. As per long-term research performed by us in various Russian cities, we constructed logistic curves which show probability of obtaining significant risk assessment results for small samplings. We recommend to apply percentiles of long-term average daily temperature distributions as temperature thresholds when identifying temperature waves; in our opinion, such thresholds correspond to perceptions of extreme (for this or that region) temperatures and provide comparable results in terms of expected waves quantity in different climatic zones. Poisson's generalized linear model for daily mortality is shown to be the most widely spread technique for calculating risks caused by hazardous environmental factors. It is advisable to allow for an apparent correlation between mortality and time and air contamination in any regression model. We can allow for meteorological conditions which influence heat balance (air humidity and wind speed) either via including them apparently into a model or via bioclimatic indexes application; research in this sphere is going on. When calculating risks, it is advisable to allow for time lags between extreme temperatures waves and changes in mortality. We revealed that minimal population of a typical city for which it is possible to obtain statistically significant assessment of risks caused by heat waves ensembles is about 200 000 people.

***Key words**: population mortality, temperature waves, time rows analysis, risk assessment, Poisson's distribution, generalized linear model, mixing factors.*

Climatic changes we are witnessing at the moment lead to heat waves becoming more repeatable, longer, and more intense; cold waves, on the contrary, occur not so frequently, are less intense and don't last as long as they used to [1]. Consequences of impacts exerted by temperature waves on population health are being examined all over the world, and PubMed, the leading medical database, contains more than 1,000 works in the field. Serious health disorders which occur during temperature waves can cause not only its heavy losses but also a decrease in a number of healthy years of life. All this, in its turn, results in GDP losses, both on a country and regional level.

This paper focuses on contemporary biological statistic techniques which allow to reveal correlations between meteorological factors and public health. In particular, it dwells on how to calculate additional population mortality caused by heat and cold waves influence. Value of daily (every day) mortality for an examined population is a random function, and this randomness cannot be eliminated (for example, we can't consider it to be a measurement error). Epidemiologic research in the field is often re-

Dmitry A. Shaposhnikov – Candidate of Physical-Mathematical Sciences, Senior Researcher at Laboratory for Environment Quality Prediction and Population Health (e-mail: dshap@newmail.ru; tel.: +7 (926) 598-22-28).

Boris A. Revich – Doctor of Medical Sciences, Professor, Head of Laboratory for Environment Quality Prediction and Population Health (e-mail: revich@yandex.ru; tel.: +7 (499) 129-18-00).

lated to regression analysis performed on time series of daily mortality. Our goal was to describe up-to-date statistic mortality models which are applied to calculate mortality risks caused by temperature waves influences. The article is conditionally divided into three sections: the first one contains definitions of temperature waves; the second describes daily mortality modeling; the third one is about statistical validity of risk assessment results obtained for small samples.

Heat and cold waves: definitions. Some researchers put the following question: which waves stimulate greater growth in mortality, heat or cold ones? To answer it correctly, it is advisable to give "symmetric" definitions for heat and cold waves, both concerning their duration and temperature thresholds. Bearing this symmetry in mind, we are giving only a definition of heat waves here, and cold waves are to be defined by analogy.

Meteorology states that a heat wave is "a considerable temperature rise which spreads to a certain direction and is related to a warm mass advection" (Meteorological glossary, 1974). Rosgidromet (Federal Service on Hydrometeorology and Environmental Monitoring) gives the following definition of "abnormally hot weather": "... average daily temperature being 7ºC or more degrees higher than the climatic standard during a period from April to September"[1]. This definition for heat waves is to be applied by EMERCOM of Russia and other state organizations when they classify dangerous weather phenomena. If we apply this definition too, we can see that most heat waves come to central Russian regions in April, and in July their number is minimal. Heat waves in meteorology are defined analogically but there is no limitations "from April to September", so heat waves can occur during all four seasons [2]. However, the major problem concerning this definition is that probability of temperature waves occurrence (or their number) vary significantly in different climatic zones.

The problem can be solved if we abandon "7ºC" criterion and apply percentiles of long-term "historical" average daily temperatures distribution instead; or we can apply root-mean-square deviation for this distribution, that is, statistic (probabilistic) features which are calculated as per a common sample comprising either all days in a year, or all days in a warm (cold) period. The World Meteorological Organization suggest to apply the upper 90th or 95th percentile of temperatures distribution during warm time of the year as a local specific threshold in the following definition: "A heat wave is a clearly defined two- (or more)-day period of extreme heat measured in daily maximum, average, and minimal temperatures, during warm time of the year" Thresholds are suggested to be set allowing for local climate [3].

A similar definition is used in epidemiologic literature [4]. For example, methodical guidelines issued by Rospotrebnadzor state that a wave heat is five and more consequent days during which average daily temperature is higher than 97th percentile of the average daily temperatures distribution over an examined long-term period[2]. Such threshold will on average "cut off" $3{,}65 \times 3 \approx 11$ of the hottest days per year and

[1] Guidelines 52.27.724-2009. Guidelines on general short-term temperature forecasts. Obninsk, IG-SOZIN Publ., 2009, 66 p.

[2] MG 2.1.10.0057-12. Population health related to the environmental situation and living conditions. Assessment of risks and damages caused by climatic changes which influence morbidity and mortality in population groups running increased health risks: methodical guidelines. Moscow Federal Service for Surveillance over Consumer Rights Protection and Human Well-being Publ, 2012, 37 p. Available at: http://36.rospotrebnadzor.ru/documents/rekdoc1/9374 (11.10.2017).

not all of them will be included into heat waves. We say "on average", because heat waves are not distributed evenly over years, and two or three cooler years are usually followed by a year when summer is hot and there are several heat waves during it. Most waves come in July which is usually the hottest month of the year.

Which of two definitions given above is stricter, that is, gives less waves due to a higher hot weather threshold? Let us consider Moscow as an example. Over 2000-2009 average June temperature in Moscow amounted to 16.5ºC; July, 19.9ºC; August, 17.5ºC. Therefore, hot weather thresholds for three summer months according to Rosgidromet definition are to be approximately (as we apply average monthly temperatures here) equal to 23.5ºC; 26.9ºC; 24.5ºC. The 97th percentile of average daily temperatures in Moscow taken for the same period amounted to 23.5ºC. We can see that the first definition is stricter: we can expect only 14 days during 10 years when temperatures will be higher than these thresholds, that is, only one or (unlikely) two heat waves will occur. The second definition, as our research performed in moderate climatic zones showed [5–8], gives on average about 8 heat waves over a ten-year period. Such quantity of waves naturally gives more data for epidemiologic research and simultaneously coincides with an intuitive idea of extreme temperatures.

Bioclimatic indexes. Statistical mortality models can include temperature, humidity, wind speed and other meteofactors as independent variables; that is, risks caused by temperature are calculated with an adjustment for other meteorological variables. However, there is another approach when models incorporate a certain combination of these variables, when temperature is given a dimension and is called, for example, "an effective temperature" (in case of heat) or wind-cold index (in case of cold). Epidemiologists are still searching for the most relevant combination of meteorological variables; it should be such a combination when a statistic test would reveal the strongest correlation with a chosen health parameter [9, 10]. Accordingly, heat waves can be defined not with a usual air temperature (measured by a dry thermometer) but with an effective one. Methodical guidelines issued by Rospotrebnadzor give the following definition for effective temperature [11]:

$$AT = -2{,}653 + 0{,}994\,T + 0{,}0153\,D^2,$$

where AT is effective temperature; T is air temperature; D is dew point temperature.

We showed in one of our works that effective temperature is more closely connected with morality occurring during heat waves, and wind-cold index is a better mortality predictor during cold ones than just usual air temperature [5]. But as for this paper, here we apply usual air temperature as a variable to identify temperature waves (that is, heat and cold ones), without limiting generality in statement.

Statement and testing of statistic hypotheses. Any statistic research starts from stating statistic hypotheses which should correspond to its specific goals. If we want to examine influences exerted by temperature waves on population health we should prove there is a statistic correlation between such waves and a number of daily outcomes for a selected health parameter. Although we apply the same statistic procedures to examine both cold and heat waves, there is one significant difference between influence on mortality exerted by cold waves and heat ones. And this difference is a time aspect: cold effects are rather long-term and come with a delay while heat acts almost instantly. This difference should be explained by pathophysiological mechanisms of heat and cold effects and by body adaptation and short-term acclimatization to extreme temperatures, but statistic research goals are to only detect any statistic regularities, and not to explain them. Therefore an expert in biologi-

cal statistics who studies death predictors (air temperature, for example) confines him or herself to such a correct conclusion as "we revealed a correlation between air temperature and mortality". In this case air temperature is considered to be a risk factor, and this factor can be a reason or just a marker of an effect.

If we take only one specific wave, than our null hypothesis (H0) can be stated as follows: mortality which occurred during a period of the wave has no statistical discrepancies from mortality expected under other conditions being equal in case the wave was absent. The same hypothesis is apparently generalized for research on an ensemble (a certain set) of waves during a long-term research period. Individual waves in this ensemble are different both in terms of their duration and intensity (amplitude). Depending on research goals, experts can examine dependence of ultimate health indexes on these parameters by comparing corresponding wave ensembles. The simplest models, especially in case of short time series, give a possibility to examine an ensemble of all the identified waves; thus it is possible to calculate only additional mortality risk which is averaged as per this ensemble. Defined exactly, a risk is a ratio of mortality expected during the examined wave ensemble to mortality expected during the same days but when there is no extreme heat.

A possible time lag between a temperature wave and a response in mortality makes null hypothesis statement more complicated as it requires additional assumptions on a delayed effect and corresponding mathematical tools.

A usual research object is a population of just one city. Population number determines a mathematical expectation of daily mortality as a random variable and a dispersion of this parameter which, in their turn, have their influence on sensitivity of a statistical test applied to verify H0.

Time series analysis. Regression analysis with Gaussian and Poisson's generalized linear models is the most widely spread technique applied to examine long time series of daily mortality [11]. An assumption stating that outcomes are independent leads to Poisson distribution of daily mortality. But in reality the basic property of Poisson distribution (mathematical expectation of daily outcomes number λ is equal to dispersion) holds only approximately for daily mortality. As λ grows, an excessive dispersion occurs, and daily mortality distribution itself becomes Gaussian when λ values are high. Apparently, one of the reasons for the phenomenon is that an assumption on independence of outcomes is false.

If a dependent variable complies with Poisson distribution, than when we apply a natural logarithm as a functional correlation in a regression models, regression remains will be distributed as per the normal law. But if a dependent variable is distributed as per the normal law, then it is correct to apply a linear functional correlation (Gaussian regression). For example, linear regression can be applied in Moscow where $\lambda \approx 300$. However, we don't "win" much by doing this: if Poisson model is applied in Moscow, we can obtain risk assessment results which are quite comparable in terms of their statistic significance.

Model specification. Let us consider a Poisson model for daily mortality Mi. As a time series Mi is a random function of a number of a day i, then a dependent variable in regression equation is an expected daily mortality value $E(Mi) \equiv \mu i$. It is convenient to divide all the predictors into those which apparently depend on time t and all the remaining regressors of daily resolution x1, x2, … xP, including ecological ones, i.e. regressors which describe influences exerted by the environment (meteorological factors and contamination) and mediate the effect [12]:

$$\log[E(M_i)] = \alpha + \sum_{j=1}^{P} g_j(x_{ij}) + f(t_i) + \beta\ DOW. \quad (1)$$

Generalized linear regression has an advantage of being flexible in selecting functional dependences gj on continuous regressors and possibility to include discrete regressors into the model without loss of generality. A good example is the last summand in the model (1) which is a vector consisting of seven categorial variables labeling days of week (DOW) with corresponding regression coefficients β.

An apparent dependence of daily mortality on time includes seasonality, a long-term trend, dependence on a day of week, holidays, flu epidemics etc. If a researcher wants to focus on seasonal changes in mortality, then the function f(t) can contain a periodical summand with a period being equal to 1 year. In general cases, allowance for smooth time dependences on various scales is achieved via including splines S(t) with a preset number of degrees of freedom (or nodes) over the whole examined period into the model.

Heat waves risk assessment. If we concentrate only on general effects exerted by heat waves on mortality, then our regression model will not include temperature explicitly. It will be quite sufficient to apply a binary variable which labels all the days included into an examined heat waves ensemble (with a preset time lag in days). Regression coefficient for this variable βheat (its exponent, to be exact) will give a numeric characteristics for mortality increase on average for this waves ensemble adjusted as per all the other factors which influence mortality and are included into the model (1).

Overall effects by heat waves can be divided into two summands. The first summand is called "a basic temperature effect" as it depends on average daily air temperatures. The second summand is a "wave addition" which occurs only under long-term exposure to heat and is a function of a number of a day in a continuous consequence of hot days. As A. Gasparrini revealed, the basic effect is several times greater than the wave addition for waves which are usual in their duration (5-10 days) [13]. However, we observed a rather opposite ratio during abnormal heat in Moscow in summer 2010 [14].

Experts have long known that the basic temperature effect is not "instant"; it is distributed over time in a complicated way, that is, it influences mortality during all days which follow the reference one. Various ways were suggested to examine delayed dependences allowing for a time lag between exposure and effects [15, 16]. Statistical functions describing non-linear models with distributed lag were integrated into the software environment R and are now freely accessible in CRAN (Comprehensive R Archive Network) [17].

Mixing factors. According to a "ventilation hypothesis", atmospheric air contamination has different influence on health during hot days and days when temperature is moderate. On hot days people keep their window open in order to ventilate their homes and spend more time outdoors; therefore, they are exposed to greater doses of air contaminants [18]. If this hypothesis is true than a certain part of high temperature risks is actually caused by contaminants concentrations in the atmospheric air (first of all PM_{10}) and greater exposure to such pollutants. As for surface ozone, here there is also a functional correlation with temperature as speeds of multiple photochemical reactions depend on air temperature. Therefore, air contamination can also be considered a heat effect mediator, and allowance for average daily levels of PM_{10}, NO_2, and ozone in the model (1) is a good practice (provided we have sufficient data on contamination).

Air pressure fluctuations also influence daily mortality [19]. If contamination is usually included into regression model as linear members (according to a hypothesis on non-threshold effects), then to describe air pres-

sure effects correctly, we need more flexible representation. Both high and low pressure, as well as drastic pressure fall statistically cause greater mortality. It is convenient to apply cubic splines to describe non-monotony dependences; such splines should have "natural" boundary conditions (the second variable at splining range boundaries is equal to zero).

Influence exerted by population number on validity of results. Difficulties in examining small samples. We examined influences exerted by temperature waves on mortality in 9 cities in Russia with different population number. Our research results can be applied to assess how probable it is to obtain statistically significant results in assessing risks caused by temperature waves at different values of λ (average daily mortality). The model which is described below should help other researchers to plan their examinations on small samples when there is a question: what minimal population number is required to obtain significant results in assessing risks caused by temperature waves? In this case we examine a binary significance sign at 95% level of regression coefficient β_{heat} in the model (1), therefore, it is only reasonable to assume there will be an increase (and not a fall) in additional mortality when a stress-factor occurs and to apply a one-sided *z*-test. Modeling a probability of obtaining or not obtaining a significant result depending on population number is quite similar to drawing up a demand curve in econometrics (whether a buyer agrees or doesn't' agree to buy a product depending on its price).

Initial data are taken from our own works accomplished according to comparable procedures in 9 cities and during comparable examination periods being equal to 10 years on average. In this research we calculated mortality risks during wave ensembles (for heat and cold separately) which lasted 5 and more days and which were identified in the examined period in this or that city. Data on daily mortality were obtained from the Federal State Statistic Service databases; data on air temperature and other meteorological variables were taken from the Rosgidromet web-site (http://cliware.meteo.ru/meteo/). Mortality risks caused by climatically dependent reasons should be more significant than for overall mortality. According to our experience, infarctions (coded I20-I25 as per ICD-10) and strokes (I60-I69) are the most climatically dependent death causes. For example, when there was extremely intense and long heat wave in Moscow from June 6 to August 18 2010, we estimated additional mortality due to all causes to be equal to 11,040 cases, 5,045 out of them were death cases caused by infarctions (46%), and 3,712, by strokes (34%) [14]. Therefore, cardio-vascular reasons accounted for up to 80% of all the additional mortality in Moscow during that period.

To obtain sufficient initial data to model how probable it was to obtain significant results in assessing heat and cold waves risks depending on λ, we calculated risks separately for "average" and "old" age groups: death cases at the age of 30-64, and death cases at the age older than 65. Such division into two different age groups is quite conventional in world practice as 65 years is an age when people retire in many countries, and, accordingly, age group of 30-64 comprises population who are able to work. Quantity of deaths among those younger than 30 is negligible. A lot of medical and statistical parameters are usually reported for these two groups separately in order to reveal any age-related discrepancies. Therefore, we examined four different mortality parameters in each city: death cases caused by infarctions and strokes separately in two age groups. We assumed that probability to obtain statistically significant results of risk assessment at a preset value of λ was approximately the same for these four parameters. Otherwise, we wouldn't be able to combine risk assessment results

for all four of them into one sample. This assumption holds in the case when the risks themselves for the examined mortality parameters are comparable. To verify validity of our assumptions, we included not only the binary variable (0 means risk is not significant, 1 means risk is significant) into the Table, but also estimates of relative increases in mortality during heat or cold waves. But by no means was the Table drawn up to compare absolute values of previously obtained risk assessments between cold and heat, or north and south.

Data sources are:

- for Arkhangelsk, Murmansk, Yakutsk, and Magadan, [8];
- for Volgograd, Rostov, Astrakhan, and Krasnodar, [6,7];
- for Krasnoyarsk, [5].

Results of assessing temperature waves risks in 9 cities

City*	Cause and age of death	λ	RR_{heat}	Significance (RR_{heat})	RR_{cold}	Significance (RR_{cold})
Arkhangelsk (350 thousand)	Infarction 30-64	1,4	0,94	0	1,18	1
	Infarction ≥65	2,1	0,93	0	1,22	1
	Stroke 30-64	0,62	1,01	0	1,13	0
	Stroke ≥65	2,5	1,30	1	1,19	1
Murmansk (325 thousand)	Infarction 30-64	1,7	1,03	0	1,18	1
	Infarction ≥65	1,7	0,76	0	1,09	0
	Stroke 30-64	0,65	0,88	0	1,07	0
	Stroke ≥65	1,7	1,25	1	1,14	0
Yakutsk (236 thousand)	Infarction 30-64	0,42	1,15	0	1,38	1
	Infarction ≥65	0,55	0,90	0	1,41	1
	Stroke 30-64	0,23	0,91	0	0,8	0
	Stroke ≥65	0,32	1,61	1	1,69	1
Magadan (100 thousand)	Infarction 30-64	0,31	1,44	0	1,01	0
	Infarction ≥65	0,31	1,23	0	1,39	1
	Stroke 30-64	0,19	1,57	0	1,37	0
	Stroke ≥65	0,25	1,23	0	1,66	1
Volgograd (989 thousand)	Infarction 30-64	3,5	1,25	1	1,12	1
	Infarction ≥65	7,6	1,39	1	1,10	1
	Stroke 30-64	1,5	1,36	1	1,29	1
	Stroke ≥65	10,7	1,55	1	1,08	1
Rostov (1053 thousand)	Infarction 30-64	2,1	1,20	1	1,16	1
	Infarction ≥65	7,0	1,39	1	1,12	1
	Stroke 30-64	1,4	1,51	1	1,23	1
	Stroke ≥65	9,7	1,75	1	1,15	1
Astrakhan (500 thousand)	Infarction 30-64	1,7	1,42	1	1,23	1
	Infarction ≥65	4,2	1,58	1	1,14	1
	Stroke 30-64	0,72	1,40	1	1,04	0
	Stroke ≥65	3,4	1,57	1	1,28	1
Krasnodar (710 thousand)	Infarction 30-64	1,4	1,24	1	1,14	0
	Infarction ≥65	5,6	1,37	1	1,17	1
	Stroke 30-64	0,93	1,50	1	1,33	1
	Stroke ≥65	6,4	1,76	1	1,08	1
Krasnoyarsk (932 thousand)	Infarction 30-64	2,2	1,10	0	1,17	1
	Infarction ≥65	5,3	1,14	1	1,04	0
	Stroke 30-64	0,96	1,19	0	1,24	1
	Stroke ≥65	4,6	1,44	1	1,11	1

Note: * – Population number is given in thousands in the middle of an examination period; λ is average mortality during an examination period, number of death cases a day; RRcold и RRheat are relative mortality risks during heat and cold waves; significance: 1 means risk is significant at 95% level; 0 means risk is not significant at 95% level.

These sources contain detailed description of Poisson models which were applied by the authors to assess risks.

Probability to obtain authentic risks assessment results at this value of λ is the most probable under the following condition: it is necessary to find such function $\pi(\lambda) \in \{0;1\}$, when

$$\mu = E(y|\lambda) = P(y = 1|\lambda) \equiv \pi(\lambda), \quad (2)$$

where λ is a predictor; E in an expected value; P is probability; $y \in \{0; 1\}$ is a binary sign or response. If we assume reasonable boundary conditions for such a task, than probability of event y_i=1 depending on λ_i is conventionally approximated with binary logistic regression:

$$\pi(\lambda) = \frac{exp(\beta_0 + \beta_1\lambda)}{1 + exp(\beta_0 + \beta_1\lambda)}, \quad (3)$$

where β_0 and β_1 are estimated values of regression coefficients which are calculated linear regression of reverse conversion:

$$\ln(\frac{\pi}{1-\pi}) = \beta_0 + \beta_1\lambda + \varepsilon. \quad (4)$$

Regression coefficient β0 characterizes probability of obtaining significant results of risk assessment when population number is equal to zero, and β1 is a marginal effect at various values of λ.

You can see triangles on Figures 1 and 2 which show initial data for taken regression from the Table; you can also see logistic curves which approximate probability $\pi(\lambda)$ within $0{,}1<\lambda<5$ range. A broken line shows a standard regression error $\mu\pm\sigma$. Regression was accomplished with *logistic* command in Stata 14.0 program.

In case of heat waves (Figure 1) both regression coefficients β_0 and β_1 are statistically significant: β_0=-1.91±0.82, p=0.020; β_1=1.32±0.54, p=0.014. Therefore, a logistic curve allows to predict at what values of λ we can expect to obtain authentic risk assessment. The condition μ>1/2 (significant result is more probable than insignificant one) holds at λ>1.5 (this result is valid for examination periods which are equal to about 10 years). But what is population number which λ≈1.5 corresponds to?

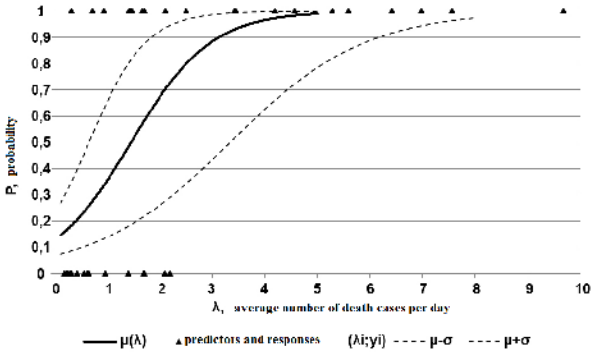

Figure 1. Probability of obtaining significant results in assessing heat waves risks

As we can see from the Table, stroke in the older age group prevails among four mortality parameters included into the model. Average daily mortality for this cause amounts to 40 cases per total population in 9 cities which is equal to 5.195 million. If we neglect a possible heterogeneity of ratios between mortality parameters in different climatic zones, we will see that 1.5 stroke cases a day correspond to the following population number: 5195×1,5/40=195 thousand people. This value is minimal population number which will allow us to obtain authentic heat wave risk assessment for at least one of the four selected mortality parameters.

In case of cold waves a logistic curve does not go lower than P=0.5 (Figure 2); therefore, we can't solve the task on minimal population number we are considering in the same manner which we described above. Most likely, it is due to a number of authentic cold waves risks assessment being overestimated in the sphere of small values of λ. Such overestimation can be caused by authors applying a great number of various lags (from one day to three weeks) in their search for the most proba-

ble lag between a cold wave and a response in mortality. Such searching for a lag makes a type II error more probable (that is, detection of discrepancies there where they don't actually exist). Selection procedure for heat waves is much stricter as only short lags with their duration being up to 5 days were included into the model

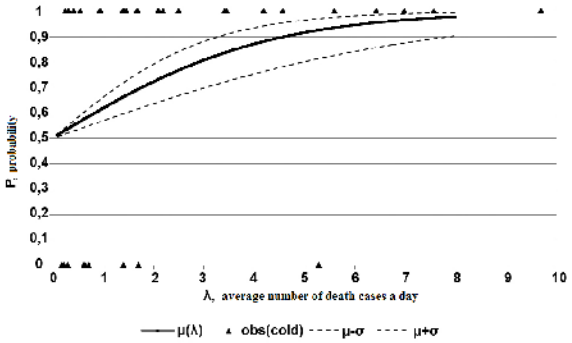

Figure 2. Probability of obtaining significant results in assessing cold waves risks

Conclusions. We recommend to apply percentiles of long-term distributions of average daily air temperatures as temperature thresholds for temperature waves identification. Such thresholds correspond to extreme temperature concepts (for this or that area) and give comparable results on expected number of waves in different climatic zones. Poisson's generalized linear model for daily mortality is the most widely spread technique applied to calculate risks caused by adverse environmental factors. We recommend to allow for an apparent dependence of mortality on time and air contamination in the regression model. One can allow for meteorological factors influencing heat balance (air humidity and wind speed) either by including them into the model explicitly or by bioclimatic indexes application; research in the sphere is going on at present. When calculating risks, it is necessary to allow for time lags between extreme temperatures waves and responses in mortality. When research is conducted in smaller cities and incorporates statistical data on daily mortality for periods equal to about 10 years, it is usually impossible to obtain authentic assessments of temperature waves risks when population is less than 200 thousand. In this work such a result was obtained for heat waves; however, it is most likely that it will be the case with cold waves as well.

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ASSESSMENT OF HEALTH RISK CAUSED BY PHTHALATES PENETRATING A BODY WITH MILK IN POLYMER AND POLYMER-CONTAINING PACKAGE

S.E. Zelenkin[1], P.Z. Shur[1], T.S. Ulanova[1], T.D. Karnazhitskaya[1], V.A. Khoroshavin[2], V.M. Ukhabov[3]

[1]Federal Scientific Center for Medical and Preventive Health Risk Management Technologies, 82 Monastyrskaya Str., Perm, 614045, Russian Federation
[2]Center for Hygiene and Epidemiology in Perm region, 50A Kuybyisheva Str., Perm, 614016, Russian Federation
[3]Perm State Medical University named after Academician E.A. Wagner, 26 Petropavlovskaya Str., Perm, 614000, Russian Federation

Since the middle of the 20th century phthalates have been widely used in food products package manufacturing. But here phthalates turned out to migrate from this package into the environment. There are some data on unfavorable impacts exerted by orally introduced phthalates on the liver and hormonal system.

Milk packed in polymer package which contains various plasticizers including phthalates is widely spread on the Russian consumer market. It determined our research goal which was to assess consumers health risks related to impacts exerted by phthalates introduced with milk packed in polymer package.

We selected 25 milk samples out of milk products bought in retail networks. Phthalates were quantitatively determined in milk via highly efficient liquid chromatography. We performed a distribution questioning to assess quantity and volumes in which milk was consumed and to determine a share of milk packed in polymer package. We detected that 57 % adult respondents, 75 % children aged 4–6, and 80 % children aged 7–17 consumed milk packed in polyethylene film and (or) in plastic bottles. 5 phthalate forms were identified in consumed milk. Adults actually consumed 0.6 liter of milk per day; children aged 4–6, 0.2 liter; children aged 7–17, 0.3 liter. Phthalates dose introduced daily with milk was equal to $5.61 \cdot 10^{-2}$ mg/kg of body weight for children aged 4–6; $6.32 \cdot 10^{-2}$ mg/kg of body weight for children aged 7–17; $4.20 \cdot 10^{-2}$ mg/kg of body weight for adults.

We calculated a lifelong risk and revealed that it occurred due to di-2-ethylexylphthalate when milk packed in polyethylene film and plastic bottles was consumed. Risk-characterizing hazard indexes reached 1.85 for the liver and endocrine system regardless of package.

Key words: *phthalates, milk, plasticizers, polymer package, package, dose, exposure, risk assessment, questioning.*

Sergei E. Zelenkin – laboratory worker (e-mail: zelenkin@fcrisk.ru; tel.: +7 (342) 238-33-37).

Pavel Z. Shur – Doctor of Medical Sciences, Professor, Academic Secretary (e-mail: shur@fcrisk.ru; tel.: +7 (342) 238-33-37).

Tatyana S. Ulanova – Doctor of Biological Sciences, Head of Department of Analytical Chemistry Analysis (e-mail:ulanova@fcrisk.ru; tel.: +7 (342) 233-10-37).

Tatyana D. Karnazhitskaya – Candidate of Biological sciences, Head of Liquid Chromatography Laboratory (e-mail: tdkarn@fcrisk.ru; tel.: +7 (342) 233-10-37).

Viktor A. Khoroshavin – Doctor of Medical Sciences, Chief Physician (e-mail: cgepo@mail.ru; tel.: +7 (342) 239-34-09).

Viktor M. Ukhabov – Doctor of Medical Sciences, Professor, head of Common Hygiene and Human Ecology Department (e-mail: rector@psma.ru; tel.: +7 (342) 235-11-35).

Phthalates (phthalic acid ethers) were first synthesized in 1920s. In 1930s manufacturers started to actively apply them to produce plastics as phthalates made these materials more durable and flexible. Since 1950s phthalates have been widely used in many industries, not only as plasticizers, but also as additives into cosmetics, food products, etc. [1].

Influence exerted by phthalates on consumers' health has been concurrently examined. There are data on contribution made by phthalates into oxidative stress evolvement, disorders in substances transport and gall excretion [2], malignant neoplasms in the liver [3] and the pancreas [4] in rats. Some research performed in various countries over the last few decades contain data on a determined direct correlation between phthalates occurrence in a body and reproductive disorders [5–7], or evidence that disorders in fetus' gonads development are quite possible [8]. A reverse correlation has been established between mono-n-butyl phthalate (MBP) contents in urine and free thyroxin (FT4) level and thyroxin (T4) level, and an assumption has been made that di-n-butyl phthalate (DBP) can violate thyroid gland activity in pregnant women [9]. The obtained data allowed to consider phthalates to be endocrine disruptors, or substances which can disrupt hormones' normal functioning.

By the end of 2014 the following phthalates were most widely spread in the industry worldwide: di-butyl-phthalate (DBP), butylbenzyl phthalate (BBP), di-2-ethylhexyl phthalate (DEHP), diisononyl phthalate (DINP), diisodexyl phthalate (DIDP), dioctyl phthalate (DOP), diethyl phthalate (DEP), dimethyl phthalate (DMP). DEP, DMP, DBP, BBP, and DEHP are the most dangerous among them; these phthalates are assigned into short-chain phthalates group according to REACH (Registration, Evaluation, Authorization and Restriction of Chemical substances) classification which is a part of the EU legislation; short-chain phthalates are considered to be the most hazardous for human health [10].

Phthalates are not bound to polymers molecules in plastics structures. They can migrate into the environment under external factors influence or regardless of it. It is the most interesting research task to analyze phthalates migration out of polymer package into food products. Polymer package is a basic source of phthalates introduction into a human body [11–13].

The Customs Union Technical Regulation 005/2011 "On package safety" sets forth maximum specific migration limit (SML) for phthalates in the Russian Federation and the Eurasian Economic Union member countries. According to this document, SML is fixed only for dioctyl phthalate and is equal to 2 mg/l. Dibutyl phthalate migration and, consequently, occurrence is not permissible at all (sensitivity limit is not fixed)[1]. And there are no existing standards for other phthalates.

As milk is usually kept and sold in polymer package (polyethylene film, plastic and polypropylene bottles), it is interesting to examine phthalates concentrations in milk as well as health risk caused by consuming milk with phthalates. Phthalates dose here depends both on the level of their migration into a product, and on milk consumption volumes.

Figures obtained in the Russian Feder-

[1] TR 005/2011. On package safety: The Customs Union Technical Regulation 005/2011. Available at: http://www.eurotest.ru/upload/iblock/6c9/6c977dbc8c9f2fc095035f49b52985f1.pdf (15.11.2017).

ation in 2013 showed that about 65% men and 75% women aged 14 and older, as well as about 80% children aged 3-13 consumed milk and dairy products daily or several times a week. Annual average milk and dairy product consumption amounted to 305.4 kg for men (14 and older); women, 276.5 kg; children aged 3-13, 296.9 kg. As for Perm region, about 70% men and 75% women aged 14 and older, as well as about 85% children aged 3-13 consumed milk and dairy products daily or several times a week. Average annual milk and dairy products consumption amounted to 278.5 kg for men and 249 kg for women [13]. According to the RF Public Healthcare Ministry recommendations, daily milk and dairy products consumption should amount to 352 kg per capita annually, and milk consumption should be equal to 50 kg per year which corresponds to a daily standard being equal to 180 ml[2]. Perm region is at the 37th place among all the Russian regions in terms of milk and dairy products consumption per capita.

People most frequently consume milk which is sold in polymer package; it is either polymer film made of low density polyethylene (LDPE); or bottles made of polyethylene terephthalate (PET) and polypropylene (PP). All the above mentioned materials contain various plasticizers to some extent, including phthalates as well [14, 15].

Our research goal was to assess health risk related to impacts exerted by phthalates which entered a consumer's body with milk kept in polymer package. Our research tasks included determination of phthalates concentrations in milk and risk and exposure assessment.

Data and methods. To perform our research, we selected 24 milk samples with fat content being equal to 2.5-3.2%; milk was kept in polymer package (19 samples were in polyethylene film, 5 were in PET bottles). We analyzed such plasticizers in milk as dimethyl phthalate (DMP), dibutyl phthalate (DBP), di -ethylhexyl phthalate (DEHP), and butylbenzyl phthalate (BBP) via high performance liquid chromatography on Agilent 1200 liquid chromatograph with a diode matrix detector in conformity with Methodical guidelines[3]. We extracted phthalates from milk with solid-phase extraction technique.

Exposure was assessed allowing for consumption of milk with the maximum calculated phthalates concentration in it. Phthalates doses which entered consumers' bodies were calculated as per Guide P 2.2.1.10.1920-04 [16]. Our calculation was based on standard values for exposure duration and averaging time for non-carcinogenic substances at oral introduction.

Lifelong average daily phthalates dose introduced with milk kept in polymer package was calculated for each detected phthalate as per the following formula:

$$\text{LADD} = \frac{(EDb \cdot ADDchb) + (EDc \cdot ADDchc) + (EDf \cdot ADDcha)}{AT},$$

[2] On approval of recommendations on rational food products consumption standards meeting contemporary healthy nutrition requirements: The Order issued by the RF Public Healthcare Ministry on August 19, 2016 N 614. Available at: http://www.garant.ru/hotlaw/federal/898204/ (15.11. 2017).

[3] MG 4.1.3160-14. Measuring phthalates mass concentrations (dimethyl phthalate, diethyl phthalate, dibutyl phthalate, benzylbutyl ohthalate, and di-ethylhexyl phthalate) in milk with high performance liquid chromatography: Methodical guidelines. Available at: http://files.stroyinf.ru/Data2/1/4293761/4293761690.htm (22.11.2017)

were *LADD* is lifelong average daily dose, mg/(kg day);

EDb is exposure duration for babies (aged 0 - <6 years);

EDc is exposure duration for children (aged 6 - <18 years);

EDa is exposure duration for adults (aged 18 and older);

ADDChb is chronic average daily dose for babies, mg/kg a day;

ADDChc is chronic average daily dose for children, mg/kg a day;

ADDCha is chronic average daily dose for adults, mg/kg a day;

AT is averaging time, number of years.

Results and discussion. At hazard identification stage we determined which organs and systems were critical for phthalates: they were the liver, the pancreas, the endocrine system, and also the overall systemic effects were detected.

When we assessed "exposure - effect" relationship, we determined reference doses at phthalates oral introduction. Thus, according to R 2.1.10.1920-04 "Guidelines on assessment of population health risk under exposure to chemicals which pollute environment" existing in the RF, reference dose under chronic oral introduction is fixed at 0.2 mg/kg of body weight for BBP (target organs are the liver and the pancreas); for DEHP, at 0.02 mg/kg of body weight (target organs are the liver and the endocrine system); for DBP, at 0.1 mg/kg of body weight (systemic effects): for DMP, at 10 mg/kg of body weight (the target organs are the kidneys); for DEP, at 0.8 mg/kg of body weight (systemic effect) [16].

As we assessed exposure, we detected that 58% milk samples in polyethylene film, and 40% milk samples in PET bottles contained phthalates (Table 1). DEHP made the greatest contribution into the total phthalates concentrations in milk in polyethylene film (70%), and DBP, in milk in PET bottles (65%).

At this stage we detected maximum phthalates doses for each group which entered consumers' bodies with milk in polymer package (Table 2). We allowed for body weight of people from the examined groups in our calculations.

According to the questioning results 75% children aged 4-6 consumed milk. Their parents bought milk only in polyethylene film. Children daily consumed 0.1-0.2 l of milk.

We revealed that 80% examined school children aged 7-17 consumed milk. Their parents bought milk in polyethylene film (in 68% cases), in PET bottles (in 16% cases), or in both packages by turns (in 16% cases). Daily milk consumption in this group amounted to 0-0.3 l. 57% of all the questioned adults consumed milk and they all chose milk in polyethylene film. Adults daily consumed about 0.1-0.6 l of milk.

As we calculated lifelong daily dose of phthalates, we determined that its value was maximum for people who consumed milk in PET bottles (Table 3).

Table 1

Maximum concentrations of basic phthalates in milk samples in different polymer package, mg/l

Package	Phthalates concentration in milk, mg/l				
	DMP	DEP	DBP	BBP	DEHP
LDPE	0,161	0,25	1,686	0,072	3,709
PET bottle	ltdl (<0,1)	нпо (<0,2)	29,808	нпо (<0,2)	12,537

Note: * – ldl means lower than detection limit

Table 2

Maximum phthalates doses which enter a body with milk in polymer package for different groups (mg/kg of body weight per day)

Group	Maximum daily milk consumption, l	Substance	Package type	Dose
Children aged 4-6	0,2	DMP	Polyethylene film	$2{,}44 \cdot 10^{-3}$
		DBP		$2{,}55 \cdot 10^{-2}$
		BBP		$1{,}06 \cdot 10^{-3}$
		DEHP		$5{,}61 \cdot 10^{-2}$
		DEP		$3{,}78 \cdot 10^{-3}$
Children aged 7-17	0,3	DMP	Polyethylene film	$1{,}43 \cdot 10^{-3}$
		DBP		$1{,}49 \cdot 10^{-2}$
		BBP		$6{,}21 \cdot 10^{-4}$
		DEHP		$3{,}29 \cdot 10^{-2}$
		DEP		$2{,}22 \cdot 10^{-3}$
		DMP	PET bottle	0
		DBP		$1{,}50 \cdot 10^{-1}$
		BBP		0
		DEHP		$6{,}32 \cdot 10^{-2}$
		DEP		0
Adults	0,6	DMP	Polyethylene film	$1{,}82 \cdot 10^{-3}$
		DBP		$2{,}83 \cdot 10^{-3}$
		BBP		$1{,}19 \cdot 10^{-2}$
		DEHP		$8{,}15 \cdot 10^{-4}$
		DEP		$4{,}20 \cdot 10^{-2}$

Table 3

Results of lifelong daily phthalates dose calculation for different package, mg/kg of body weight a day

Substance	Package	
	Film	PET
DMP	$1{,}79 \cdot 10^{-3}$	$1{,}22 \cdot 10^{-3}$
DBP	$1{,}22 \cdot 10^{-2}$	$6{,}63 \cdot 10^{-2}$
BBP	$5{,}24 \cdot 10^{-3}$	$4{,}99 \cdot 10^{-3}$
DEHP	$2{,}47 \cdot 10^{-2}$	$3{,}68 \cdot 10^{-2}$
DEP	$1{,}84 \cdot 10^{-2}$	$1{,}76 \cdot 10^{-2}$

Table 4

Lifelong risk which occurs milk in polymer package is consumed: assessment results

Substance	Hazardous index (HI)			
	The liver		The endocrine system	
	Film	PET	Film	PET
BBP	0,03	0,02	Is not a critical system	
DBP	Is not a critical organ		0,12	0,66
DEHP	1,24*	1,84*	1,24*	1,84*

Note: * – means risk is unacceptable

In this case DBP makes the greatest contribution into this dose. As for people who consume milk in polyethylene film their dose is formed mostly due to DEHP.

At the stage when risk was characterized we detected that consumption of milk in polymer package caused unacceptable lifelong risk of hazardous effects evolvement (HI up to 1.84) in the liver and the endocrine system (Table 4). DEHP makes the greatest contribution into this risk regardless of milk package.

So, we detected that when milk in polymer and polymer-containing package is consumed, it can cause unacceptable lifelong risk which occurs due to phthalates content in milk.

Conclusions. Overall, the obtained results allowed us to reveal that:

– dimethyl phthalate (DMP), dibutyl phthalate (DBP), di-ethylhexyl phthalate (DEHP), and butylbenzyl phthalate (BBP)

occur in milk in polymer package. Phthalates were detected in 40% samples in PET bottles and in 70% samples in polyethylene film;

– 57% adults, 75% children aged 4-6, and 80% children aged 7-17 of all the respondents consume milk in polyethylene film and (or) PET bottles;

– actual daily milk consumption amounts to 0.1 to 0.6 l for adults; 0.1–0.2 l, for children aged 4-6; 0.1–0.3 l, for children aged 7–17;

– phthalates doses entering a body with milk amount to $5.61*10^{-2}$ mg/kg of body weight for children aged 4-6; $6.32*10^{-2}$ mg/kg of body weight for children aged 7-17; $4.20*10^{-2}$ mg/kg of body weight for adults;

– lifelong risk calculation allowed to reveal that risk occurred due to DBP when milk in polyethylene film and PET bottles was consumed. Risk-characterizing hazardous indexes reach 1.84 for the liver and the endocrine system regardless of package.

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INFLUENCE EXERTED BY NATURAL-CLIMATIC CONDITIONS ON AIR QUALITY ON AREAS WHERE OPEN-AIR SPORT FACILITIES ARE LOCATED (ON THE EXAMPLE OF KAZAN)

N.Kh. Davletova[1], E.A. Tafeeva[2]

[1]Povolzhskaya State Academy for Physical Culture, Sport and Tourism, 35 Universiada Viollage, Kazan', 420010, Russian Federation
[2]Kazan State Medical University, 49 Butlerova Str., Kazan', 420012, Russian Federation

Atmospheric air contamination holds the first place among priority factors which determine environmental risks for sportsmen's health at open-air sport facilities. Training processes especially those aimed at aerobic endurance development and improvement are inefficient under ecologically unfavorable conditions. Our research goal was to assess atmospheric air quality on territories where open-air sport facilities were located in Kazan. Our initial materials were data on contaminants emissions on Kazan territory, results of instrumental research on air quality, data taken from state Reports on natural resources and environmental protection issued in Tatarstan in 2006–2016.

We examined impacts exerted by meteorological conditions on dispersion and accumulation of emissions from stationary sources and automobile transport in close proximity to open-air sport facilities. We charted all the open-air sport facilities and enterprises and assessed mutual influences by various city districts on each other depending on prevailing winds which determined contaminants transfer from place to place. Our analysis on winds repeatability from May to September over 2006–2016 revealed that North-West wind prevailed in July, and West wind, in May, June, August, and September. Conditions which were favorable for contaminants dispersion were observed only in 30.9 % of months over the examined period; partially favorable or even unfavorable ones occurred in 69.1 % of time. So, natural-climatic conditions existing in Kazan create specific qualitative composition of city air and contaminants are present in atmospheric air above open-air sport facilities in concentrations exceeding maximum permissible ones. It causes potential risks for sportsmen' s health. The obtained data give grounds for air monitoring planning at periods when sport events take place; for organizing work at priority enterprises when meteorological conditions are unfavorable; they can also be applied when changes are made into architectural and design plans for the city territory including transport routes development; or when activities aimed at environment protection are developed and implemented.

Key words: *atmospheric air, contamination sources, natural climatic conditions, contaminants, open-air sport facilities, sportsmen's health.*

Atmospheric air contamination holds the leading place among priority factors causing environmental health risks for sportsmen at open-air sport facilities [1–4]. Breathing speed of a sportsman under maximum loads during 20-30 minutes can reach 100-120 breaths per minute [5]. Such an increase in ventilation is provided by greater breathing frequency and volume, and here frequency can rise to 60-70 breaths per minute, and breathing volume, from 15 to 50% of the lung vital capacity. As per data taken from various research, training process efficiency under unfavorable environmental conditions is very low. It is especially true in case of a training

Nailya Kh. Davletova – Candidate of Medical Sciences, Associate Professor at Medical-biological Subjects Department (e-mail: davletova0681@mail.ru; tel.: +7 (843) 294-90-86).

Elena A. Tafeeva – Doctor of Medical Sciences, Associate Professor at Hygiene and Occupational Medicine Department (e-mail: tafeeva@mail.ru; tel.: +7 (843) 236-97-02).

process which is aimed at "aerobic endurance" developing and improving. Unfavorable ecologic conditions don't exert such a drastic impact on training speed and strength physical qualities related to "anaerobic endurance". It is caused by the fact that aerobic capabilities which have been developed in a highly qualified sportsman are a specific reserve for their own self-recovery [6–8].

Industrial enterprises (stationary) and motor transport (moving) are basic sources causing atmospheric air contamination above open-air sport facilities in a big city [9]. A peculiarity of stationary air sources is that contaminants emitted by them can be distributed over large territories due to emissions mostly occurring at big heights. Moving air contamination sources have their own peculiarities, namely, they are located at the surface (at breathing zone level), they are distributed over territories with boundaries which are hard to define, and they constantly move from place to place.

Kazan, Tatarstan capital city, is a large industrial center. A lot of open-air facilities are located on its territory. Given the fact, that training and competitions first of all involve more frequent breathing, we can assume that contaminants enter a sportsman's body with the atmospheric air in quantities which are always greater than in case of any average statistical person living near an open-air sport facility. Therefore, an issue of air contamination above open-air sport facilities becomes truly vital for Kazan.

Our research goal was to assess atmospheric air quality on territories where open-air sport facilities were located.

Data and methods. We based our analysis of atmospheric air quality in a district where an open-air sport facility was located on data on total contaminants emissions; these data were obtained from reports on air quality, social-hygienic monitoring system, State reports on natural resources and environmental protection issued in Tatarstan in 2006–2016.

We examined influence exerted by meteorological conditions on dispersion and accumulation of emissions from stationary sources and motor transport as per data taken from the Kazan city official weather archive [10, 11]. In particular, we analyzed data on the following values and phenomena: wind speed and direction, temperature inversions and fogs, precipitation during periods from May to September 2006-2016. Applying the above mentioned data, we built wind roses and calculated meteorological coefficient for air self-cleaning. This coefficient was calculated as per a conventional procedure developed by T.S. Selega [12].

Results and discussion. Air contamination above an open-air facility in a large city depends on stationary sources locations, emissions from motor transport, contaminants distribution (movement) around a city (district) area, as well as on natural-climatic conditions.

Along with admixtures concentrations in the air which are always present near specific objects, background air contamination also occurs in a city; it happens due to mutual overlap and mixing of emissions from many sources. In relation to that high toxicants concentrations in the air can occur even on territories which are not directly influenced by specific objects. Background air contamination caused by meteorological conditions can be observed above the whole city during a day; when emissions from enterprises are constant, it can enhance or weaken under weather conditions influence [13, 14].

16 large open-air sport facilities are located in Kazan: 5 objects in Vakhitovsliy

district; 5, in Privolzhskiy district; 2, in Novo-Savinovskiy district; 2, in Sovetskiy district; 1, in Moskovskiy district; 1, in Aviastroitelniy district. large indutrial enterprises which are stationary air contamination sources are also located in the same districts (Figure 1).

Motor transport makes the greatest contribution into contamination of air above open-air sport facilities in Kazan, its share on average being equal to 70%; other contamination sources are such enterprises as Kazanorhsyntes PLC, Heating plant 1, Heating plant 2, Heating plant 3, Kazenergo, and Kazan reinforced concrete structures plant LLC. Annually about 80.2 thousand tons of contaminants are emitted into air in Kazan by motor transport, and about 30.6 thousand tons, from stationary sources. Contaminants emissions dynamics comprising substances being emitted into the atmosphere in Kazan both from stationary sources and motor transport is shown on Figure 2.

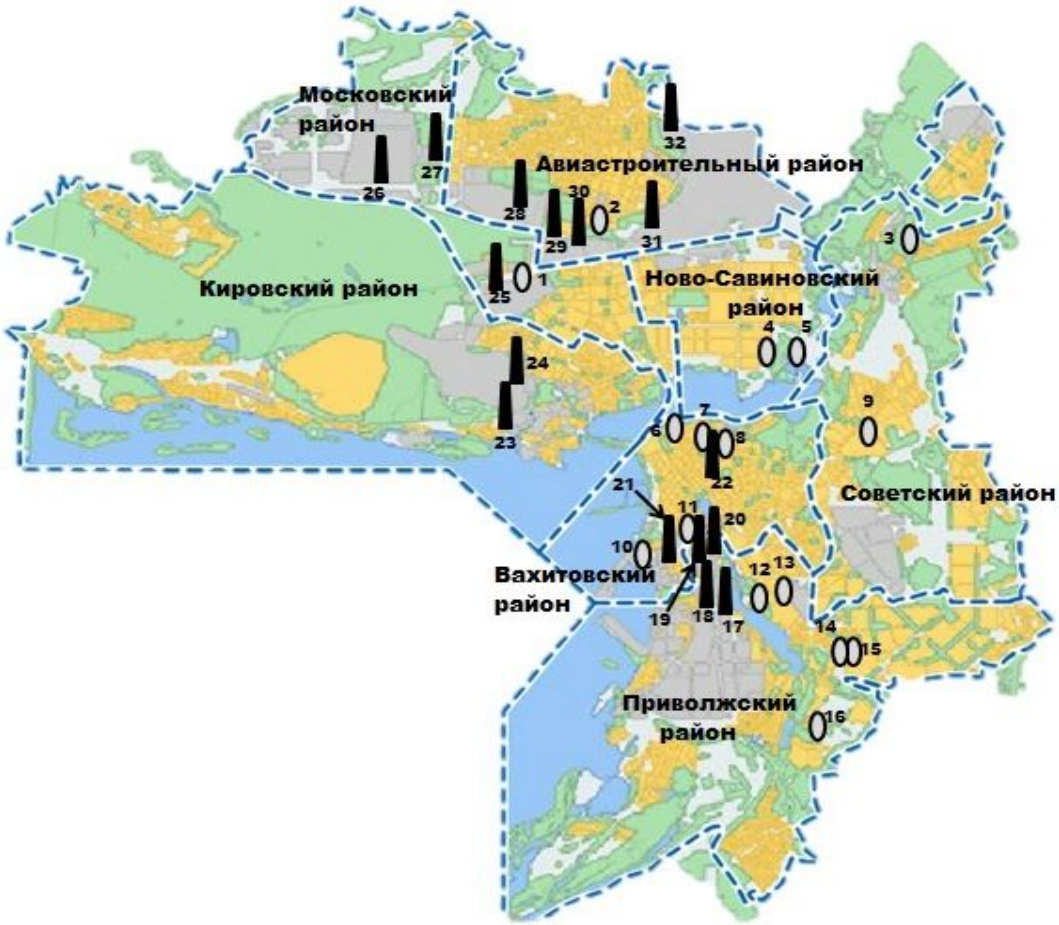

Figure 1. Open-air sport facilities and industrial enterprises location in Kazan

1 is "Tasma" stadium, 2 is "Rubin" stadium, 3 is "Raketa" stadium, 4 is a football stadium at "Olymp" sport complex, 5 is "Kazan-Arena" stadium, 6 is "Centralniy stadium", 7 is "Dinamo" stadium, 8 is "Trudovye reservi" stadium, 9 is "Miras" stadium, 10 is "Vodnik" stadium, 11 is "Electron" stadium, 12 is Rowing center, 13 is "Field hockey center" stadium, 14 are open tennis courts at Tennis Academy, 15 is 'Burevestnik" stadium, 16 is a stadium at s"Tulpar" sport complex, 17 is Heating plant 1, 18 is Kazan medical-instrumental plant, 19 is "Tochmach" Kazan plant, 20 is "Nephis Cosmetics" PLC, 21 is Kazenergo, 22 "Kazan plant Electropribor" PLC, 23 is "Santechpribor" PLC, 24 is State Gunpowder Plant, 25 is Chimgrad, 26 is Heating plant 3, 27 is "Kazanorgsyntes" PLC, 28 is Kazan helicopter plant, 29 is Heating plant 2, 30 is Kazan silicate building panels plant, LLC, 31 is Kazan reinforced concrete structures plant, 32 is Kazan aviation plant.

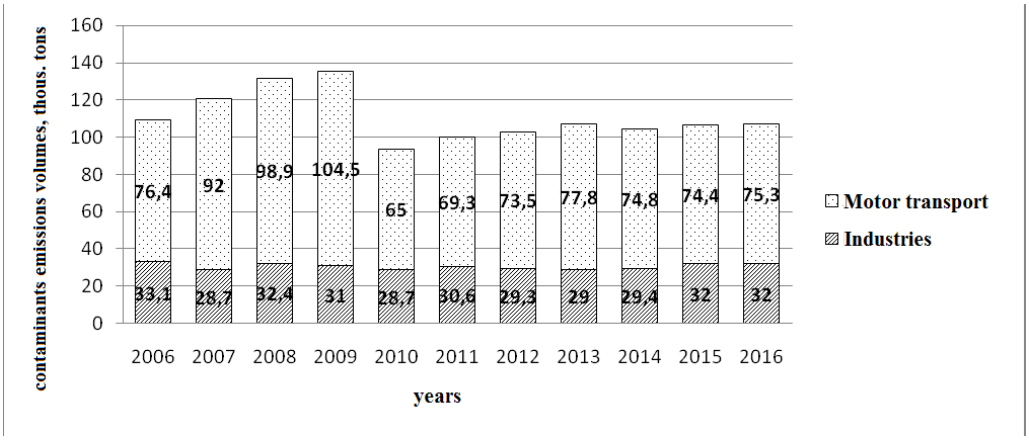

Figure 2. Dynamics of contaminants emissions into the atmosphere in Kazan over 2006–2016.

Gaseous and volatile organic substances, nitrogen oxides, carbon oxide, hydrocarbons, and suspended substances, are basic contaminants which pollute the atmospheric air. At each period from May to September, 2006-2016, on average 695 cases when pollutants concentrations exceeded maximum permissible levels were registered in Kazan, 108 of them being related to suspended substances; 72, to carbon oxide; 244, to nitrogen dioxide; and 113, to formaldehyde.

The detected excesses cause risks for sportsmen's health. Registered air quality allows us to predict unfavorable impacts on respiratory organs, eyes mucous tunics, as well as specific immune disorders (including allergic reactions evolvement). The highest risks occur for respiratory organs, and it is vital, first of all, for sportsmen who participate in competitions being held at open-air sport facilities in the city. Maximum hazard index (HI) related to respiratory organs is predicted to be equal to 32.8 on Kopyilova street in a zone where a sport complex is located which is 30 times higher than the permissible level. Risk for respiratory organs higher than 10 HI is predicted in a zone close to "Rubin" stadium. 6-7 HI which can be estimated as high risks can occur under certain conditions in a zone where "Electron" stadium is located.

The detected risks of acute inhalation impacts are caused by a set of admixtures, however, basic contributions are made by not more than 10 priority admixtures out of 280 examined at an exposure assessment stage.

We determined that risks for respiratory organs is primarily caused by the following substances: nitrogen oxides, sodium hydroxide, sulfur anhydride, and dusts, including fine-dispersed ones. Contribution made by nitrogen dioxide into hazard indexes varies from 12.9% to 62.3% in different locations; nitrogen oxide, from 1.4% to 12.4%; dusts mixture, from 8% to 73.7%; sodium hydroxide, from 2.65% to 26.9%; sulfur dioxide, from 3.6% to 20.7%; ammonia, from 0.38% to 6.9%; nitric acid, from 0.59% to 19.6%. Totally these contaminants cause from 84% to 97% acute inhalation impacts risks for respiratory organs in various city districts. Other admixtures contribution doesn't exceed 1%. Share contributions made by priority admixtures change depending on a sport object location; however, priority contaminants remain the same.

Natural-climatic conditions exert substantial influence on hazardous substances accumulation in the atmosphere. Such factors as weak winds, surface inversions, and calm weather, are well-known to greatly influence hazardous substances distribution in the atmosphere thus determining its capability to clean itself [2, 15]. A ratio of repeatability of conditions making for admixtures accumulation (weak winds and fogs) to repeatability of conditions which, in their turn, make for admixtures elimination (strong wings and precipitations) is called air self-cleaning coefficient [16].

In our research we calculated air self-cleaning coefficient during a period from May to September, 2006-2016, and detected that the air in the city has partially favorable capability to clean itself from May to August (C`m= 0.96–1.14), and favorable conditions for admixtures dispersion were detected in September (C`m=1,27). Long-term average air self-cleaning coefficient values indicate that partially favorable conditions for admixtures dispersion prevail from May to September (Figure 3).

According to our analysis, favorable conditions for contaminants dispersion were observed only in 30.9% months over the examined period; in 69.1%, conditions were partially favorable or even unfavorable. Weak winds (0–1 m/sec) repeatability makes the greatest contribution into occurrence of unfavorable conditions for air self-cleaning. On average, mild winds (less than 4 m/sec) or even calm weather is observed on 27-30% days in Kazan [12]. Admixtures accumulation in the atmosphere enhances in case of fog. A number of foggy days varied from 8 to 29 per year on average, and a number of days when conditions for contaminants dispersion were unfavorable, from 58 to 128 per year (Table 1).

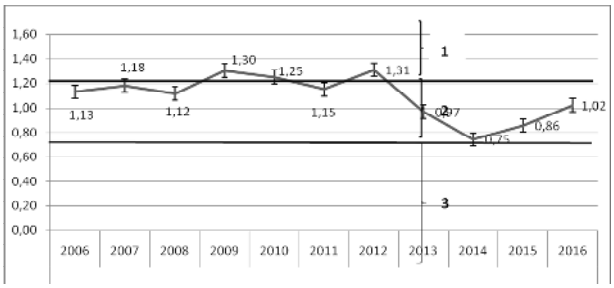

Figure 3. Air self-cleaning coefficient variability over 2006–2016 in Kazan:
1 – C'm >1,2 means favorable conditions for air self-cleaning; *2* – 0.8<C'm < 1,2 means partially favorable conditions for dispersion; *3* – C'm < 0,8 – unfavorable conditions for dispersion

Wind direction also plays a considerable role in contaminants transfer in the atmosphere surface layers. We analyzed winds repeatability from May to September, 2006-2016 and detected that northwest winds prevail in July, and west winds, in May, June, August, and September (Figure 4).

Table 2 contains data on mutual influences exerted by air flows in various Kazan districts depending on wind direction.

Table 1

Number of days when meteorological conditions were unfavorable for admixtures dispersion in the atmosphere and foggy days in Kazan over 2006–2016

Number of days	Years										
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Unfavorable for hazardous substances dispersion	71	127	129	99	81	58	114	97	118	122	90
Foggy	24	29	8	12	12	15	12	17	19	14	16

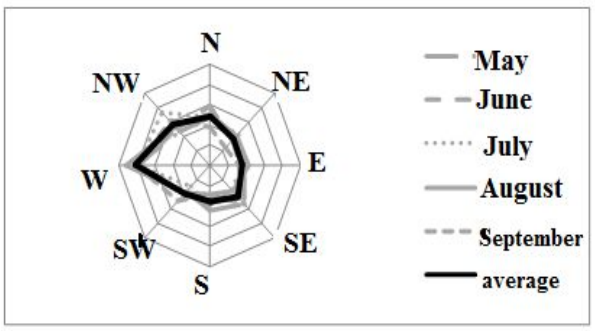

Figure 4. Wind rose in Kazan from May to September, 2006–2016

As we can see from Table 2, contaminants can be transferred from Aviastroitelniy, Bakhitovskiy, Moskovskiy, Kirovskiy, and Privolzhskiy districts territory when north-west and west winds prevail. West winds repeatability from May to September amounted to 24.6%, and north-west winds, 16.6%. When winds blew in other directions relative to industrial enterprises and sport objects locations, contaminants were detected in the air above open-air sport facilities..

Conclusions. So, natural-climatic properties in Kazan are responsible for peculiar chemical structure of the atmospheric air in the city. The atmosphere above sport objects is polluted due to contamination sources which are located in the same administrative districts as open-air sport facilities and also due to contaminants transfer from the neighboring districts. Our analysis proves it is necessary to perform further examinations of environmental quality on areas where sport objects are located in a large industrial center. Besides, all the accumulated data should be applied in:

– planning air monitoring during periods when sport events are held;

– organizing work of priority enterprises during periods when meteorological conditions are unfavorable in order to minimize health risks for mass sport events participants and guests;

– making changes into architectural and design plans on the city territory including transport routes development;

– further development and implementation of environmental protection measures at industrial enterprises in the city as Kazan strives to provide healthy life-style for its population and hopes to welcome both Russian and international sport events on its territory.

Table 2

Mutual influences exerted by Kazan districts on each other depending on wind directions

Contaminated districts	Contaminating disricts				
	Aviastroitelniy	Vakhitovskiy	Moskovskiy	Kirovskiy	Privolzhskiy
Aviastroitelniy	N, NE, E, ES, S, SW, **W***,**NW**	SE, S	S, SW, **W**	SE, S, SW	S, SW
Vakhitovskiy	N, NE, **NW**	N, NE, E, SE, S, SW, **W, NW**	S	S, **NW**	SE, S, SW
Sovetskiy	**NW**	SW, **W, NW**	**W, NW**	SW, **W**	SE, S, SW
Novo-Savinovskiy	N, NE, **NW**	SE, S, SW	**W, NW**	SW, **W, NW**	SE, S, SW
Moskovskiy	E, SE	NE, E, SE	N, NE, E, SE, S, SW, **W, NW**	SE, S, SW	SE, S
Kirovskiy	N, NE, E	E, SE	N, SE, E, **NW**	N, NE, E, SE, S, SW, **W, NW**	SE, S
Privolzhskiy	N, **NW**	N, NE, **NW**	N, **NW**	N, **NW**	N, NE, E, SE, S, SW, **N, NW**

Note: * means wind directions prevailing in Kazan from May to September; ▭ means winds, which carry potentially contaminated air masses.

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CONSEQUENCES WHICH MOTHERS' IRRASIATION HAS: RISKS OF CHILDREN'S CONGENITAL MALFORMATIONS

S.F. Sosnina, P.V. Okatenko

Southern Urals Biophysics Institute of Federal Medical-Biological Agency, 19 Ozerskoe shosse, Ozersk, 456780, Russian Federation

It is vital to examine radiation-induced effects in children whose parents were exposed to radiation at their workplaces as it allows to work out standards for technogenic irradiation doses permissible for people in their reproductive age. It also helps to predict adverse consequences of parents being exposed to radiation for their children. Our goal was to analyze congenital malformations (CM) in children whose mothers were employed at "Mayak" Production Association (Mayak PA) and had accumulated pre-conception external gamma-radiation doses. Retrospective examination was performed on 1,190 people born in 1949–1969, 238 of them being children of female workers employed at radiation-hazardous production. We achieved maximum comparability of groups made of children population living in Ozersk in terms of age, birth year, and parents' age at a childbirth, via careful sampling. CM frequency was compared with χ^2 criterion, Fisher's exact criterion. We calculated odds relations (OR) with 95% confidence interval. To detect any latent factors, we applied factor analysis via principal components method with consequent Varimax normalized rotation. Gonads in female workers employed at Mayak PA were exposed to external gamma-radiation doses within 0.09–3523.7 mGy range; average accumulated dose was equal to 373.6 ± 34.2 mGy. Each tenth child in a group of children born by irradiated mothers was born by a mother who had an accumulated pre-conception external gamma-radiation dose on her gonads which was higher than 1 Gy. CM comparative analysis revealed that there were no statistically significant differences between groups in terms of CM frequency in general and as per various nosologic forms. OR in general was equal to 0.86 (0.46–1.59); 0.88 (0.35–2.2) among boys; 0,84 (0.36–1.94) among girls. We also detected difference in CM structure: CM of the nervous system, respiratory organs (23 % each), and the musculoskeletal system CM (15.3 % among all the malformations) prevailed among all the CM in children born by irradiated mothers; CM of the musculoskeletal system (23.3 %) and the nervous system (21.7 %) were most widely spread among children born by intact parents. We also noted there were gender discrepancies in the CM structure in the compared groups. We didn't register any chromosome pathologies in both groups. CM were diagnosed in those children born by those irradiated mothers whose gonads were exposed to accumulated pre-conception external gamma-radiation doses within 1.9–1635.5 mGy, with average dose being equal to 307.5 mGy. Factor analysis performed on children born by female workers employed at atomic production revealed four factors which characterized pre-concepption mothers' irradiation (21.5 % dispersion), antenatal children's period (17.1 % dispersion), obstetrician-gynecological case history (12.9 % dispersion), and mothers' bad habits, namely alcohol intake and smoking (11 %) dispersion). Given all the detected peculiarities, it is highly advisory to continue research on larger children's groups and longer observations periods.

Key words: *congenital malformations, children, radiation exposure, pre-conception irradiation, reproductive age, odds relation, factor analysis.*

Svetlana F. Sosnina – Candidate of Medical Sciences, Researcher at Radiation Epidemiology Laboratory (e-mail: sosnina@subi.su; tel.: +7 (351) 307-66-27).

Pavel V. Okatenko – Head of Computer and Software Support Group, Radiation Epidemiology Laboratory (e-mail: okatenko@subi.su; tel.: +7 (351) 307-69-03).

Long-term industrial irradiation has its remote effects on workers' health; to assess them is a vital task both in terms of providing radiation safety for people in their reproductive age and predicting unfavorable consequences for their offspring. A lot of authors stated in their works that cytogenetic effects and genomic instability could possibly be transferred to offspring across the generations [1, 2]. But at the same time some authors don't find any correlations between irradiation of gonads and genetic diseases occurrence in offspring [3]; they even think that trans-generation effects are not very likely to be detected in any actual epidemiologic situation [4]. Epidemiologic research which focused on parents irradiation as a potential teratogenic risk factor was conducted among offspring of those who had suffered atomic bombing [5, 6]; among children whose parents underwent diagnostic and curative exposure to radiation [7, 8]; offspring of professionals who had contacted ionizing radiation [9–12]. In spite of great number of research works in the field, radiation-induced effects in offspring of irradiated parents are still being widely discussed.

"Mayak" Production Association (Mayak PA) is the first nuclear cycle enterprise in our country which started its operations in 1948; it is located near a closed town called Ozersk. Personnel cohort employed at Mayak PA has a very distinctive peculiarity: women account for approximately 25% of all the production staff, and it is a relatively big share as opposed to any other atomic production in Russia [13]. This peculiarity allows to consider offspring of female workers employed at Mayak PA to be quite representative in terms of assessing consequences which mothers' irradiation has for their children' bodies.

Our research goal was to analyze congenital malformations (CM) in children born by female workers employed at Mayak PA who had accumulated preconception doses of external gamma-irradiation.

Data and methods. We performed our retrospect research basing on the data obtained from the Ozersk Children's Health Register, a computer database which contains personal medical data (clinical, social and epidemiological ones) taken from children's outpatient cards (112/u unified format) [14]. At present this Register contains data on 15,568 children younger than 15 who spent their childhood in Ozersk.

Dosimetric characteristics of parents' occupational irradiation were obtained from the "Mayak-2008 Workers Dosimetric System" [15]. We applied values of accumulated pre-conception external gamma-irradiation on ovaries. Doses of external gamma-irradiation were calculated as per Monte-Carlo technique according to individual dosimeters readings and spatial-energy distribution of photon radiation field at a workplace. To make a comparison, we also give values of an equivalent for an absorbed external gamma-irradiation dose on the body surface Hp (10) and preconception absorbed doses of external gamma-irradiation on the large intestines.

Data on health of mothers employed at Mayak PA, including their obstetrician-gynecological case histories, chronic pathologies, and any bad habits, were obtained from patients' cards of Mayak PA personnel.

To include a child into our focus group, we applied the following criteria: 1) a child should be born in Ozersk in 1949-1969; 2) a child's mother was employed at Mayak PA and had an accumulated preconception dose of external gamma-irradiation on her gonads; 3) a child's fa-

ther didn't have any accumulated doses of pre-conception occupational irradiation, he hadn't moved to Ozersk from territories contaminated with radiation, and he hadn't previously taken part in liquidation of any radiation disasters. As a result, our basic group of Mayak PA female workers' offspring was made up of 238 children (148 girls and 90 boys) who corresponded to all the above mentioned criteria and whose medical documentation was available to us.

Our reference group was created basing on data from the Ozersk Children's Health Register: we carefully sampled a control for each child from the focus group, the ratio being 1:4, allowing for sex, year of birth, parents' age at the moment when a child was born, and medical documentation availability.

We applied the following criteria to include children into our reference group: 1) a child should be born in Ozersk in 1949-1969; 2) a child's parents had never been exposed to any occupational irradiation, had never taken part in any elimination of radiation disasters and had never lived on territories with radiation contamination. As a result, our reference group included 952 children (592 girls and 360 boys). The groups which were made up of Ozersk children population were comparable in terms of scope and quality of medical services available to them, climatic and geographic conditions of their living, and possible technogenic changes in the surrounding environment.

We analyzed the category XVII "Congenital malformations, deformations, and chromosomal disorders" (codes Q00–Q99) in the X International Classification of Diseases (ICD-10) [16] in this work; we concentrated only on such cases when the malformations and diseases were first diagnosed in children younger than 15.

The data were statistically analyzed with STATISTICA Version 10 software package (StatSoft, USA). The descriptive statistics for normally distributed signs is given with mean values (M) ± standard deviation (s); when distribution was not normal, we applied a median and interquartile range (25th and 75th percentiles). Frequencies were compared with χ^2 criterion and Fisher's exact test; discrepancies were considered to be valid at $p<0.05$. We calculated odds relation (OR) with 95% confidence interval. To detect any latent factors which explained correlations between the examined variables, we conducted a factor analysis via basic components technique with the consequent Varimax normalized rotation [17]. We selected this rotation technique due to more obvious interpretation of factor loadings as opposed to other rotation strategies. A number of factors was determined as per Kaiser's criterion, factors' own values being not less than 1. Factor loadings being > 0.7 were considered to be significant for the interpretation.

Results and discussion. Mothers of children from the focus group started their work at Mayak PA in 1948-1966. External gamma-irradiation doses including preconception ones and intrauterine doses are characterized in Table 1. As doses distribution was closed to normal the Table contains both mean values and medians.

The highest doses were detected among workers employed at Mayak PA during the first years of its functioning. A maximum dose of external gamma-irradiation on gonads reached 3,523.7 mGy among irradiated mothers. An average accumulated dose of external gamma-irradiation on gonads amounted to 373.6±34.2 mGy among Mayak PA female workers. We should note that there were data on intrauterine irradiation of 182 children (76.5%). The doses varied from 0.01

Table 1

Characteristics of external gamma-irradiation doses accumulated by mothers and intrauterine doses

Dose	Doses range	Mean value of a dose ± standard deviation	Median [interquartile range]
Dose on gonads, mGy	0,09–3523,7	373,6 ± 34,2	136,8 [29,3; 533,2]
Dose on the large intestines, mGy	0,09–3898,7	388,9 ± 36,2	139,9 [30,7; 554,8]
Dose Hp (10), mSv	0,13–4533,2	481,9 ± 43,9	191,1 [37,8; 731,3]
Dose in utero, mGy	0,01–261,9	25,8 ± 2,8	8,4 [0,56; 28,2]

Table 2

Distribution of offspring depending on an accumulated pre-conception dose of external γ – irradiation on mother's gonads

Dose range, mGy	Focus group overall (n=238)			Boys (n=90)			Girls (n=148)		
	Abs.	%	Average dose, mGy	Abs.	%	Average dose, mGy	Abs.	%	Average dose, mGy
0,01–25,0	54	22,7	8,6	22	24,4	10,4	32	21,6	7,3
25,1–100,0	56	23,5	53,1	18	20,0	47,1	38	25,7	55,9
100,1–250,0	26	10,9	165,4	8	8,9	183,9	18	12,2	157,2
250,1–500,0	36	15,1	358,7	15	16,7	362,9	21	14,2	355,7
500,1–1000,0	43	18,1	703,6	18	20,0	686,8	25	16,9	715,7
>1000,0	23	9,7	1652,3	9	10,0	1744,6	14	9,4	1592,9
Всего	238	100	373,6	90	100	400,6	148	100	357,1

to 261.9 mGy; an average dose amounted to 25.8±2.8 mGy, as mothers were exposed to radiation at early stages of their pregnancies.

Pre-conception irradiation of female workers employed at Mayak PA which we observed can be explained not only by imperfect production technology, very tight production schedules existing at enterprises in the state defense sphere, and absence of any experience in working with sources of ionizing radiation, but also with the concepts on permissible radiation exposure at production which existed at that time. Distribution of offspring depending on a mother's pre-conception external gamma-irradiation dose on gonads is given in Table 2.

Most children were born within mothers' irradiation range up to 100 mGy, and their distribution as per sex was different. Almost one quarter of boys (24.4%) were born by workers with an accumulated pre-conception dose of external gamma-irradiation on their gonads up to 25 mGy, while girls' mothers in more than one quarter of cases (25.7%) had an accumulated dose on their gonads which was within 25.1 - 100 mGy range. Each tenth child was born by a mother with an accumulated external gamma-irradiation dose on their gonads being more than 1 Gy.

CM analysis in children born by mothers who were exposed to occupational irradiation revealed that 13 CM cases in 12 children out of 238 live-birth infants were registered (one child had both cerebral malformations and the larynx malformations). As for the reference group, 60 malformations were registered in 55 children out of 952 (one child had three different malformations, and two children had two CM each). Data on CM distribution as per systems in both groups are given in Table 3.

We didn't reveal any statistically significant discrepancies either in overall CM frequency or in the groups ($p>0.05$). In order to check a hypothesis on a possible

Table 3

CM structure in the compared groups

CM (as per ICD-10)	Focus group						Reference group					
	Boys (n=90)		Girls (n=148)		Both sexes (n=238)		Boys (n=360)		Girls (n=592)		Both sexes (n=952)	
	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%	Abs.	%
CM in the nervous system (Q00-Q07)	2	33,3	1	14,3	3	23,1	6	22,2	7	21,2	13	21,7
CM of the eyes, ears, face and neck (Q10-Q18)	0	0	0	0	0	0	7	25,9	2	6,1	9	15,0
CM in the circulation system (Q20-Q28)	0	0	1	14,3	1	7,7	3	11,1	6	18,2	9	15,0
CM in the respiratory organs (Q30-Q34)	2	33,3	1	14,3	3	23,1	1	3,7	1	3,0	2	3,3
Cleft lip and cleft palate (Q35-Q37)	0	0	0	0	0	0	2	7,4	0	0	2	3,3
Other congenital anomalies in the digestive organs (Q38-Q45)	0	0	1	14,3	1	7,7	5	18,5	1	3,0	6	10,0
CM in the genitals (Q50-Q56)	1	16,7	0	0	1	7,7	1	3,7	0	0	1	1,7
CM in the urogenital system (Q60-Q64)	0	0	1	14,3	1	7,7	0	0	0	0	0	0
CM in the musculoskeletal system (Q65-Q79)	1	16,7	1	14,3	2	15,3	2	7,4	12	36,4	14	23,3
Other CM (Q80-Q89)	0	0	1	14,3	1	7,7	0	0	4	12,1	4	6,7
Chromosomal anomalies not classified in other categories (Q90-Q99)	0	0	0	0	0	0	0	0	0	0	0	0
TOTAL	6	100	7	100	13	100	27	100	33	100	60	100

influence exerted by mother's preconception irradiation on CM occurrence in children, we calculated odds relation with 95% confidence interval. OR value in the compared groups showed there was no statistically significant correlation between mothers' occupational irradiation and malformations in their children: OR without division by sex amounted to 0.86 (0.46–1.59); OR value among boys was 0.88 (0.35–2.2); OR value among girls, 0.84 (0.36–1.94).

We should note that our analysis of outpatient cards which contained exacted diagnoses up to an age of 15 years inclusive helped us to allow for malformations which were diagnosed not only at a child's birth but also at older ages.

CM in the nervous system and the respiratory organs were most frequently diagnosed among children born by irradiated mothers (23.1% of all the malformations in the overall focus group). Three cases of microcephalia were registered among CM in the nervous system. Congenital malformations in the respiratory organs were congenital larynx stridor, congenital pulmonary collapse, and nose sinuses hypoplasia. CM in the musculoskeletal system took the second place among children born by irradiated mothers (15.1% of all the malformations); they were ribs anomalies and the navicular bone anomaly. CM in the

circulatory system, digestive organs and urogenital organs have equal shares, 7.7% each.

CM structure among boys was different from that among girls. Thus, CM in the nervous system and respiratory organs were registered among boys more frequently, 2 cases each (33.3%), while we detected similar shares (14.3%) of CM in the nervous system, respiratory organs, digestive organs, circulatory system, urogenital system, and the musculoskeletal system among girls.

A case of microcephalia with the right hemisphere atrophy was detected in the boys sub-group. A number of authors [18, 19] state that cerebral damages occurring at the early stages of ontogenesis are the leading cause of perinatal mortality and account for 60-70% of children neurologic pathology; they also mention that neurological symptomatology in children with cerebral malformations is polymorphic and non-specific.

A combined congenital heart disease (Botallo's duct non-closure and interatrial septum defect) was detected among girls. A CM in the urogenital system with an abnormal ureter passage was diagnosed in a girl suffering from obstructive chronic pyelonephritis. We didn't detect any chromosome pathologies in children born by Mayak PA female workers.

As for the reference group, CM were most frequently registered there in the musculoskeletal system (23.3%); they were congenital thigh deformations, dentofacial anomalies, and disorders in sternocleidomastoid muscle development. The second place belonged to CM in the nervous system (21.7%) with 6 microcephalia cases among them. CM in the eyes, ears, face and neck (Q10-Q18) and CM in the circulatory system made equal contributions (15% each) in the CM structure among children born by intact parents.

Boys born in families where parents weren't exposed to any production irradiation most frequently (25.9%) had eyes anomalies, such as congenital cataract, lacrimal apparatus malformations, and ear anomalies. Two children had cleft palates. CM in the digestive organs among boys in this group were represented by a congenital hypertrophic pyloric stenosis and Hirschsprung's disease.

CM in the musculoskeletal system were most frequently registered among girls in the reference group (36.4%); most of them were congenital thigh malformations. We detected three rare congenital malformations among those girls: acoustic meatus atresia, congenital erythroblastosis, and internal organs inversion (Situs viscerum inversus). We didn't detect any chromosome anomalies in the reference group either. Genitals malformations in both groups were represented by single cryptorchism cases.

We compared congenital frequency as per nosologic forms and didn't detect any significant discrepancies both in overall groups and in boys and girls sub-groups ($p>0.05$). The data on CM structure presented here are a bit different from national statistics and EUROCAT international register where the greatest contribution into CM structure is made by CM in the circulation system, musculoskeletal system, and urogenital system [20, 21]. However, relatively small number of CM in the examined groups doesn't allow us to make any ultimate conclusions.

CM cases in the focus group were registered within mothers' pre-conception doses range of 1.9-1,635.5 mGy of external gamma-irradiation on gonads, an average accumulated dose amounted to 307.5 mGy. Given the concept of the true threshold for

CM induction which is equal to 100 mGy [22], in future we plan to analyze dependence of CM in children on a preconception dose accumulated by their mothers.

Undoubtedly, apart from parents exposure to radiation, there are multiple exo- and endogenous factors which can be teratogenic; such factors include a mother's health prior to conception, parents' age at the moment a child was born, mother's bad habits, data on pregnancy course, gestation terms etc. Scientists are still searching for possible teratogenic factors and assessing their influences on an embryo. Thus, C. Malagoli et al [23] analyzed magnetic fields effects; J.A. Makelarski et al [24] described increased risks of anencephalia and encephalocele caused by cumulative pesticides effects; C.A. Snijder et al [25] focused on congenital heart diseases risks caused by a father's pre-conception exposure to chemicals; G. Vermes et al.[26] consider acute and chronic infectious diseases of mothers as leading anorectal malformations causes.

In order to reveal non-radiation teratogenic factors in both children groups, we analyzed pre-morbid background including data on gestation age, anthropometric parameters of newborns, obstetrician-gynecologic case histories of their mothers, and mothers' chronic pathologies.

195 children (81.9%) among those born by Mayak PA female workers were full-term; there were 756 full-term children (79.4%, $p>0.05$) in the reference group; prematurity was detected in 8 (3.4%) newborn infants in the focus group and in 40 (4.2%) newborns in the reference group ($p>0,05$). Multiple pregnancy in the focus group was detected in 4 cases (1.7%), and there was no statistically significant discrepancy with the reference group (14 cases 1.5%). Deliveries were normal in 186 cases (78.2%) in the focus group and in 768 cases (80.7%, $p>0.05$) in the reference group. Abnormal deliveries and cesarean operations were detected in 11 (4.6%) cases in the focus group and 26 (2.7%) cases in the reference group ($p>0.05$). Distribution as per an ordinal number of a pregnancy didn't have any statistically significant differences in both groups: first-time mothers prevailed in them ($p>0.05$), the second and the following births were registered for 79 (33.2%) female workers employed at Mayak PA and 283 (29.7%) of women who were not exposed to occupational irradiation, $p>0.05$. Average age of a mother at the moment of childbirth amounted to 26.5 in both groups. Anthropometric parameters in newborns from both groups in general didn't have any statistically significant discrepancies.

We analyzed bad habits of Mayak PA female workers and revealed that smoking mothers accounted for only 5.9% (14 people); most women (78.2% or 186 people) had utterly negative attitudes towards smoking; smoking status of the remaining 15.9% (38 people) wasn't known. 58.4% (139 people) didn't drink alcohol at all; 6.7% (16 people) drank very little; 10.1% (24 people) were moderate drinkers; 3.4% (8 people) were heavy drinkers; there were 2 registered cases of chronic alcoholism (0.8%); there is no information about the remaining women.

86 (36.1%) mothers of children in the focus group had problems in their obstetrician-gynecological case histories, such as abortions, acute and chronic gynecologic pathology prior to conception. Two mothers of children from the focus group had stillbirths in their case histories; we detected 16 stillbirths among mothers of children from the reference group, $p>0.05$. According to data taken from outpatient cards of female workers employed at Mayak PA,

123 (51.7%) women suffered from chronic somatic pathologies, which mostly were chronic pathologies in the gastrointestinal tract, bronchopulmonary diseases, and chronic tonsillitis.

In order to reveal any latent factors which explained correlations between the examined variables, we performed a factor analysis in the focus group applying basic components technique with Varimax normalized rotation (Table 4).

Table 4

Results of factor analysis performed on the focus group

Factor Loadings (Varimax normalized) Extraction: Principal components (Marked loadings are >,700000)				
Variables	Factor - 1	Factor - 2	Factor - 3	Factor - 4
Mother's age at the moment of childbirth	0,234932	–0,099351	0,604849	0,004919
Number of previous pregnancies	–0,075804	–0,063024	**0,895051**	0,020828
Number of previous abortions	–0,045748	0,142250	**0,858895**	–0,022471
Gestation age	0,038028	**0,850093**	0,087218	0,033758
Multiple pregnancy	–0,035862	**0,821534**	0,096067	–0,069278
Parity of delivery	–0,004183	**0,798718**	0,088540	0,046689
Family's living conditions	0,028691	0,260954	0,346532	0,209597
External gamma-irradiation dose in utero	0,320166	–0,211909	–0,277238	0,169278
Alcohol intake by a mother	0,100919	0,026284	–0,044865	**0,876280**
Smoking status of a mother	0,095016	–0,009167	0,003251	**0,900915**
Dose on gonads*	**0,990472**	0,027625	0,059691	0,029901
Dose on the large intestines*	**0,990072**	0,025616	0,055103	0,024006
Dose Hp (10)*	**0,990920**	0,032839	0,059017	0,028047
Chronic somatic diseases of a mother	0,018702	0,384251	–0,175641	–0,081635
The current pregnancy course	0,131938	0,095392	–0,115523	–0,193230
Expl.Var	3,149281	2,342627	2,182580	1,707441
Prp.Totl	0,209952	0,156175	0,145505	0,113829

Note: * means mother's accumulated absorbed doses of external gamma-irradiation.

4 complex independent factors were spotted out among 15 features in the group of children born by mothers employed at Mayak PA. The total share of the explained dispersion amounted to 62.5%. The most significant factor was that related to mothers' pre-conception irradiation as it made the greatest contribution (21.5%) into the dispersion; factor loadings of such variables as "Dose on gonads", "Dose on the large intestines", and 'Dose Hp (10)" were also high (0.99 each).

The second factor included gestation age of a child, multiple pregnancy, and parity of delivery (factor loadings were 0.85, 0.82 and 0.79 correspondingly). It accounted for 17.1% of the overall dispersion. The greatest loadings in the third factor were represented by the variables which characterized a mother's obstetrician case history, a number of previous pregnancies and abortions; this factor accounted for 12.9% of the overall dispersion. The least contribution into the dispersion (11%) was made by the factor characterizing bad habits of a mother, alcohol intake and smoking (factor loadings were 0.87 and 0.9 correspondingly). P.M. Sullivan at al. [27] examined 14,128 congenital heart diseases cases against 60,938 control cases and proved that smoking during pregnancy was a risk factor for certain phenotypes of congenital heart diseases.

To make a comparison, we conducted a factor analysis according to the same procedures on the reference group which included children born by intact mothers. As a result, two factors with their overall

share of the explained dispersion equal to 63.8% were detected in this group. The second factor included gestation age of a child, multiple pregnancy, and parity of delivery, accounted for 38.4% of the overall dispersion (factors loading were 0.86, 0.9 and 0.79 correspondingly). The second factor was related to a parity of pregnancies and a number of previous abortions (factor loadings were 0.89 and 0.8 correspondingly). The second factor accounted for 25.4% of the overall dispersion.

It is interesting to note that after all the variables which described mother's occupational pre-conception irradiation were excluded, factors solution among children born by Mayak PA female workers became similar to that existing in the reference group: contributions made by a mother's obstetrician case history and their children's antenatal period remained significant and explained 61.8% of the overall dispersion. Therefore, the factor analysis performed with basic components technique allowed to reveal latent factors which explained correlations between the observed features in the group of children born by Mayak PA female workers.

Conclusion. We performed retrospect analysis of CM in 1,190 children aged under 15, 238 of them being born by mothers who had accumulated pre-conception doses of external gamma-irradiation. The analysis revealed that:

1) there were no statistically significant discrepancies in CM frequency both overall and as per nosologic forms between two groups: overall, OR amounted to 0.86 (0.46–1.59); OR among boys, 0.88 (0.35–2.2); OR among girls, 0.84 (0.36–1.94);

2) there were some discrepancies in CM structure: CM in the nervous system and respiratory organs (23% each) and CM in the musculoskeletal system (15.3%) prevailed among children born by irradiated mothers; CM in the musculoskeletal system (23.3%) and CM in the nervous system (21.7%) prevailed among children born by intact parents;

3) there were some sex-depending discrepancies in the CM structure: CM in the nervous system and respiratory organs were more frequently registered among boys from the focus group (33.3% each) while contribution made into CM structure by CM in the nervous system, respiratory organs, digestive organs, circulatory system, urogenital system, and the musculoskeletal system were the same among girls (14.3% each).

4) there were no chromosome pathologies in either group;

5) CM were diagnosed in children born by mothers with accumulated pre-conception doses of external gamma-radiation on their gonads within 1.9–1,635.5 mGy, an average dose being equal to 307.5 mGy.

Factor analysis performed on the group of children born by female workers employed at atomic production spotted out 4 factors characterizing mothers' pre-conception irradiation (21.5% of the dispersion), offspring's antenatal period (17.1% of the dispersion), obstetrician-gynecological case history (12.9% of the dispersion), and bad habits of mothers, such as alcohol intake and smoking (11% of the dispersion). After we excluded all the variables which characterized mothers' pre-conception occupational irradiation, factors solution in the compared groups didn't have any significant discrepancies.

Damaging factors are multiple and variable, and it doesn't always allow to get a clear concept of what actually prevails in CM etiology [20, 28, 29] and to confirm the leading role which parents' irradiation plays in CM induction. If we take bigger

offspring groups and an extended period of observations, it will allow us to continue analyzing remote consequences of parents' occupational irradiation including quantitative assessment of the contribution made by mothers' pre-conception irradiation into CM risks run by their offspring.

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ASSESSMENT OF SENSORIMOTOR REACTIONS PECULIARITIES DETECTED IN CERTIFIED TEST LABORATORY CENTER STAFF DURING THEIR OCCUPATIONAL ACTIVITIES

I.G. Nenakhov, Yu.I. Stepkin, I.A. Yakimova

Voronezh State Medical University named after N.N. Burdenko, 10 Studencheskaya Str., Voronezh, 394036, Russian Federation

Our research was performed on 90 people working at Voronezh Center for Hygiene and Epidemiology, a certified test laboratory center. Our research goal was to assess peculiarities of sensorimotor reactions detected in personnel of hygienic and epidemiologic laboratories as per simple visual-motor reaction parameters and complex visual-motor reaction. To examine visual-motor reactions, we applied EffectonStudio software, "Jaguar. Perception. Reactions. Research on precision and speed qualities and human working capacity" package, and Maslash and Jackson procedure supplemented with a mathematical model developed in Bechterev's Saint-Petersburg Scientific Research Psychoneurological Institute to assess occupational burnout risks. The paper dwells on how fatigue develops during a working week and on contributions made by each working day into overall fatigue experienced by personnel employed at a certified test laboratory center. We examined occupational burnout peculiarities detected in laboratory center workers as per emotional exhaustion parameters, depersonalization, and reduction in professional competences; we calculated integral burnout index for them. We reveled health risks for certified test laboratory center personnel which were caused by their emotional burnout and determined cause-and effect relations between the central nervous system functional state and emotional burnout. On the basis of the obtained data we made recommendations on prevention activities aimed at working conditions optimization and occupational burnout prophylaxis. Our research supplements and enlarges this knowledge sphere in occupational hygiene in terms of examining and preventing fatigue occurring in personnel at their workplaces.

Key words: *emotional exhaustion, occupational burnout, depersonalization, reduction in professional competences, visual-motor reaction, working conditions optimization.*

Work in laboratories is usually quite intense and it requires prophylaxis activities aimed at occupational morbidity prevention. Work tasks performed by a laboratory worker at any test center mostly involve the nervous system; artificial and natural stimuli which influence such worker's visual analyzer make his or her work worse thus making the motor reactions slow down [1–4]. When we performed our research, we focused on simple and complicated visual-motor reactions (SVMR and CVMR) in workers employed by a certified test laboratory center (CTLC) at Voronezh Regional Center for Hygiene and Epidemiology. SVMR and CVMR assessment determines responses from the central nervous system (CNS) [5, 6]. Examination of both simple and complicated visual motor reaction allows to reveal people with

Ivan G. Nenakhov – Post-Graduate Student at Hygienic Courses Department (e-mail: rayhd@yandex.ru; tel.: +7 (920) 427-02-40).

Yurii I. Stepkin – Doctor of Medical Sciences, Professor, Head of Hygienic Courses Department (e-mail: san@sanep.vrn.ru; tel.: +7(473) 263-52-41).

Irina A. Yakimova – a fifth-year Student at Medical-Prevention Faculty (e-mail: yakimova.irene@yandex.ru; tel.: +7(903) 852-37-71).

the strained CNS (excitation or inhibition) among laboratory center workers; such strain in the CNS leads to occupational burnout syndrome [7, 8]. There are several symptoms which can be considered health risks caused by occupational burnout development; they are 1) physical responses from a body (chronic fatigue and lower body immune state which lead to crises in occupational activities and body exhaustion); 2) social and behavioral signs which become apparent through discontent and attempts to "shift responsibility"; 3) psychoemotional symptoms which involve occupational motivation loss and a decrease in working capacities in laboratory center workers [7, 9, 10]. Determination of occupational burnout risks and timely prophylaxis will help to prevent diseases caused by nervous system overstrain which, in its turn, results from emotional one [10–12].

Our research goal was to assess sensorimotor reactions peculiarities in personnel of CLTC at Voronezh Regional Center for Hygiene and Epidemiology during their occupational activities.

Our research tasks were:

1. To examine sensorimotor reactions peculiarities in laboratory center personnel..
2. To determine occupational burnout risks as a factor influencing personnel's health depending on their occupational activities.
3. To detect cause-and-effect relations between the CNS functional state and occupational burnout in CLTC workers.
4. To work out prophylaxis measures aimed at lowering health risks via occupational burnout prevention and improving working conditions for the center personnel.

Our research object was personnel employed by the CLTC at Voronezh Regional Center for Hygiene and Epidemiology which has 11 laboratories in its structure. We examined 90 workers aged from 23 to 65.

Data and methods. To perform our research, we divided all the workers into two groups as per their occupational activities: a hygienic profile group and an epidemiologic profile group. Hygienic profile laboratories included: prophylaxis toxicology laboratory (PTL), physical-chemical examinations laboratory (PCEL), nutrition hygiene laboratory (NHL), air control laboratory (ACL), communal hygiene laboratory (CHL), laboratory for control over physical factors (LCPF), and radiation laboratory (RL). Epidemiologic profile laboratories were bacteriological laboratory (BL), extremely dangerous infections laboratory (EDIL), virology laboratory (VL), and parasitological laboratory (PL).

To predict working capacity of laboratory personnel, we assessed their CHS functional state, or simple and complicated visual-motor reactions [4]. We detected regularities in visual-motor reactions dynamics via analyzing changes in reactions time (RT):

$$RT = Tnn + Tnp + TM,$$

where *RT* is a reaction time; *Tnn* is sensory-perceptive process time; *Tnp* is time for assessing and making a decision, and *TM* is a motor response time [5, 13].

We applied certified software developed by EffectonStudio, "Jaguar. Perception. Reactions. Research on precision and speed qualities and human working capacity" package. It allowed us to determine an average reaction time which en examined worker spent when he or she had to react to a known simple visual analyzer stimulus. An examined worker had to press a computer button when an element on a screen changed its color. When we examined complicated visual-motor reactions, we measured which average reaction time it took an examined worker to react to a

complicated visual analyzer stimulus: he or she had to press a button only when a definite color appeared on a PC screen. Each action was measured in milliseconds. We allowed for the overall time it took examined workers to pass each test and a number of errors made by an examined worker during tests. Workers had to abandon their usual occupational activities for 5 minutes only to take part in our research. We performed our research on workdays and it helped us to determine fatigue dynamics as per weekdays and a contribution made by each working day into workers' fatigue.

To assess occupational burnout syndrome risks, we chose a procedure developed by Maslach and Jackson, edited by Vodopyanova, and added with a mathematical model developed in Bechterev's Saint-Petersburg Scientific Research Psychoneurological Institute [14]. Questioning blanks were developed in accordance with procedures for occupational burnout diagnostics. It took workers as little time as 3 minutes to fill in the blanks. They were offered 22 questions related with their work tasks. Answers varied from "never" (0 scores) to "every day" (6 scores). Scores sum was calculated basing on the obtained results for the following sub-factors: emotional exhaustion (EE), depersonalization (DP), and reduction in professional competence (RPC). Emotional exhaustion results from lower emotional tonus with apparent affective psyche instability. It becomes apparent not only through workers becoming "fed up" with their occupational activities, but also with them feeling themselves unsatisfied with their life in general. This parameter directly influences relations in a work team. Depersonalization is detachment from all the events which happen around. It frequently becomes apparent through cynicism and "occupational labeling" in a team when one workers "label" others. Reduction in professional competence is a parameter which shows how a respondent sees him- or herself as a professional. When it decreases, a worker becomes unsatisfied with his or her work tasks and processes, and their occupational motivation also goes down.

Owing to the mathematical model developed in Bechterev's Saint-Petersburg Scientific Research Psychoneurological Institute which was a perfect supplement to the applied procedure, we calculated integral burnout index (IBI) [14]:

$$IBI = \sqrt{(EE-EE(x)/54)^2+(DP-DP(x)/30)^2+(1-RPC(x)/48)^2/3},$$

where EE=0, DP=0 and RPC=48 are ideal burnout syndrome parameters as per Maslach and Jackson test, and EE(x), DP(x) and RPC(x) are an examined worker's parameters as per corresponding Maslach and Jackson test scales. The result varies from 0 to 1, where 0 means there is no occupational burnout, and 1 means maximum occupational burnout.

Basing on integral burnout index, we determined health risks for laboratory personnel employed by a Rospotrebnadzor' organization. IBI value from 0 to 0.6 meant acceptable risk, but if IBI was higher than 0.6, it meant risk was unacceptable.

We calculated correlations in certified Microsoft Office Excel.

Results and discussion. Time of simple and complicated visual-motor reactions, time needed to pass each test, as well as a number of errors in examined workers' reactions varied depending on a laboratory profile. Average time of a simple visual-motor reaction in hygienic laboratories amounted to 483±24 msec, while it was equal to 457±23 msec in epidemiologic ones. Average CVMR time was also dif-

ferent: it amounted to 484±24 msec in hygienic laboratories, and to 445±22 msec in epidemiologic ones. Averaged number of wrong reactions occurred more frequently in hygienic laboratories: 1.5±0.1:1.4±0.1. We compared average time needed to pass a test and revealed that workers with hygienic profile spent 1 second longer time than workers from epidemiologic laboratories (Table).

SVMR and CVMR time taken in working week dynamics was also different depending on a laboratory profile.

Maximum SVMR time in epidemiologic laboratories was detected on Monday. Maximum working capacity was detected ion Thursday (445±22 msec), and fatigue occurred by Friday.

A different situation was observed in hygienic laboratories where fatigue grew by the middle of a week.

Thus, on Wednesday SVMR time amounted to 520±26 msec in hygienic laboratories, while on the same day it was 460±23 msec in epidemiologic ones. The parameter came to the same level by Friday in both groups and amounted to 514±26 msec , which proves that fatigue occurred at the end of a working week. (Figure 1).

The CNS functional state in workers from different laboratories of CLTC at Voronezh Regional Center for Hygiene and Epidemiology

Parameters	Hygienic laboratories	Epidemiologic laboratories
Simple visual motor reaction		
Average SVMR value	483 ± 24 msec	457 ± 23 msec
Time needed to pass a test	51 ± 3 sec	50 ± 3 sec
Complicated visual motor reaction		
Average CVMR value	484 ± 24 msec	445 ± 22 msec
Time needed to pass a test	157 ± 8 sec	156 ± 8 sec
Wrong reactions number	1,5 ± 0,1	1,4 ± 0,1

A difference between time of a simple visual motor reaction and a complicated one is known as "central delay" which is divided into two stages: processing of information on a stimulus in the CNS and making a decision on how to react to this or that stimulus. Both these stages significantly depend on the CNS functional state. Our examination of complicated visual motor reaction time also revealed discrepancies between different laboratories.

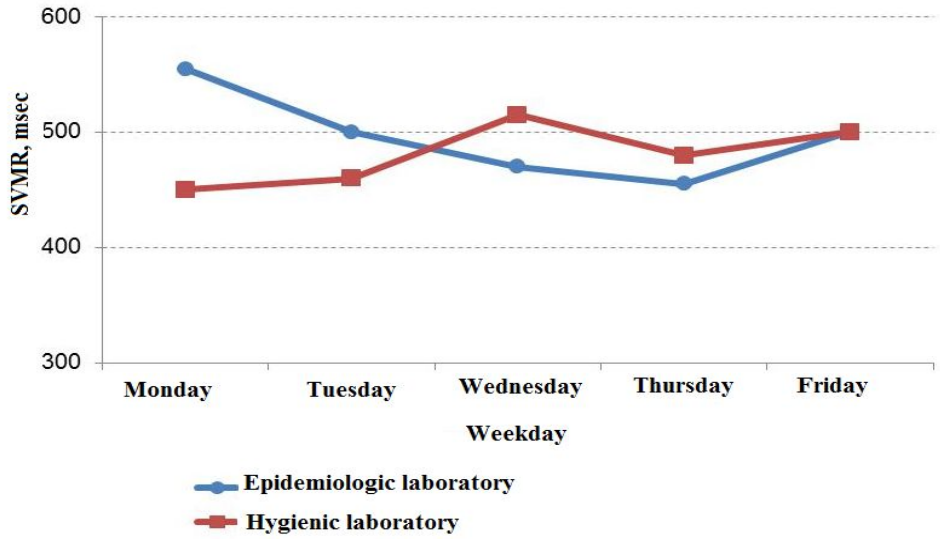

Figure 1. SVMR parameters in a working week dynamics

Thus, the greatest CVMR times were detected on Monday and Friday in epidemiologic laboratories: 528±26 msec and 524±26 msec correspondingly, but as for hygienic laboratories, their greatest times, 520±26 msec and 479±24 msec, were detected on Wednesday and Friday. The highest CNS functional parameter was equal to 431±21 msec and was detected on Wednesday in epidemiologic laboratories. As for hygienic laboratories, this parameter had its highest value on Thursday, after a drop on Wednesday, and amounted to 449±22 msec. In means that fatigue occurs at the beginning of a working week due to weaker nervous processes in the brain cortex. A formed excitation focus here is a dominant which determines whether a worker is ready to perform his or her working tasks and maintains a body functional state with consequent protective inhibition occurrence. In future it can cause the nervous system exhaustion and stress evolvement [15, 16]. Constant stress leads to a body exhaustion and emotional burnout which consequently causes occupational burnout development [7, 14].

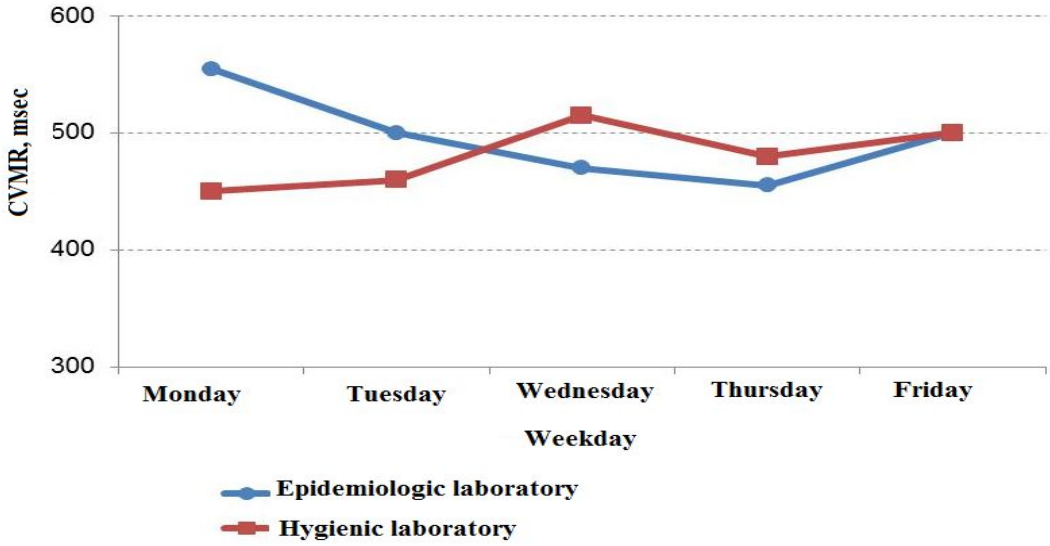

Figure 2. CVMR parameters in a working week dynamics

The obtained data prove that fatigue and increased strain in the CNS can occur not only by the end of a working week, but on other days too. A contribution made by Wednesday into fatigue evolving in hygienic laboratories personnel amounted to 21.5%.

We analyzed the results obtained with Maslach and Jackson procedure edited by Vodopyanova, and added with a mathematical model developed in Bechterev's Saint-Petersburg Scientific Research Psychoneurological Institute, and revealed that occupational burnout occurred both in hygienic and epidemiologic profile laboratories. Emotional exhaustion was detected in 16% respondents from the laboratory center in general. Increased cynicism level which evidenced depersonalization was detected in more than a half CLTC workers (58% respondents). Reduction in professional competence was observed in 27 people (30% workers).

We calculated a correlation coefficient for SVMR and CVMR speed and integral burnout index (IBI) and obtained the following results: $r=0.71$ and $r=0.70$ correspondingly, which proves there is a strong cause-and-effect relation with statistic error probability being less than 5% ($p< 0.05$).

Conclusions. Personnel working in hygienic laboratories undergo greater emotional stress during a working week than those working in epidemiologic ones. A contribution made by Wednesday into fatigue evolving in workers from both laboratory groups amounts to 21 %.

Occupational burnout risk is acceptable both in hygienic and epidemiologic laboratories; however, integral burnout index was higher in hygienic laboratories than in epidemiologic ones which means workers in these laboratories run higher occupational risks.

Correlation coefficients calculated for SVMR and CVMR speed and integral burnout index (IBI) amounted to r=0.71 and r=0.70 correspondingly which means there is a strong cause-and-effect relation between them ($p< 0.05$).

To reduce occupational burnout risks, we developed a set of prophylaxis activities which includes:

– lower workloads in hygienic laboratories on Monday and Tuesday and more correct distribution of workloads during a working week;

– change of tasks which a worker has to perform in order to reduce a number of the same actions during a working week;

– optimization of time a worker has to spend doing his or her work via computerization and automation of routine tasks in the certified laboratory test center;

– improvement of sanitary-hygienic and psychophysiological conditions for workers employed at the certified laboratory test center.

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FATIGUE RISK ASSESSMENT FOR WORKERS WITH NEURO-ENMOTIONAL LABOR

I.V. Bukhtiyarov[1,2], O.I. Yushkova[1], M.A. Fesenko[1], A.G. Merkulova[1]

[1]Izmerov's Research Institute of Occupational Health, 31 Budennogo avenue, Moscow, 105275, Russian Federation
[2]I.M. Sechenov First Moscow State Medical University, 8 Trubetskaya Str., build. 2, Moscow, 119991, Russian Federation

The papers dwells on the results obtained during fatigue risk assessment as per subjective and objective parameters in civil aviation crew members.

Our research goal was to assess fatigue and overfatigue risks as per subjective and objective cardiovascular system parameters and central nervous system parameters in workers with morning and evening biorhythms under neuro-emotional workloads and shift work performed by planes crew members, air traffic controllers, and operators. Our examined workers were mostly people aged 35–45 with working period equal to 5–15 years.

Fatigue which occurred during flights was assessed subjectively by crew members questioning as per Epworth Sleep Scale, Karolinska Sleepiness Scale, and crew state control as per Samn-Perelli. Working efficiency was studied via PVT test (psychomotor vigilance test), sleep monitoring, and actigraphy. Circadian rhythms dynamics was examined as per changes in minimal body temperature which aircrew members had. We applied Ostberg's questionnaires to assess biorhythmologic activity type. Workers' functional reserves were assessed via stress testing. We calculated functional changes index to assess functional abilities of the circulatory system and adaptation state during a working shift in workers with various biorhythmologic types.

The paper outlines the examination results for physiological reactions appearing in the cardiovascular system and central nervous system of workers with morning and evening biorhythms. We revealed that functional state peculiarities in operators when they performed their work tasks in a shift regime were closely connected with their biorhythmologic activity type. "Early risers" had more adverse physiological reactions during their work activities. We developed ways to lower risks related to fatigue and overfatigue caused by shift work. It was shown that regulatory mechanisms stress occurring in the circulatory system, lower labor motivation, and poorer health in people with the morning biorhythmologic type made it necessary to correct the body functional state during shift work, especially when labor was very intense.

Key words: *neuro-emotional labor, shift work, physiological reaction, fatigue risk, biorhythmologic activity type, regulatory mechanism.*

Fatigue or fatigability risk assessment is a vital problem nowadays; as a rule, it involves hazardous factors detection, risk assessment and risk lowering [1, 2–4]. "Fatigability" concept is widely used in publications issued by International Civil Aviation Organization, or ICAO [5], however, the authors prefer to apply such conventional concepts as

Igor V. Bukhtiyarov – Corresponding Member of the Russian Academy of Science, Doctor of Medical Sciences, Professor, Director; head of the Department of Occupational, Aviation, Space, and Diving Medicine (e-mail: ivdukhtiyarov@mail.ru; tel.: +7 (495) 365-02-09).

Olga I. Yushkova – Doctor of Medical Sciences, Professor, Chief Researcher at Occupational Physiology and Ergonomics Laboratory (e-mail: doktorolga@indox.ru; tel.: +7 (495) 366-44-55).

Marina A. Fesenko – Doctor of Medical Sciences, Head of the Laboratory for Workers' Reproductive Health Disorders Prevention (e-mail: marnast@mail.ru; tel.: +7 (495) 365-29-81).

Anastasia G. Merkulova – Candidate of Biological Sciences, researcher at Occupational Physiology and Ergonomics Laboratory (e-mail: anastasia.merkoulova@gmail.com; tel.: +7 (495) 365-09-63).

fatigue and over-fatigue in this work. As per ICAO definition, fatigue an aircraft crew member has is a physiological state when mental or physical capacity goes down due to sleeplessness or long-term wakefulness, a daily rhythm phase and/or workload (mental or physical one) which can reduce a crew member's activity and ability to manage an aircraft or perform his or her job responsibilities.

Two knowledge spheres, namely hypnology and chronobiology, are the leading sciences which concentrate on fatigue experienced by civil aviation crew members [6]. Research on the brains activity which takes place during sleep gave ground for working out practical recommendations on sleep inertia reduction and sleep deficiency compensation, as well as ways to make disturbances during sleep as minimal as possible and to organize work and rest regimes most rationally. The same problem related to work and rest regime organization and keeping to it exists for car drivers and maintrack locomotive drivers [18]. Generally, sleep deficiency to a greater extent exerts its influence on complicated mental activities, such as decision-making, than on performing relatively simple tasks. It can take more than two nights of recovery sleep for the central nervous system functions to come to their normal state after a period when sleep was limited.

Research performed on 67 Boeing 747-400 crews revealed that lack of sleep led to an increase in number of errors made by crew members [2]. Aircraft commanders often faced situations when detected inaccuracies were not eliminated. As for decision-making, crew tended to choose less risky actions which could lead to a certain decrease in potential fatigue risk.

According to chronobiology, circadian rhythms disorders in civil aviation personnel are likely to occur during night cargo flights on internal lines or when they pass through several time zones and are exposed to drastic changes in "day-night" cycle. It was shown that civil aviation personnel made mistakes more frequently during a certain period of time, so called minimal circadian activity window (MCAW) and this fact was taken into account when aviation accidents were investigated.

Time zones change syndrome (desynchronization) was given special attention; researchers here concentrated on a number of time zones which crew members passed through and a flight direction. Body functions adapted faster when a flight was from east to west. A separate resynchronization was detected as per research results when one rhythms had their phase shifted towards advance, and others, on the contrary, towards a delay.

Shift work is a working regime which requires a crew wakefulness during such hours in their biological cycle which correspond to night hours, that is, sleep time [8, 9]. Crew members who had night cargo flights suffered from incomplete adaptation of their circadian rhythms to a night work regime. In some cases they had to perform their flight when sleepiness reached its peak, or during so called MCAW. And only one thing saved them from necessity to adequately react to non-standard situations: their tasks were rather routine.

Literature data tell that ability to work in a shift regime is extremely individual. 20% of all shift workers are thought to adapt fully to work in a multi-shift regime. Another 20% can't adapt to such working activities and, as a result, suffer from physical and mental overloads [10–13]. Research on workers' biorhythmologic activity helped to create a "human circadian system". According to it, heart rate is at its maximum at 3-4 p.m.; systolic blood pressure, stroke and minute blood volume, at noon-4 p.m. [14,15]. A standard daily rhythm curve is a curve with its peak in the middle of a day or in its second half. There was also research on daily changes in body functional state of healthy people who had to work in shifts [16–18].

Adaptation to work in a shift regime depends on working activities and a biorhythmologic activity type [10]. Nowadays some attempts are being made to spot out people with a morning and an evening biorhythmologic type; these types are usually called "early risers" and "late risers" in literature. Besides, some authors [19] describe the third biorhythmologic type, which is called "arrhythmics". There are tests which can help to assess people's biorhythmologic activity; however, there have been practically no examinations dedicated to peculiarities of workers' functional state depending on their biorhythmologic type. But shift schedules are widely used in various mental activities, including, for example, operators or traffic controllers, and it calls for such research.

Literature analysis revealed that an issue of studying functional state, stages in physiological processes related to fatigue transferring into overfatigue, or physiological criteria which specific stages have is a central one in occupational physiology and is not only of theoretical interest but also has considerable practical value [12, 20]. However, "physiological costs" of activities performed by people with different biorhythmologic types (a morning or an evening one) depending on labor intensity have not been studied enough and it doesn't allow to give grounds for practical measures aimed at achieving maximum personnel efficiency in such occupations with great responsibilities as civil aviations crew members or operators and traffic controllers working in shifts.

Our basic task was to assess fatigue and overfatigue risk as per subjective and objective parameters of the cardiovascular and central nervous system in workers with the morning and evening biorhythms types under work with neuro-emotional loads and shifts (civil aviation crew members, operators, and air traffic controllers).

Data and methods. Fatigue during flights was assessed subjectively via crew members questioning as per Epworth Sleep Scale, Karolinska Sleepiness Scale, and crew state control as per Samn-Perelli. They working capacity was assessed objectively as per PVT test (psychomotor vigilance test), sleep monitoring with use of diaries, and actigraphy (movement registration and detecting wakefulness and drowsiness periods). Circadian rhythms dynamics was examined as per changes in crew members minimal body temperature.

Workers from four occupational groups were examined in their actual working conditions. The first group was made up of cigarettes-making lines operators employed at "Dukat" factory; the second group included robot-handled technological stations (RTS) operators; the third one were air traffic controllers working at one of Moscow airports; group four included PC operators. Most examined were 35-45 years old with their working period being 5-15 years.

We applied Ostberg's questionnaires to assess biorhythmologic activity types [10,15], trying to examine workers with polar biorhythmologic types, "early risers" and "late risers". Job analysis with labor intensity determination was performed in conformity with P 2.2.2006-05 Guide [21]; correction sample with Landolt's rings was applied to assess attention concentration (a perceived information volume, PIV, was calculated); we applied "numerical memory" test to assess short-term memory, and chronoreflexometry, to assess perception speed and speed of visual and audio signals processing [22]. We assessed the cardiovascular system state as per heart rate, systolic and diastolic blood pressure, which helped us to calculated pulse and average dynamic blood pressure, stroke blood volume, minute blood volume, and peripheral resistance [23, 24]. We also calculated proper parameters of the general hemodynamics (proper minute volume or PMV, proper peripheral resistance or PPR). We determined circulation types (hyperkinetic, eukinetic, or hypokinetic) on the basis

of comparing actual data with proper cardiovascular system parameters [25].

Functional reserves which workers' bodies had were assessed via stress tests. We applied a cycle ergometer (load capacity 100 Wt, 1.5 minute duration) to perform a sample with a dosed physical load. All the circulatory system parameters were registered before the load, during its performance, and when its consequences occurred during the first 5 minutes after it was over.

To assess circulatory system functional abilities and adaptation in workers with different biorhythmologic types in a shift dynamic, we calculated functional changes index in accordance with methodical guidelines issued by the RSFSR public health ministry [20].

Examinations were performed 3-5 times during a morning, an evening, and a night 8-hour shift on RTS operators; a day and a night 12-hour shift on cigarettes-making lines operators and air traffic controllers. As a results we obtained daily activity curves for all the examined parameters depending on a worker's biorhythmologic type (1 group were "morning" people, 2 group were "evening" ones).

Results and discussion. Job analysis of activities performed by civil aviation crew members revealed emotional loads prevalence was caused by each error being greatly significant, responsibility for other people's lives being too high, personnel's own lives being at risk, and conflict situations being quite possible. Intellectual loads were related to an individual leadership in difficult situations, work under time deficiency, and perception of signals when all the parameters were to be assessed as a complex. All the above-mentioned, plus high sensory loads and unfavorable work regime, allowed us to rank civil aviation crew members labor as having 3.3 hazard degree in terms of labor intensity [21].

We examined the structure of activities performed by robot-handled technological stations operators and found out that their labor intensity was determined by sensory loads level including apparently long periods of concentrated observation, perception of data coming from robot-handlers control consoles as well as from displays which showed machines functioning. Working regime was organized in three 8-hour shifts.

Cigarettes-making lines operators work in 12-hour shifts. Their job responsibilities involve control and monitoring over NC machine tools displays, correcting disorders in automated systems, and constant quality control under a strict time regime as per their job description. Overall assessment of RTS operators and cigarettes-making lines operators labor allowed us to rank it as having the 2nd permissible category in terms of labor intensity according to the Guide P 2.2.2006-05 [21].

Neuro-emotional loads which air traffic controllers had to undergo were determined by highly dense visual signals including data coming from VDUs, audio signals and messages per a time unit, long-term periods of concentrated attention, work under time deficiency, complicated job tasks, high responsibility for other people's lives, and any error being greatly significant. Air traffic controllers' job peculiarities rank their labor as 3.2 hazard category in terms of labor intensity; and PC operators labor, as applied to flight labor, as 3.1 hazard category.

Circadian biological rhythms of crews who had long-distance flights didn't manage to adapt to any of time zones at their destination points. NASA research performed on a 3-member crew (aircraft commander, co-pilot, and flight engineer) revealed that they didn't return to their home time zone to spend any long period of time there when they performed trans-Pacific flights [26, 27]. A shift in internal biological rhythms cycle was observed in crew members as per time periods during which their body temperature reached its minimal value. It took them several additional days off to normalize their

psychophysiological state after they returned home.

A more favorable situation was observed when crew members periodically stayed in their home time zone during breaks in flights. Daily biological rhythms were able to synchronize with local time existing in a home time zone. Sometimes circadian biorhythms adapted to a time zone at a destination point when crews stayed there and performed local flights in that zone for several days.

Results of research performed on aircraft crew members activities detected their peculiarities related to various flight types [28]. Crews consisting of two members and performing short-distance flights had the longest working hours a day and the shortest rest periods. Fatigue here was thought to be caused by limited sleep due to short rest periods, early wakening and early working day beginning, as well as high workloads.

Crews consisting of two pilots and a flight engineer and performing night cargo flights had rest periods during daytime and they had to work at night. Examinations conducted on temperature changes rhythms allowed to detect absence of circadian biorhythms adaptation to such working schedule.

Long working hours and long wakefulness period (20.6 hours) determined by absence of places where crew members could get some rest were basic reasons which caused fatigue in crew members performing long-distance flights (Table 1). In some cases crew members had to fly their aircraft during an unfavorable period in their circadian rhythm when they had to make additional efforts to maintain their working capacity in spite of their fatigue and feeling not quite well. Sleep divided into short periods during breaks between flights also caused greater fatigue.

Research revealed that sleep loss consequences accumulated in crew members and fatigue accumulation rate depended on sleep deficiency growth. Sleep in places aimed for crew members rest on an aircraft is less deep and qualitative while homeostatic process determines a body demand for slow-wave sleep. Sleep at night turns out to be more preferable. Sleepiness peaks were detected due to research results; the first appeared during early morning hours or so called minimal circadian activity window (MCAW) from 3 a.m. to 6 a.m.; a middle-day peak (day drowsiness window) appeared during a period from 3 p.m. to 5 p.m. Time frames of sleepiness peaks differ in people with morning biological activity type ("early rises") and evening biological activity type ("late risers").

Research results revealed that mental working activities involved stable levels formation for basic central nervous system (CNS) functions which were determined as per three components: efficiency, stability, and reliability. Thus, short memory efficiency (quantity of numbers remembered) measured before a working shift started amounted to 6.40± 0.21 among cigarettes-making lines operators from the first group (early risers), and to 6.51±0.14, among late risers; at the end of a working shift it was equal to 6.56±0.15 and 6.43±0.22 correspondingly, discrepancies between groups being insignificant. Functions stability varied within 3.2%. Levels of such short memory parameter as reliability were quite stable. The same data were obtained for such functions as attention and simple information perception.

When labor intensity was high (3.2 hazard category), a decrease in CNS functions activity was detected by the end of a working shift. CNS parameters didn't reach high functional level. There was a 15.3% decrease in attention concentration over a shift dynamics in air traffic controllers who were early risers, and a 13.4% decrease in those who were late risers, after 12 hours of work; it was higher than physiological

Table 1

Job-related reasons for fatigue in aircraft crew members

Factors related to fatigue	Flight type		
	Short-distance flights	Night cargo flights	Long-distance flights
Limited sleep due to short rest periods	+		
Limited sleep due to necessity to come to a work place at early hours	+		
Multiple periods of high workloads during a flight shift	+		
Flying through a lot of sectors	+	+	
Flying under intense air traffic.	+		
Long working hours a day	+		+
Long wakefulness periods during a working day			+
High workload during periods of low circadian activity		+	+
Short sleep periods not conforming to body circadian rhythms		+	+
Circadian rhythms disorder caused by night work		+	+
Sleep divided into short periods during breaks between flights		+	+
Circadian rhythms disorder caused by passing through multiple time zones			+
Phase shift in circadian biological rhythms caused by longer work and rest sequence cycle			+

standards for body strain and indicated that mental working capacity went down significantly and fatigue occurred.

Analysis performed on daily curves showing CNS parameters revealed lower short memory efficiency during evening hours than during night and morning ones. At the same time attention function, visual and audio information perception were quite stable and didn't differ in the afternoon and at night. In other words, we detected that daily curves showing basic CNS parameters flattened regardless of a biorhythmologic group. It is seemingly caused by requirements set forth for operators' activities and it eliminated reduction in working capacity thus forming additional body strain.

Physiological research performed on the cardiovascular system revealed that daily periods for heart rate didn't change in RTS operators with the evening biorhythmologic type when their labor wasn't significantly intense (the 2nd permissible category). It was also proved by lower statistically authentic heart rate parameters detected in late risers during a night shift against their counterparts with the morning biorhythmologic type which on average amounted to 69.90±1.17 and 74.22±1.40 strokes/minute, correspondingly ($p<0.05$), during a shift. Heart rate parameters in morning type operators (early risers) didn't have any discrepancies during a night shift (74.27±1.04 strokes/minute) and a morning one (72.0±1.95 strokes/minute). It showed that heart rate remained the same in late risers, that is, people with the evening biorhythmologic type. Heart rate disorders in "early risers" (people with a morning biorhythmologic type) can lead to additional strain in cardiovascular system regulation related to work in shifts.

When we compared blood pressure parameters in people with insignificantly intense labor (corresponding to the 2nd per-

missible category), we didn't reveal any statistically significant changes in blood pressure parameters during a day in people with the morning and evening biorhythmologic type. Thus, average systolic blood pressure level during a shift amounted to 118.43±1.07 mmHg in people from the 1st group, and to 116.84±0.97 mmHg, in people from the 2nd one; against a morning shift, correspondingly: 112.29±0.75; 110.84±1.27; and a night shift: 114.84±2.30: 111.87±2.36 mmHg. Diastolic blood pressure remained at almost the same level during morning and evening research periods.

The same data were obtained when the research was performed on cigarettes-making lines operators whose labor could also be ranked as having the 2nd permissible category in terms of its intensity. These workers' work activities differed from the previous occupational group ones as their working day was longer and lasted 12 hours.

Blood pressure examinations during stress tests showed that systolic blood pressure reached its peak when namely early risers had to undergo physical loads. By the end of an evening shift it amounted to 150.0±3.20 mmHg; to 140.0±1.91 mmHg, when a night shift began; and to 144.09±3.80 mmHg, by the end of a night shift. The same parameters were lower in late risers: 146.11±3.61; 135.83±3.59; 140.62±3.33 mmHg. Systolic blood pressure as a reaction to loads, as a rule, grew most considerably by the end of a working shift and varied within 24.5–26.4%. Besides, we detected slower blood pressure recovery to its standard levels in people with the morning biorhythmologic type. Systolic blood pressure parameters in workers with the evening biorhythmologic type recovered by the 4th minute while it took longer in workers with the morning one, especially at the end of a night shift, and their blood pressure reached standard values only when 5 minutes after a shift passed. Individual parameters analysis revealed even later recovery in some cases which proved there was a hazardous response from the cardiovascular system related to work strain accumulation.

The calculated values for stroke blood volume (SBV), minute blood volume (MBV), and peripheral resistance (PR) revealed that all the detected levels fully corresponded to age standards. There were no dynamic changes in these parameters caused by work. To determine circulation types peculiarities, we compared the obtained minute blood volume and peripheral resistance values to proper ones. Our determination of a circulation type as per average groups comparison of actual MBV and PR values with their proper ones allowed us to detect that hyperkinetic and eukinetic circulation types prevailed both in "early risers" and in "late risers", and it could be considered a favorable results as their bodies seemed to adapt to work loads.

We performed a comparative analysis of research results for workers with different biorhythmologic types whose labor was highly intense (3.2 hazard category) and revealed statistically significant discrepancies in blood pressure, both at the beginning of a shift, and over a shift dynamics. Systolic blood pressure in air traffic controllers with the morning biorhythmologic type ("early risers") amounted to 134.28 ± 2.29 at the beginning of a shift, and to 140.91±1.28 mmHg by the end of it; diastolic blood pressure, to 82.16±2.13 and 84.22±1.46 mmHg correspondingly. Initial systolic blood pressure in air traffic controllers with the evening biorhythmologic activity type amounted to 127.51±2.64 mmHg at the beginning of a shift, and to 126.0±1.78 mmHg by the end of it. Discrepancies between

groups were statistically significant ($p<0.05$).

Blood pressure examinations performed on workers with different biorhythms showed that systolic and diastolic blood pressure tended to be higher in "early risers" than in "late risers". Parameters were higher than physiological standards set forth for workers with mental activity type. We also detected high average dynamic blood pressure levels at the beginning of a shift (99.53±1.45 mmHg) and during a whole shift (from 101.71±1.24 to 103.12±1.16 mmHg). It proved the circulation system in workers with the morning biorhythmologic type was under strain. But when it comes to "late risers", we should note that blood pressure parameters in them corresponded to physiological standards.

As we analyzed these data, we saw that there were no authentic discrepancies between blood pressure during day and night shifts. "Early risers" didn't have statistically significant discrepancies in average shift systolic blood pressure during day and night working hours (138.39±1.45 and 139.03±1.48 mmHg, correspondingly, $p>0.05$), as well as in diastolic one (83.45 ± 0.48 and 83.82±0.42 mmHg). The same data were obtained among "late risers" as per systolic blood pressure parameters (126.82±1.24 and 125.59±1.01 mmHg, $p>0.05$) and diastolic blood pressure parameters (72.35±0.48, $p>0.05$; 72.16±0.76 mmHg, $p>0.05$). The obtained results prove there was a disorder in daily blood pressure periods both in air traffic controllers with the morning biorhythmologic type and the evening one. Instead of an expected decrease in blood pressure parameters during a night shift related to higher parasympathetic nervous system activity, we detected high blood pressure levels during day working hours which showed that desynchronization occurred.

Similarity in physiological reactions occurring in people with two different biorhythmologic types whose labor was apparently very intense (3.2 hazard category) was that they all had disorders in daily systolic and diastolic blood pressure periods. Discrepancies were revealed in blood pressure parameters being higher than physiological standards set forth for workers with mental activities in people with the morning biorhythmologic type, but the same parameters in people with the evening one corresponded to them.

Hemodynamics peculiarities analysis allowed us to reveal that a great share of "early risers" had hypokinetic circulation type; more favorable eukinetic type prevailed among operators from "late risers" group. Hypokinetic circulation type formation in workers is known to indicate primary hypertension risk.

Calculated functional changes index (FCI) which characterizes circulatory system adaptation potential [20] amounted to 2.20±0.05 scores for early risers and to 2.19±0.04 scores for late risers as per average shift level during a morning work shift of an occupational group with working conditions belonging to the 2nd hazard category (RTS operators). The same parameter in the same group amounted to 2.40±0.04 and 2.27±0.05 scores correspondingly during an evening shift, and to 2.29±0.06 and 2.21±0.04 scores correspondingly during a night one. According to a scoring scale these FCI values correspond to satisfactory adaptation. However, we detected a trend for a bit higher values in early risers, especially during evening shifts.

Cigarettes-making lines operators whose working conditions also belonged to the 2nd hazard category had functional strain as FCI amounted to 2.64±0.05 scores in early risers from this occupational group during a day shift, and to 2.66±0.03 in late

risers; it was 2.57±0.01 and 2.59±0.05 scores correspondingly during a night shift. The obtained results are likely to be caused by a long 12-hour working shift. When labor intensity grows and labor can be ranked as having 3.2 hazard category, adaptation becomes unsatisfactory in people with the morning biorhythmologic type. Values of functional changes index for the circulatory system here amounted to 2.93±0.05 scores during a day shift and to 2.64±0.06 scores during a night one. These values were lower in people with the evening biorhythmologic type (2.64±0.06 scores during a day shift; 2.63±0.05 scores during a night one). The detected statistically significant discrepancy in values ($p<0.05$) obtained for two groups of the examined people with different types ("early risers" and "late risers") means there is less apparent functional body strain in people with the evening biorhythmologic type ("late risers") and it allows to assume their adaptation to work in shifts is more successful.

The obtained results show that daily rhythms of circulatory system functional changes index in RTS operators react to workloads and rearrange themselves within satisfactory adaptation limits. But at the same time there were no differences in functional changes index during a day and a night in cigarettes-making lines operators whose labor has the same hazard degree as RTS operators' (the 2nd permissible hazard category) but whose working day is longer. This regularity is also detected in air traffic controllers with labor ranked as having 3.2 hazard category and reveals a disorder in FCI daily rhythm as an integral parameter showing the cardiovascular system state and indicates that desynchronization occurs.

Physiologic research results are also validated by data obtained via subjective estimations of one's health and labor motivation. Air traffic controllers (with highly intense labor) estimated their health as being poor, they were less active and had bad mood during a night shift in comparison with a day one; it was especially apparent in case of people with the morning biorhythmologic type (the 1st group). Cigarettes-making lines operators (the 2nd hazard degree) didn't have any statistically significant discrepancies in their health, activity, and mood. Labor motivation of air traffic controllers, as it can be seen from the Table 2, was authentically lower during a night shift than during a day one. Decrease in air traffic controllers' labor motivation was the most apparent in people from the 1st biorhythmologic (morning) group which showed fatigue occurrence in them.

Table 2

Labor motivation parameters in people with different biorhythmologic type during different shifts

Occupational group	Biorhythmologic type	Health		Activity		Mood		Motivation		Hazard category
		day	night	day	night	day	night	day	night	
Cigarettes-making lines operators	Early risers	5,92 ± 0,14	5,90 ± 0,14	5,86 ± 0,15	5,91 ± 0,17	5,67 ± 0,21	5,41 ± 0,19	5,87 ± 0,13	5,61 ± 0,15	2
	Late risers	6,02 ± 0,23	6,0 ± 0,13	5,83 ± 0,17	5,88 ± 0,15	5,56 ± 0,11	5,60 ± 0,14	5,90 ± 0,16	5,85 ± 0,15	
Air traffic controllers	Early risers	5,0 ± 0,20	4,38* ± 0,14	5,515 ± 0,17	4,66* ± 0,14	4,91 ± 0,12	4,40* ± 0,13	4,80 ± 0,11	4,31* ± 0,14	3.2
	Late risers	5,51 ± 0,12	5,02** ± 0,13	5,60 ± 0,14	5,34** ± 0,16	5,31** ± 0,12	5,0** ± 0,16	5,23** ± 0,15	5,19** ± 0,18	

Note: * means discrepancies between shifts are statistically authentic ($p<0,05$)

** means discrepancies between "early risers" and "late risers" are statistically authentic ($p<0.05$)

We judged on fatigue accumulation as per two criteria: functions which didn't fully recover after work and a week dynamics in the examined parameters. Analysis of the results obtained for PC operators occupational group revealed there was a decrease in their health, activity, and mood, as well as nervous processes instability, poorer functioning of analyzer systems and vegetative activity provision systems; all these parameters became worse each consequent weekday in comparison with the previous one. Here initial parameters were worse on Wednesday and Friday than on Monday, and they were also worse each consequent day than on a previous one as per subjective evaluations. Thus, mood parameter amounted to 5.95±0.56 scores at the beginning of a work shift on Monday; to 5.55±0.32 scores, on Tuesday; to 5.66±0.33 scores, on Wednesday; to 5.50±0.43 scores, on Thursday; to 5.43±0.29 scores on Friday. Initial time level of a simple visual-motor reaction was equal to 226.07±1.32 msec on Monday, to 230.88±1.30 on Wednesday, and to 236.81±1.57 msec on Friday, and it indicates that functions don't fully recover, and fatigue accumulates. Research performed during weekly cycles of operators' work revealed that 40% operators had poorer parameters by the end of a week cycle, as well as from week to week, and it proved functional shifts slowly accumulated.

To prevent overfatigue, we tested various functional state correction techniques in actual working conditions. We detected that autogenic training was an efficient technique for cardiovascular system state correction: heart rhythm stabilized and heart rate went down in people from all the occupational groups regardless of their labor intensity and shift regime, hypotensive effect also occurred in all of them. We didn't observe such changes after electric analgesia and electric puncture. Autogenic training in general exerted positive effects on body functional state during shift work and it allows us to recommend this technique to people with the morning biorhythmologic type.

Conclusions. Fatigue risk analysis performed on aircraft crew members revealed basic reasons for unfavorable overfatigue occurrence: limited sleep due to short rest, sleep divided into short time periods during breaks between flights, disorder and phase shift in circadian rhythms caused by night work or multiple passing through various time zones, high work load, and long working hours.

We detected an increased fatigue risk for operators with the morning biorhythmologic type ("early risers") which became obvious through disorders in daily heart rate periods under average labor intensity (RTS operators), blood pressure parameters being higher than permissible levels (set forth for workers with mental activity) under high labor intensity (air traffic controllers), as well as through prevalence of unfavorable circulation regulation type (hypokinetic one).

Vegetative provision of body functioning in operators with the evening biorhythmologic type as per cardiovascular system state showed there was a favorable hemodynamics response to workloads: their heart rate preserved its daily rhythm, systolic, diastolic, and average dynamic blood pressure, and functional changes index were within physiologically permissible levels and were stable during their working day.

We developed certain techniques aimed at lowering risks related to fatigue and overfatigue occurring during shift work. Strain in circulatory system regulation, lower labor motivation and poorer health in people with the morning bio-

rhythmologic type call for body functional state correction when they have to work in shifts and especially when their labor is highly intense.

Practical recommendations developed for civil aviation personnel include several stages: crew members fatigue measuring, risk assessment, developing and implementing activities aimed at risk reduction (rules for controlled rest in a cockpit etc.).

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CONDITIONS WHICH CAUSE RISK FACTORS FOR RAILROAD TRANSPORT WORKERS AND POPULATION: HYGIENIC ASSESSMENT (ON THE EXAMPLE OF SOUTH-EASTERN RAILWAY)

V.A. Loginova[1], G.G. Onishchenko[2]

[1]Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, Railway transport office, 17 Dubininskaya Str., Moscow, 115054, Russian Federation
[2]Russian Academy of Sciences, 32a Leninskii prospect, Moscow, 119334, Russian Federation

We performed comparative hygienic assessment of environmental factors and health of population living near the South-Eastern railway and railroad transport workers over 21012–2016 and revealed a trend for environmental quality improvement both at railroad objects and on territories influenced by them. This trend was confirmed by a 3.8 times decrease in specific weight of atmospheric air samples with hazardous substances concentrations exceeding MPC; a decrease in drinking water samples taken from distribution networks which deviated from standards (by 31.5 % as per sanitary-chemical parameters, and by 26.5 %, as per microbiological ones); lower share of soil samples not corresponding to standards (it went down to 0 as per sanitary-chemical parameters, and there was a 1.8 times decrease in it as per microbiological parameters); there was also a decrease in a number of workplaces not corresponding to hygienic standards in terms of physical factors (noise, by 1.6 times lower, microclimate, by 3.1 times, luminance, by 1.7 times) and in terms of MPC levels related to vapors and gases concentrations in working area air (by 4.3 times), as well as dust and aerosols (by 1.6 times). At the same time there are persistent negative trends for dynamic parameters of water reservoirs quality: a specific weight of water samples not corresponding to standards increased, by 3.4 % as per sanitary-chemical parameters, and by 29.2 %, as per microbiological ones. Occupational risks for railroad transport workers still exist. Industrial noise is considered to be a priority risk factor and it corresponds to occupational morbidity structure. 19 occupational morbidity cases were detected at South-Eastern railway over the examined period. Occupational morbidity went down from 1.3 to 0.2 cases per 10 000 workers (from 1.5 to 1.14 per 10 000 workers for the whole railways network). Sensorineural hearing loss amounts to 63.2 % in occupational pathology structure (up to 73 % for the whole railways network). Working conditions of locomotive team members remain the most unfavorable.

Negative environmental factors continue to exert their influence on health. Although primary morbidity among population in general and workers employed by "Russian Railways" PLC ("RR" PLC) over 2012–2016 (by 13.1 % and 13.6 % correspondingly), an increase in respiratory organs diseases is detected both among population in general (by 11.2 %), and workers employed by "RR" PLC (by 18.5 %). Besides, respiratory organs diseases make the greatest contribution into primary morbidity. Their specific weight amounts to 26.5–39.8 % among population in general, and to 37.9 %, among "RR" PLC workers. As a whole, morbidity among "RR" PLC workers employed at the South-Eastern railway tends to be 34.7–43.9 % higher than among population in general (by 24.3–36.4 % for the whole railways network), and this fact proves there are additional negative influences exerted by occupational factors. It is also shown that morbidity with temporary disability among 1st category workers has a negative trend (a 5 % increase).

Key words: *environmental factors, primary morbidity, occupational diseases, railroad transport, hygienic assessment, occupational risk.*

The World Health Organization states that the top priority among primary prevention tasks is to create and maintain a healthy environment. The environment is a most vital component in health protection, and various activities which are an essential part of it play an important role in risks determination. Examples of such activities are en-

Vera A. Loginova – Deputy Director (e-mail: va-loginova@mail.ru; tel.: +7 (495) 633-27-19).
Gennadiy G. Onishchenko – Member of the Russian Academy of Sciences, Doctor of Medical Sciences, Professor, Assistant to the RF Government Head (e-mail: journal@fcrisk.ru; tel.: +7 (495) 954-39-85).

ergy production, industries, water supply and sanitation, agriculture, housing, and transport [1].

Results obtained in various research prove that physical environmental factors and contamination of atmospheric air, drinking water, and soils, are priority environmental factors which influence population health. More than 80% population live on territories which are exposed to complex chemical loads. Industrial factors also exert adverse effects on a worker's body and are risk factors causing various diseases evolvement. Hygienic assessment of factor influence performed within health risk analysis methodology is an instrument for efficient management of sanitary-epidemiologic situation [2–7].

As per data taken from state report on sanitary-epidemiologic welfare at railways in 2012-2016 there was a positive trend in environmental situation at objects influenced by railway transport. There was a 3.8 times decrease in a share of examined samples with MPC higher than the standard as per hazardous substances content in the atmospheric air and soils; drinking water quality in distribution networks also improved [8–10]. Morbidity with temporary disability apparently tended to go down [11–13].

Our research goal was both to perform hygienic assessment of sanitary-epidemiologic situation on railway transport objects, and to assess priority risk factors occurrence (on the example of the Southern-Eastern railway).

Data and methods. We examined dynamics in basic sanitary-epidemiologic parameters at the Southern-Eastern railway (as a typical region where a railway network is located) and compared them with overall parameters obtained for the whole railway network. Our examination and comparison was based on data taken from the state statistic reports issued in 2012-2016 by Rospotrebnadzor offices and bodies for railway transport. We performed this comparison in order to detect adverse environmental factors which exerted their influence on railway workers' health. We also conducted a comparative assessment of sanitary-epidemiologic situation concerning the following environmental objects: atmospheric air, communal and drinking water supply facilities, and soils, which were influenced by railway transport infrastructure; our assessment also included working conditions and occupational morbidity of workers with basic railway transport occupations. We analyzed health of such workers in the branch as per parameters of morbidity with temporary disability.

Results and discussion. Rospotrebnadzor's territorial offices and institutions in the railway transport sphere are organized in such a way that their structure reflects specific features of management and operation systems which exist at railway transport. The basic structural principles here are:

- objects under surveillance are often observed beyond a territory where an office is located as railways go through various Russian regions and railway structure is organized accordingly;

- surveillance and control are often performed allowing for the linear structure which is characteristic for the railway transport system;

- surveillance and control over safety and sanitary-epidemiologic welfare of passengers and cargo transportation are organized in such a way that they can be performed at any point at any route.

Railway Transport Office of the Federal Service for Surveillance over Consumer Rights Protection and Human Well-being is the central authority among surveillance and control bodies which represent federal

state sanitary-epidemiologic surveillance over railway transport. Its main function is to supervise and coordinate structural bodies' activities aimed at providing sanitary-epidemiologic safety at railway transport objects and infrastructure; the function is performed via 15 regional Rospotrebnadzor offices at 15 railways in the Russian Federation [14,15].

The Southern-Eastern railway is a branch of "Russian Railways" PLC ("RR" PLC). It is located in the center of the whole railways network, goes through the Centralno-Chrnozyomniy economic district and connects eastern regions and the Urals with the Central Russia, as well as northern, northern-western and central Russian regions with the North Caucasus, Ukraine, and Transcaucasia states. It is linked to several other railways: Moskovskaya, Kuybyishevskaya, Privolzhskaya, and North-Caucasian one. Regional square it operates on is equal to about 160,000 km or 0.9% of the Russian Federation territory. The operational length of the Southern-eastern railway is equal to 4.3 thousand kilometers or 5% of the total railways length in the Russian Federation. 83.6% of cargo turnover is made due to electrical traction; the remaining transportations are made with thermal traction. The Southern-Eastern railway goes through 3 regions: Liskinskiy, Belgorodskiy, and Michurinskiy. At present 5 pairs of high quality long-distant trains run on it.

Basic cargoes which are transported by the Southern-Eastern railway include iron ores, ferrous metals, construction materials, agricultural products, oil, cement, chemical and mineral fertilizers, industrial raw materials, and flux materials.

The Southern-Eastern department of the Rospotrebnadzor's Railway Transport Office is responsible for surveillance over about 6.9% of the overall number of objects under surveillance which are included into the railways network structure (the number was 1.657 in 2016). The greatest specific weight in the objects structure belongs to communal objects (34.9%) and industrial ones (30.9%). Transport vehicles are about 9% of the total number; objects which deal with food products retailing and catering are about 23.9%; children and teenagers facilities account for 1.3%.

Over the analyzed period (2012-2016) specific weight of objects belonging to the 3rd group as per their sanitary-epidemiologic welfare (extremely unsatisfactory) decreased from 12.6% in 2012 to 10.0% in 2016; average parameter for the overall railways network was 9.1%. The structure of the 3rd group objects is as follows: communal objects account for 31.9% (average network parameter is 34.9%); industrial objects, 30.9% (average network parameter is 20.8%); food products retailing and catering, 23.9% (average network parameter is 16.3%); transport vehicles, 9.1% (average network parameter is 21.4%); children and teenagers facilities, 1.3% (average network parameter is 1.9%).

Atmospheric air quality at railway transport objects depends on their own location and hazardous chemical objects being located near railways. Besides, there are potential sources of chemical contamination which can pollute atmospheric air: large industrial enterprises in the railway transport sphere; petrochemicals storage facilities; open-air coal storage facilities; enterprises dealing with manufacturing and storing wooden sleepers; places where railway tanks are cleansed, washed, and steamed (when oil and petrochemicals are transported). Accidents which happen at railways can also contribute into environmental contamination when hazardous chemicals are transported. Chemicals emitted and spilt into the environment cause health risks for

people who live in settlements located near places of such accidents [16].

We analyzed atmospheric air quality on territories influenced by the railway transport objects and revealed that its hygienic characteristics improved. Specific weight of samples with chemicals concentrations higher than MPC summarily as per all ingredients went down 3.8 times from 2012 to 2016 and amounted to 0.4%. Concentrations higher than 5 MPC were registered in single cases (less than 0.01%).

As per data obtained in route and field examinations performed on territories influenced by industrial enterprises in the railway transport sphere, there also was a positive trend in the air quality. A share of atmospheric air samples with hazardous substances concentrations higher than MPC decreased 7.5 times in terms of all the basic contaminants.

The data obtained during social-hygienic monitoring revealed that nitrogen oxides, carbon disulphide and sulfur oxides, carbon oxides, carbon black, saturated and unsaturated hydrocarbons were the basic contaminants which polluted atmospheric air on territories influenced by the railway transport [14,15]. Concentrations higher than MPC were most frequently registered for suspended substances - 2.5% examined samples (including concentrations 5 times higher than MPC in 0.01% cases); phenol and its derivatives, 1.4% (higher than 5 MPC in 0.01% cases): formaldehyde, 0.5% (higher than 5 MPC in 0.05% cases); hydrocarbons, 0.3% (higher than 5 MPC in 0.06% cases). Concentrations in the atmospheric air higher than MPC were also registered for sulfur dioxide (1.0%), carbon monoxide (0.9%), nitrogen dioxide (0.8%), heavy metals (0.4%), ammonia and carbon disulphide (0.2%). In 2016 suspended substances concentrations which exceeded MPC were registered on territories influenced by the Southern-Eastern railway objects; there were 0.5% samples not corresponding to hygienic standards summarily as per all ingredients; 2.4% samples, as per suspended substances.

Drinking water is mostly supplied to the Southern-Eastern railway objects from underground water sources, just like to the whole railways network in general; 135 artesian wells account for 97.95% of all water sources. Specific weight of centralized water supply sources which didn't conform to the hygienic standards decreased by 24.6% from 2012 and amounted to 10.4% in 2016 at the railways network in general. As for the Southern-Eastern railway, we detected a reverse trend here: specific weight of centralized water supply sources not conforming to the hygienic standards increased by 66.4% from 2012 and amounted to 21.97%. 79.2% cases of poor sanitary situation at water supply sources is caused by absence of sanitary protection zones or by violation of requirements to their organization. Besides, quality of water which comes from underground water sources at Southern Eastern railway is significantly poorer than at the railways network in general: specific weight of samples unsatisfactory as per sanitary-chemical parameters amounted to 30.8-42.6% in the analyzed period and was16.8% higher than on average at the railways network (Table 1).

Specific weight of samples which were unsatisfactory as per microbiological parameters was considerably lower than at the railways network in general. However, if taken in dynamics, this parameter has an apparent deteriorating trend as water quality obviously gets poorer. Specific weight of unsatisfactory samples increased from 2.4% in 2012 to 3.1% in 2016. But in spite of low quality water taken from water supply sources, 94.6% people who live near the Southern-Eastern railway are provided

with good quality drinking water which is a bit higher than at the railways network in general (94.2%).

Water quality assessment in distribution networks revealed that it improved both at the Southern-Eastern railway and at the railways network in general. Specific weight of water samples which were unsatisfactory as per sanitary-chemical parameters decreased from 23.8% in 2012 to 16.3% in 2016 at the Southern-Eastern railway (from 17.6% to 16.7% at the railways network in general); as per microbiological parameters, from 4.9% to 3.6% (from 4.6 to 3.2% at the railways network in general). Unsatisfactory sanitary-chemical parameters of water are caused by it being too hard and by high iron contents in it; they consequently lead to unsatisfactory organoleptic water properties.

We analyzed surveillance and control activities and revealed that a big quantity of water samples not conforming to standards, especially as per sanitary-chemical parameters, was caused by unsatisfactory situation at communal networks, their overall decay, and untimely repair and maintenance procedures. Low quality of distribution networks is due to their long-term operation, changing conditions at places where they are located, application of pipes without any anti-corrosion coats, and low quality lock valves which are used at distribution networks.

Oil and its products, heavy oil, diesel oil, lubricants, as well as remains of transported cargoes and industrial wastes, are the most widely-spread contaminants on territories where railway transport enterprises are located. Besides, there are other contaminants on these territories, such as crushed stone which can no longer be used in construction, ferrous metals scrap, dredged soil which remains after excavation, ash and slag, sleepers.

A number of soil samples not corresponding to sanitary-epidemiologic requirements as per sanitary-chemical, microbiological and parasitological parameters tends to grow on territories where settlements are located.

Assessment of soils quality and sanitary state performed at the Southern-Eastern railway revealed that there was a descending trend in number of soil samples not corresponding to hygienic standards as per sanitary-chemical, microbiological, and parasitological parameters. but still chemical contamination in 2012-2016 was 2.7 times higher than on average at the railway network. Microbiological soils contamination was also 8.4% higher than at the railways network on average (Table 2).

Objects under surveillance which are included into the railway networks structure are specific, and most of them are objects belonging to the "RR" PLC and its branches and subsidiaries. Therefore, laboratory examinations of soils samples were conducted mostly in zones influenced by industrial enterprises and transport (71% of examined samples).

Table 1

Qualitative parameters of water taken from water sources at intake points

Parameters	Underground sources									
	2012		2013		2014		2015		2016	
	Whole network	S-E railway	Whole network	S-E railway	Whole network	S-E railway	Whole network	S-E railway	Whole network	S-E railway
Sanitary-chemical	31,1	34,9	30,7	42,6	32,1	38,7	31,6	30,8	30,7	36,1
Microbiological	6,6	2,4	6,04	3,9	6,0	2,2	5,5	1,5	4,9	3,1

Note: S-E railway means Southern-Eastern railway

Table 2

Soil quality characteristics

Parameters		Specific weight of samples not conforming to hygienic standards					In settlements				
		2012	2013	2014	2015	2016	2012	2013	2014	2015	2016
Sanitary-chemical	overall	5,0	3,9	5,3	5,9	2,0	0,6	0,5	0,5	2,6	2,7
	SUR	**20,97**	**12,8**	**16, 4**	**12,2**	**0**	**0**	**0**	**0**	**0**	**0**
Micro-biological	overall	3,9	3,3	8,8	3,2	3,3	4,3	3,4	16,5	2,9	3,7
	SUR	**10,6**	**4,4**	**4, 0**	**4,1**	**5,7**	**0**	**0,8**	**0**	**1,2**	**0**
Parasitological	overall	2,0	1,7	1,9	0,4	0,3	1,0	1,1	0,73	0,4	0,4
	SUR	**1,4**	**1,2**	**0**	**1,5**	**1,1**	**0**	**0**	**0**	**0**	**0**

Note: SUR means Southern-Eastern railway

The highest chemical contamination was detected in such zones (16.8% samples not conforming to hygienic standards), oil products and heavy metal salts being priority contaminants.

Objects under surveillance which are included into the railway networks structure are specific, and most of them are objects belonging to the "RR" PLC and its branches and subsidiaries. Therefore, laboratory examinations of soils samples were conducted mostly in zones influenced by industrial enterprises and transport (71% of examined samples). The highest chemical contamination was detected in such zones (16.8% samples not conforming to hygienic standards), oil products and heavy metal salts being priority contaminants.

We analyzed primary morbidity among population who were exposed to the railways network impacts in dynamics over the examined period (2012-2016) and revealed there was a slight increase in the overall morbidity equal to 0.07%. Population morbidity on territories influenced by the Southern-Eastern railway decreased by 13.1%. Morbidity structure as per basic nosologies didn't change. Such nosologic forms as respiratory organs diseases (26.5-39.8%), injuries, intoxications, and other outer causes (10.7-11.8%), urogenital system diseases (7.5-9.7%), ear and mastoid diseases (7.5-9.4%), skin and subcutaneous tissue diseases (6.2-7.8%) made the greatest contribution into primary morbidity both at the Southern-Eastern railway, and at the railways network in general.

Workers employed by "RR" PLC and its brunches and subsidiaries account for 32.9% among population influenced by railway transport objects at the Southern-Eastern railway (37.2% on average at the railways network in general). Therefore, assessment of hazardous influence exerted by specific industrial factors on railway workers is a significant part of hygienic monitoring [17,18].

Railway objects include repairing plants, repairing depots for locomotives and carriages, railways maintenance stations, communication, and power supply stations. Their analysis performed at the Southern-Eastern railway revealed that specific weight of objects belonging to the 3rd sanitary-epidemiologic category (extremely unsatisfactory) decreased from 19.7% in 2012 to 11.5% in 2016. Besides, we noted that a share of such 3rd category objects was on average 17.3% lower that at the railways network in general.

Laboratory examination of working area air performed in 2012-2016 revealed there was a descending trend in specific weight of samples with steams and gases concentrations higher than MPC, both in general, and in terms of substances belonging to the 1-2 hazard category (from 2.6 to 0.6% and from 2.3 to 1.9% correspondingly). This dynamics is also true for the railways network in general. As working area air quality improves due to decrease in dust

and aerosols contents at the Southern-Eastern railway objects, specific weight of air samples with dust and aerosols contents exceeding MPC goes down from 10.9 to 6.8%; as for substances belonging to the 1-2 hazard category, from 8.9 to 0.9%. There is a reverse trend at the railways network in general: specific weight of samples with dust and aerosols concentrations higher than MPC increased from 13.5 to 15.3%; as for substances belonging to the 12- hazard category, from 13.5 to 22.6% [19,20].

There was a decrease in specific weight of working places not corresponding to hygienic standards at industrial objects related to the Southern-eastern railway; the same trend was detected at the railways network in general. Here are the figures for several parameters: 1) noise level, a drop from 30.3% to 18.5% (at the railways network in general from 21.4% to 19.97%); 2) microclimate, from 56.0 to 1.6% (from 5.3 to 4.6%); luminosity, from 15.6 to 9.2% (from 19.6 to 16.9%). But as for vibration, specific weight of working place where this parameter didn't conform to hygienic standards increased from 8.1 to 9.3% while the average railways network parameter decreased from 17.7 to 10.99% [19,20].

Our analysis of control and surveillance activities results revealed that there were several factors causing unsatisfactory working conditions inside industrial facilities, namely: machine tools (metal processing units, wood processing ones, forging machines etc.) were in operation for very long time periods, and their wear and tear was great; ventilation either was absent at working places or didn't function properly; in some cases, ventilation systems were not constructed relevantly and with any allowance for production processes peculiarities (incorrect technical solutions); temperature regime was unbalanced (not enough heating units in workshops, or heating systems didn't function in tact with gates opening); improper ventilation during welding; most hazardous processes were not isolated.

Occupational morbidity had an apparent descending trend. From 2012 to 2016 a number of detected occupational diseases decreased from 133 cases to 97 cases, and morbidity index fell from 1.5 to 1.14 per 10,000 workers (the average country index was 1.47 per 10,000 workers in 2016) [16].

Occupational morbidity structure doesn't change significantly in terms of occupations and nosologic forms. Locomotive drivers and their assistants have the greatest share in it (32.5-51.5%), as well as track walkers who check railways (19.3-24.3%). Sensorineural hearing loss holds the leading place among diseases (up to 73%); the second place belong to diseases with dust etiology (up to 13%); vibration disease takes the third place (up to 5%). Peripheral nervous system (PNS) diseases and musculoskeletal system diseases are at the fourth place (up to 9% together).

There are peculiarities in occupational morbidity among locomotive teams members; they are determined by their specific working conditions. The greatest share among diseases here belongs to sensorineural hearing loss (93.4%); vibration disease has the second place (9.4%), and peripheral nervous system (PNS) diseases and musculoskeletal system diseases are at the third place (1.3%) [8–10].

Over 2012-2016 single cases of occupational diseases were registered among workers employed at the Southern-Eastern railway: 7, 2, 5, 4, 1 correspondingly, and 47.4% cases were registered among locomotive drivers. Sensorineural hearing loss prevails in occupational pathology structure with its specific weight being 63.2%; respiratory organs diseases account for 26.3%, and musculoskeletal system diseases, for 10.5%.

There is an overall descending trend in primary morbidity among workers employed by "RR" PLC, both at the Southern-Eastern railway (-13.6%), and at the railways network in general (-8.8%). Primary morbidity detected at the Southern-Eastern railway is on average 6.99% lower that at the railways network in general and amounts to 528,1‰. However, overall morbidity index among "RR" PLC workers at the Southern-Eastern railway is 34.7-43.9% higher than among the RF population in general (24.3-36.4% higher among workers at the railways network in general).

Primary morbidity structure for "RR" PLC workers is as follows: the leading place belongs to respiratory organs diseases with 37.3% at the Southern-Eastern railway and 36.9% at the railways network in general; injuries, intoxications and other outer causes have the second place and account for 13.1% and 13.7% correspondingly; skin and subcutaneous tissue diseases have the third place and account for 10.4% and 6.5% (it is the 5th place at the railways network in general) correspondingly. The fourth place belongs to urogenital system diseases with 6.6% (9.7% and the third place at the railways network in general); the fifth place is musculoskeletal system diseases which account for 4.4% (6.9% and the fourth place at the railways network in general). Besides, we detected a 18.5% increase in primary morbidity with respiratory organs diseases, and a 4.3% increase, with digestive organs diseases.

We analyzed morbidity with temporary disability over 2012-2016 and revealed that a number of temporary disability cases per 100 workers fell from 52.4 to 48.5, and a number of days, from 652.4 to 605.1. At the same time, a number of temporary disability cases per 100 workers increased by 5.9% (from 52.7 to 55.8) among the 1st category workers (those directly responsible for trains movement), but a number of days in a temporary disability period per 100 workers decreased by 3.3%.

Conclusion. So, we can conclude that the environment in zones influenced by the Southern-Eastern railway improved over 2012-2016. Improvements were detected as per most analyzed factors. Atmospheric air quality improved in terms of chemicals concentrations (specific weight of samples with concentration higher than MPC decreased 3.8 times and 7.5 times in zones influenced by industrial enterprises). Drinking water quality in distribution networks also improved (a number of samples unsatisfactory as per sanitary-chemical parameters decreased by 31.5%, and microbiological ones, by 26.5%), as well as soil quality (a number of samples not conforming to hygienic standards as per sanitary-chemical parameters fell down to 0, and decreased 1.8 times as per microbiological ones). Working conditions for workers employed in the railway transport branch became safer as specific weight of samples with stem and gases concentrations higher than MPC dropped 4.3 times; aerosols and dust, 1.6 times; number of working places not conforming to hygienic standards in terms of noise decreased 1.6 times; microclimate, 3.1 times, luminosity, 1.7 times.

There was a positive trend in the examined period in overall ranking of railways transport objects and transport infrastructure in terms of their sanitary-epidemiologic state: a share of the 3rd category objects (extremely unsatisfactory ones) dropped by 20.6%.

But still, there are negative trends in some areas: quality of water taken from underground sources remains poor (a number of water sources not conforming to hygienic standards increased by 66.4%; number of water samples which were unsatisfactory as per sanitary-chemical parameters grew by 3.4%, and as per microbiological

ones, by 29.2%). Working places didn't correspond to safety standards in terms of vibration (and the share of such working places grew by 14.8%).

Occupational risk for railway workers also remains. Industrial noise is a priority risk factor and it corresponds to occupational morbidity structure. 19 occupational diseases cases were detected in the examined period at the Southern-Eastern railway. Occupational morbidity index decreased from 1.3 to 0.2 per 10,000 workers (from 1.5 to 1.14 per 10,000 workers at the railways network in general). Sensorineural hearing loss accounts for 63.2% in occupational morbidity structure (up to 73% at the railways network in general). Locomotive teams members have to work in the most unsatisfactory working conditions.

Environmental factors continue to exert negative influence. Although primary morbidity decreased both among population in general and among workers employed by "RR" PLC over 2012-2016 (by 13.1% and 13.6% correspondingly), morbidity with respiratory organs diseases grew both among population in general (by 11.2%), and among "RR" PLC workers (by 18.5%). Besides, respiratory organs diseases make the greatest contribution into primary morbidity with their specific weight being equal to 26.5-39.8% (37.9% among the "RR" PLC workers). Overall, morbidity among "RR" PLC workers employed at the Southern-Eastern railway tends to be higher than among population in general by 34.7-43.9% (by 24.3-36.4% at the railways network in general), and it proves there is additional negative influence exerted by adverse industrial factors.

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EXPERIMENTAL MODELS AND INSTRUMENTAL SURVEYS FOR RISK ASSESSMENT IN HYGIENE AND EPIDEMIOLOGY

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RESEARCH ON ACUTE TOXICITY OF NANODISPERSE MANGANESE OXIDE AEROSOL FOR PREDICTING HEALTH HAZARDS FOR WORKERS AND POPULATION UNDER INHALATION EXPOSURE

N.V. Zaitseva, M.A. Zemlyanova

Federal Scientific Center for Medical and Preventive Health Risk Management Technologies, 82 Monastyrskaya Str., Perm, 614045, Russian Federation

Our research object was nanodisperse manganese oxide synthesized at Mn^{2+} and MnO_4 ions interaction when nano-reactors, namely bromide cetyltrimethylammonium micelles, were present but they didn't become a part of an end product. We applied scanning electronic microscopy, X-ray phase analysis, dynamic laser light scattering, Brunauer, Emmeth, Taylor and Barret, and Joyner and Halenda techniques to confirm that the synthesized substance was a nanomaterial with particles sections having a needle form and being equal to mostly 13–29 nanometers (95.6 % of the total particles number).

Acute inhalation toxicity was assessed in conformity with the procedures stated in "OECD Guidelines for the Testing of Chemicals, Section 4: Health Effects, Acute Inhalation Toxicity – Acute Toxic Class Method" (OECD, Test № 436:2008, IDT); it revealed that synthesized nanodisperse manganese oxide had acute toxicity when it was inhaled as an aerosol. CL_{50} under 4-hours exposure which male and female Wistar rats with body weight being equal to 190 ± 10 grams had to undergo was 120 mg/m^3. Acute intoxication had the following clinical picture: irritating and neurotoxic effects, and respiratory depression. As per CL_{50} criterion (>50–500) mg/m^3 the tested substance is of the 2nd hazard degree (in accordance with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) and of the 1st hazard degree (according to the State Standard 12.1.007.76. Classification and general safety requirements). The obtained inhalation toxicity parameters which nanodisperse manganese oxide has prove the substance can exert hazardous impacts on workers' health when they are exposed to it at the work places or on population health; they also call for safety precautions development.

Key words: *nanodisperse manganese oxide, aerosol, inhalation exposure, particles concentration, toxicity, health hazard.*

Nano-sized manganese oxide particles are a very promising nano-material for creating high technological components which are applied in up-to-date domestic industries such as nanoelectronics, nano-optics, and nanochemistry. In relation to that, manufacture and consumption of products with nano-disperse manganese oxide being one of their components have been growing quite rapidly over the last decade. Nano-disperse manganese oxide is widely used in manufacturing semi-conductor thermistors [1], solar batteries, various electrical appliances, cathode accelerators, nano-magnetic materials, and sorbents [2]. Sensory electrodes and biological sensors

Nina V. Zaitseva – Member of the Russian Academy of Sciences, Doctor of Medical Sciences, Professor, Research Supervisor (e-mail: znv@fcrisk.ru; tel.: +7 (342) 237-25-34).

Marina A. Zemlyanova – Doctor of Medical Sciences, Head of Biochemical and Cytogenetic Diagnostic Techniques Department (e-mail: zem@fcrisk.ru; tel.: +7 (342) 236-39-30).

creation is another specific and very promising field where threadlike particles of manganese oxide can be applied [3].

Research results by Hussan, Stefanescu, and Frick [4–6] allow to assume that under specific conditions manganese oxide particles when introduced into a body via inhalation can cause adverse impacts on health, including toxic effects. Some data imply that catalytic generation of active oxygen forms (AOF) occurs in human alveolar epithelial cells and it enhances after 24-hour exposure [6]. Also, extracellular and intracellular oxidized glutathione form (GSSG) grows by 30 and 80% correspondingly in case of such exposure [4]. Elder et al. and Oberdorster describe certain conditions under which manganese oxide nanoparticles sized up to 30 nm are able to penetrate into PC-12 neuron-like brain cells via the olfactory bulb [7, 8], as well as accumulate in astrocytes and other brain cells [8, 9]. Researchers observed slight inhibition of mitochondrial activity in their experiments; it was combined with dose-dependent decrease in concentration of dopamine and its metabolites, 3,4-dihydroxyphenylacetic acid and homovanilinic acid. All the detected phenomena were shown to be accompanied with a significant increase in AOF [5, 10], and neuro-degenerating disorders which occurred already after 2-3 weeks of exposure [7, 8], proteolytic breakdown activation mediated with caspase-3 and protein kinase Cδ (these enzymes take part in apoptosis, necrosis, and inflammatory processes). Phosphorylation cycle activation was also proved [10–13].

Crittenden and Filipov [14] described that when manganese nano-oxide particles concentration grew, it led to a linear increase in the level of p38 mutagen-active protein kinase. The latter, in its turn, stimulates apoptosis mechanism or early cells death. Elder et al. indicated there were facts proving that exposure to the substance in the olfactory bulb, frontal cortex, midbrain, and striate body, make gene expression of tumor necrosis factor-α double [7]. Long-term inhalation exposure to manganese oxide nano-particles is detected to cause transferrin activation in dopaminergic nervous cells. Researchers also revealed structural changes in Beclin 1 and LC3 proteins, which, in its turn, may indicate at potential autophagia process activation [5].

Given all the above stated, if we want to implement promising production technologies which involve nano-sized manganese oxide application efficiently and on a large scale, it is necessary to provide safety for workers and population. And here it becomes truly vital to examine toxicity parameters of nanodisperse manganese oxide aerosol at inhalation introduction into a body [15].

Data and methods. We performed our experiment on water suspension of nanodisperse magnesium oxide which was synthesized via direct interaction between Mn2+ and MnO4 ions with micelles cetyltrimethylammonium bromide (CTAB, C16H33(CH3)3NBr) acting as nonreactors [16]. To do this, weighed CTAB was dissolved in alcohol at a room temperature under vigorous stirring for 30 minutes (CTAB/EtOH = 1:10). The alcohol CTAB solution was added with the water solution of 0.4M MnSO4·5H2O. The mixture was constantly stirred for 24 hours and a water solution KMnO4 of 0.05M was added into it slowly, drop-wise. This new mixture was also stirred continuously for another 24 hours to complete the reaction. The dark brown residue was washed with the distilled water. CTAB was removed by an extraction with ethanol, the extraction degree being not less than 98%. The residual concentra-

tion of cetyltrimethylammonium bromide after extraction was determined via chromato-mass spectrometry with tandem mass-spectrometric detector Agilent. The suspension matrix was the bidistilled water corresponding to the specifications TU 6-09-2502-77[1].

Size and shapes of manganese oxide particles in the water suspension were evaluated with dynamic laser light scattering performed with Horiba LB-550 analyzer ("Horiba", Japan) (The Department for Chemical and Analytical Research Techniques at the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies), via electronic microscopy performed with S-3400N ("HITACHI", Japan) high resolution scanning microscope (3-10 nm, maximum magnification equal to 300000X) with energy dispersive X-ray attachment for microanalysis ("Bruker", Germany) (Chemical Technology Department at Perm National Research Polytechnic University).

Textural parameters were determined via nitrogen sorption at 196 □C with ASAP 2020 (Micromeritics, США) but previously the examined material was degassed in vacuum during 3 hours. The samples specific surface area (SBET) was calculated as per a procedure developed by Brunauer, Emmett and Taylor [17]. The total pores volume (Vtot) was calculated from the amount of nitrogen adsorbed at a relative pressure p/p0≈0.99. Pores size distribution was determined by the desorption isotherms with a procedure developed by Barrett, Joyner and Halenda [18]. The structure of the sample was studied by X-ray diffraction (XRD) with XRD-7000 diffractometer (Shimadzu, Japan) under CuKα-radiation in the range of angles 2α=1–8°.

Mass concentration of manganese oxide in the suspension was determined via mass spectrometry with inductively coupled plasma (on Agilent 7500cx with octopole reactive/collision cell), with helium used as a reagent gas. Prior to any evaluations, the substance was dispersed with Sonopuls Hd 3200 ultrasound homogenizer by "Bandelin" in order to destroy any aggregates and agglomerates which could possibly occur due to the sample ageing. We achieved homogenous distribution of the particles in the volume via continuous pulsation during 2 minutes at a room temperature.

We assessed acute toxicity of nanodisperse manganese oxide at inhalation introduction as an aerosol according to the established procedure fixed in State Standard 32646-2014[2]. We performed our acute experiment on pubescent Wistar rats (bucks and does) with body weight equal to 190±10 grams. All the animals were kept in standards cages made of polypropylene, two rats in each, and they all before the experiment underwent 14-day quarantine. The cages were placed in a ventilated room, air temperature was 23.0±2.0 ^{o}C, air humidity was 60.0±5.0 %. The experimental animals were provided with semi-synthetic nutrition ration which fully satisfied their biological needs. They had free access to food and water. All the examinations and procedures strictly conformed to

[1] TU 6-09-2502-77. Highly purifiem water, OSCh trademark 27-5. technical conditions. 1978, 31 p.

[2] State Standard 32646-2014. Experimental techniques for assessing impacts exerted by chemicals on a human body. Acute inhalation toxicity – a procedure for acute toxicity class determination (ATC procedure). Moscow, Standardinform Publ., 2015. Available at: http://docs.cntd.ru/document/1200116047 (28.07.2017).

the principles and standards set forth by the European convention for the protection of vertebrate animals[3]. Experiments were controlled by the Ethical Committee of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies.

Inhalation introduction of manganese nano-oxide was provided via an inhalation system with a chamber for the whole body (TSE Systems GmbH) and integrated software. To prevent particles ingestion off hair we placed the experimental animals into individual cages. They were divided into two experimental groups, each made of 3 bucks and 3 does. The first experimental group underwent 4-hour inhalation exposure with manganese oxide concentration being 0.05 mg/dm3; the second experimental group also underwent 4-hour exposure but the admixture concentration in its case was equal to 0.5 mg/dm3. The speed of air flow in and out of the inhalation chamber was equal to 10 l/min. The suspension was fed into the aerosol generator at a speed being equal to 0.014 ml/min and 0.17 ml/min correspondingly. It allowed us to create homogenous substance circulation in the chamber. Air pressure in the chamber was maintained at -0.2±0.2 millibar, and air temperature, at 22–25°C. Oxygen level in the chamber was equal to about 19%; carbon dioxide concentration didn't exceed 1%.

Actual manganese oxide concentration in the inhalation chamber was estimated via mass spectrometry technique with inductively coupled plasma on Agilent 7500cx. Air sampling in the inhalation chamber was performed with the use of AFA-VG-10-1 filter (Russia) at the speed equal to 2 l/min during 5 minutes after 2 and 4 hours of exposure. Nanoparticles quantity in the chamber (concentrations) was performed with a diffuse aerosol spectrometry made by "AeroNanoTech" LLC (Russia).

The experimental animals didn't receive any food during exposure.

After exposure was over, the animals were under observation during 4 days allowing for any possible delayed toxicity effects. We determined hazard category as per average lethal concentration of a substance (CL50) according to animals deaths parameters, applying a procedure described in the State Standard 32646-2014[2], as well as inconformity with the State Standard 12.1.007.76[4].

Results. Examinations performed on the sample suspension in concentration equal to 36±2.3 mg/ml with CTAB residual in it being lower than the detection limit (0.00001 mg/ml) revealed that the particles distribution as per their cross section size is as follows: 13 nm (1.2 % out of the total particles number), 15-29 nm (94.3 % out of the total particles number), and 33-87 nm (4.1 % out of the total particles number). The greatest share in the suspension belongs to particles sized 19±4 nm (41.2 % out of the total number) (Table 1).

Scanning electron microscopy revealed that the particles being visualized (those exceeding 20 nm in size) were mostly threadlike (97.8% from the whole number of visible particles).

[3] The European convention for the protection of vertebrate animals used for experimental and other scientific purposes. Strasburg, 1986, 13 p.

[4] ГОСТ 12.1.007-76. System of Labor Safety Standards (SLSS). Hazardous substances. Classification and overall safety requirement (with Alterations No. 1 and 2). Available at: http://docs.cntd.ru/document/5200233 (28.07.2017).

Table 1

Manganese oxide nanoparticles dispersity in water suspension

Particles size in suspension, μm	Particles share, %	Particles size in suspension, μm	Particles share, %
0,0131	1,2	0,0387	0,38
0,0150	9,6	0,0443	0,64
0,0171	16,4	0,0507	0,90
0,0196	20,0	0,0581	0,73
0,0225	21,2	0,0666	0,42
0,0257	13,9	0,0762	0,39
0,0295	13,2	0,0873	0,15
0,0338	0,44		

The adsorption-desorption isotherm of nitrogen corresponds to the type IV (isotherm with a distinct capillary condensation). The shape of the hysteresis loop belongs to H3 type with the distinct area of mesopores filling within the range of relative pressures (p/p0) 0.7–1. Mesopores filling at higher relative pressures verifies the presence of large diameter mesopores (Figure 2). The specific surface area (SBET) of the nano-disperse manganese oxide particles amounted to 150.2 ± 2.6 m2/g; the total pore volume, to 0.676 cm3/g. The results of X-ray phase analysis showed the absence of the mesopores ordered structure (Figure 3).

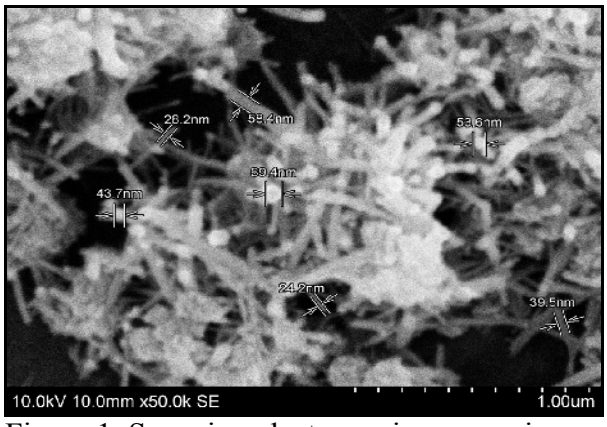

Figure 1. Scanning electron microscopy image of nanodisperse manganese oxide particles

Data on physical parameters of manganese oxide nanoparticles obtained via template synthesis corresponded to properties needed for sensory electrodes creation [3] and correct acute inhalation exposure modeling.

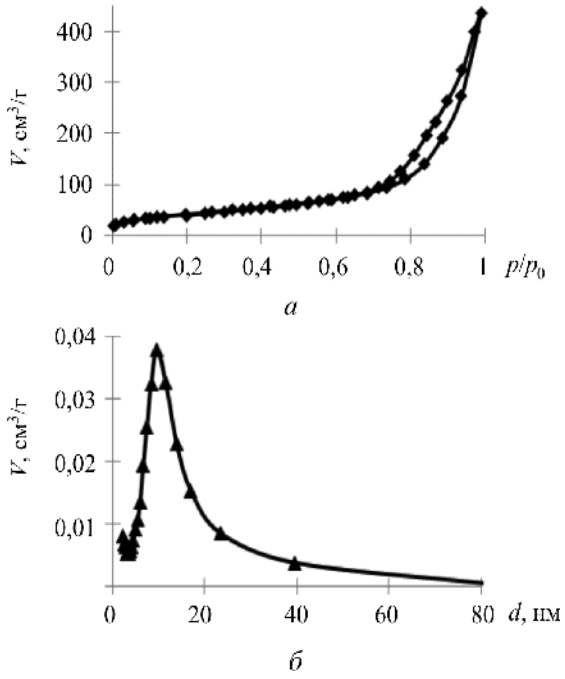

Figure 2. Nitrogen absorption-desorption isotherm (A) and pores distribution as per size d(нм) (B) for nanodisperse manganese oxide

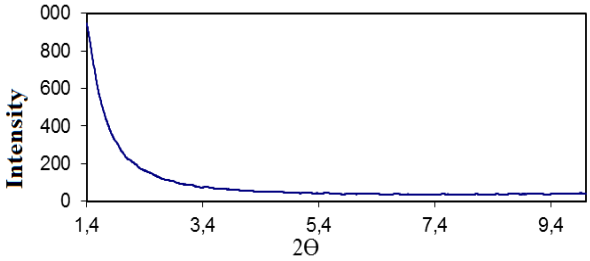

Figure 3. X-ray pattern of the nanodisperse magnesium oxide

Data obtained due to analytical measuring proved that if preset manganese oxide concentration was equal to 0.05 mg/l, then actual concentration in the inhalation chamber amounted to 0.029±0.001 mg/dm3; and with preset concentration equal to 0.6 mg/l, the actual one was 0.472±0.005 mg/l. Estimation of nanoparticles quantity in the air in the chamber revealed that when nanodisperse fraction was fed into it and transformed into aerosol, it didn't agglomerate up to micro-meter sizes (Table 2). The greatest number of particles at the examined actual concentrations didn't exceed 100 nm in size after 2- and 4-hour exposure.

Table 2

Examinations of nanodisperse manganese oxide particles concentrations and sizes in the inhalation chamber air

Parameters	Initial level	After 2-hour exposure	After 4-hour exposure
Manganese oxide concentration, mg/dm3	0,002	0,456	0,472
Particles concentration, sized 0-20 nm, un./dm3	63	10421	9980
Particles concentration, sized 20-40 nm, un./dm3	48	35 930	31 207
Particles concentration, sized 40-60 nm, un./dm3	42	35 602	36 783
Particles concentration, sized 60-80 nm, un./dm3	22	26 370	25 809
Particles concentration, sized 80-100 nm, un./dm3	8	17 783	14 320

Table 3

Dynamics of the experimental animals deaths during research on acute inhalation toxicity which nanodisperse manganese oxide had when introduced as water suspension aerosol

Animals group	Actual concentration, mg/l	Number of animals in group, abs.	Observation duration in days (hours)				Number of dead animals	
			1 (1)	2 (2)	3 (3)	4 (6)	abs.	%
No. 1	0,029 ± 0,001	6	0/6	0/6	0/6	0/6	0	0
No. 2	0,472 ± 0,005	6	0/6	0/6	5/6	6/6	6	100

Clinical picture at an initial stage of acute intoxication with nanodisperse manganese oxide aerosol in actual concentration being equal to 0.029±0.001 mg/l included the following effects: all the animals started to sneeze and cough, they had colorless discharge from their noses which evidenced inflammation evolvement in the respiratory tracts. Starting from the 3rd hour of exposure and up to the 4th one, animals had tachypnea and dyspnea. And here we registered that animals' accessory muscles had to participate in their respiration; we also detected forced postures (backs bent, heads tilted, etc.). When the 4th hour of exposure started, the animals became depressed and sluggish, they had no reaction to sound stimuli, and their movement coordination was disordered. During 24 hours after exposure we detected body trembling, motor activity absence, and extremely weak reaction to sound stimuli in the experimental animals; they also refused to eat or drink. 72 hours after exposure there were no signs of depression, and the animals ate their food. However, we detected that motor activity and reactions to sound stimuli were rather weak. We didn't register any animals death in this experiment over 96 hours of observation.

Clinical picture of animals intoxication under exposure to nanodisperse manganese oxide in actual concentration equal to 0.472±0.005 mg/l was rather different. Thus, respiratory failure was detected already starting from the 30th minute of exposure. After 3 hours of exposure we registered respiratory depression and animals deaths. We fixed that the animals were sluggish before they took the lateral position; motor activity and any reactions to sound stimuli were completely absent. 83% of the exposed animals died within 150-190 minutes after the experiment started (Table 3).

According to acute inhalation toxicity assessment, CL_{50} of the examined nanodisperse manganese oxide was assumed to be equal to 120 mg/m^3. This concentration is within 50-500 mg/m^3 range, which allows us to rank the examined substance, nanosized manganese oxide, among the sub-

stances with the 2nd hazard class as per The Globally Harmonized System of Classification and Labelling of Chemicals (GHS) and among the substances with the 1st hazard class according to the State Standard 12.1.007.76[3]

Discussion. Threadlike particles of nanodisperse manganese oxide are applied as an active matrix in sensory electrodes and storage batteries manufacture; it is seen as a most promising technology. Application of the substance causes its probable occurrence in the working area air and its further spread over territories located in the vicinity of production plants. And it leads to hazards of possible inhalation exposure for workers employed at such productions and for population living on territories close to them.

The results which we obtained in our research prove that the examined nanosized manganese oxide particles are able to cause negative effects: irritating and neurotoxic ones, as well as respiratory depression; their combination probably caused the experimental animals deaths.

Toxic impacts exerted by the substance on the nervous system cells and negative neuropsychological effects occurring under exposure even to low doses have been proved both for manganese oxide nanoparticles and its micro-disperse analogue [10, 12, 19]. Neurotoxic mechanism can be based on functional disorders in neuron membranes which result from membrane lipids peroxidation caused by direct cytotoxic effects exerted by nanoparticles; these effects were detected for dopaminergic neurons [10, 12, 20]. These effects can be much more apparent when they are caused by nanodisperse particles in comparison with their microdisperse analogue; it is due to the fact that nanodisperse particles have greater specific surface area. Clinical picture of acute intoxication proves toxic effects exerted by nanodisperse manganese oxide particles which have been described in the previous research works [21]. Respiratory failure occurrence can be related to a potential ability of the examined nanoparticles to cause inflammatory changes with the consequent alveolar epithelial cells apoptosis. And given the fact that nano-sized manganese oxide particles are more resistant mucociliary clearance, they contact the respiratory tract cells much longer than their microdisperse analogue [22]. The CL50 value for the substance is equal to 120 mg/m3; therefore, nanodisperse manganese oxide belongs to substances having the 2nd hazard class according to the international classification for chemicals' hazards [23] and to substances having the 1st hazard class according to the State Standard 12.1.007.763.

Conclusions. Nanodisperse manganese oxide with its threadlike particles having their cross section sizes mostly equal to 13-29 nm had acute toxicity at inhalation introduction as an aerosol. CL50 for Wistar rats amounts to 120 mg/m3 under 4-hour exposure. Clinical picture of acute inhalation exposure involves the following: irritating and neurotoxic effects as well as respiratory depression. Neurotoxic effects remained in the animals who survived the experiment even 92 hours after the exposure. So, the substance has the 2nd hazard class (according to CL50 criterion) as per the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) and the 1st hazard class as per the State Standard 12.1.007.763[3].

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INFLUENCE EXERTED BY NEW PYRIMIDINE DERIVATIVES ON CEREBRAL CIRCULATION AUTO-REGULATION AND VASODILATATING FUNCTION OF VESSELS ENDOTHELIUM IN RATS' BRAINS UNDER CHRONIC HEMIC HYPOXIA

A.V. Voronkov, A.S. Lysenko, A.F. Bandura

Pyatigorsk Medical Pharmaceutical Institute of Volgograd Medical State University, 11 Kalinina avenue, Pyatigorsk, 357532, Russian Federation

Our research goal was to examine influences exerted by new pyrimidine derivatives coded as BL0 and BL2 on cerebral hemodynamics auto-regulation parameters and vasodilatating function of vessels endothelium as risk factors causing ischemic and hemorrhagic strokes under chronic hemic hypoxia.

We performed an experiment on white Wistar rats to prove that endothelial dysfunction which evolves under chronic hemic hypoxia leads to disorders in endothelium-mediated mechanisms for cerebral circulation auto-regulation in rats. We modeled hypoxia in animals via granting them free access to 0.2 % sodium nitrite solution instead of ordinary drinking water. Endothelial dysfunction was confirmed as per disorders in vasodilatation and vasoconstriction reactions at intravenous introduction of acetyl choline (0.1 mg/kg) and methyl ether hydrochloride nitro-L-arginine (10 mg/kg). Cerebral blood flow speed was measured with MM-D-K-Minimax v.2.1. ultrasound Doppler. We assessed cerebral circulation auto-regulation as per compression test results which allowed us to calculate overshoot coefficient and auto-regulation power. Examined pyrimidine derivatives and comparison preparations were introduced orally 60 minutes prior to taking readings. Mexidol doses were calculated on the basis of interspecific recalculation of a maximum daily dose for a man. Nicergoline dose was taken as a most effective one as per literature data.

When new pyrimidine derivatives BL0 and BL2 are applied under chronic hemic hypoxia, it causes overshoot coefficient to grow authentically higher than in a negative control group but it doesn't exert any positive influence on collateral reserve parameter, namely auto-regulation power. BL0 and BL2 improve endothelium vasodilatating function at intravenous acetylcholine introduction (0.1 mg/kg) and don't exert any influence on vasoconstricting function at L-NAME intravenous introduction (10 mg/kg). The examined substance BL0 has more apparent pharmacological effects thus exceeding the second substance BL2 and such comparison preparations as Mexidol and Nicergoline in some parameters.

Key words: *chronic hemic hypoxia, cerebral hemodynamics auto-regulation, new pyrimidine derivatives, Mexidol, Nicregoline, rats.*

Endothelial function disorder is known to increase ischemic and hemorrhage strokes risks considerably, and such strokes can cause death or grave disability [1–3]. Oxidation stress activation which occurs due to various hypoxia types, including hemic one, is a basic pathogenetic factor causing endothelium functional defects [4, 5]. Oxidation stress intensifies circulation disorders, damage to vessels endothelium, changes in nitrogen oxide production, negative rheological changes etc., and it deteriorates a basic pathological process [6–8]. Endothelial dysfunction leads to disorders

Andrei V. Voronkov – Doctor of Medical Sciences, Associate Professor, Head of Pharmacological Department with Clinical Pharmacology course (e-mail: prohor.77@mail.ru; tel.: +7 (879) 332-92-66).

Aleksandr S. Lysenko – post-graduate student at Pharmacological Department with Clinical Pharmacology course (e-mail: a.s.lysenko@bk.ru; tel.: +7 (962) 42-42-161).

Aleksandr F. Bandura – Candidate of Pharmaceutical Sciences, a lecturer at Pharmacy Organization and Economics Department (e-mail: alex_paris@mail.ru; tel.: +7 (918) 824-34-07).

in cerebral blood flow auto-regulation with its main function being maintenance of constant flow speed in cerebral vessels [9–14]. Necessity to find means aimed at minimizing risks of pathologies related to disorders in cerebral hemodynamics auto-regulation under cerebral hypoxias is a vital and interesting task..

Our research goal was to examine influence exerted by new pyrimidine-4-on derivatives, BL0 and BL2, on cerebral circulation auto-regulation and vasodilatating function of cerebral vessels endothelium, our research objects being rats' brains under chronic hemic hypoxia.

Data and methods. We performed our experiment on 60 male Wistar rats with body weight being equal to 200-250 grams. Animals were divided into 6 groups (n=10); the first group was an intact one; the second group included animals with chronic hemic hypoxia; animals with chronic hemic hypoxia from the 3rd group were given new pyrimidine-4-on derivative, BL0 (50 mg/kg): animals with chronic hemic hypoxia from the 4th group were given new pyrimide-4-on derivative, BL2 (50 mg/kg); animals with chronic hemic hypoxia from the 5th group were given a reference medication, Mexidol (74 mg/kg)[15]; animals with chronic hemic hypoxia from the 6th group were given another reference medication, Nicergoline (10 mg/kg).

We modeled chronic hemic hypoxia via granting the experimental animals free access to 0.2% sodium nitrite solution instead of ordinary water, during 14 days [9, 16].

New examined pyrimidine-4-on derivatives and two reference medications were introduced orally 60 minutes prior to parameters reading. Mexidol dose was calculated basing on interspecific recalculation of a maximum daily dose for a man. Nicergoline dose was taken as the most effective one as per literature data [17].

After two weeks of chronic hemic hypoxia formation, we assessed functionality of brain vessels endothelium [11, 18].

Brain vessels ability to regulate themselves was assessed as per carotid test results. Overall carotid artery compression results in drastic decrease in blood flow speed, and its decompression, to a drastic increase in linear speed. Data obtained via this test allow to assess auto-regulation reserves as per calculated coefficients: overshoot coefficient (OC) (1) and auto-regulation power (2):

$$\text{ÊÎ} = \frac{V_3}{V_1}, \quad (1)$$

$$\text{ÑÀÐ} = \frac{V_3 V_2}{V_1^2}, \quad (2)$$

where *V1* is cerebral blood flow speed before compression; *V2* is cerebral blood flow speed during compression; *V3* is cerebral blood flow after deocclusion.

We treated data statistically with Microsoft Office Excel 2010 standard software. Validity was assessed as per Mann-Whitney criterion.

Results and discussion. As per compression test results, overshoot coefficient was equal to 1.01±0.02 in the control group and it was authentically lower than the same parameter in the intact group where it was equal to 1.25±0.03. Overshoot coefficient values in animals' groups which were given new pyrimidine-4-on derivatives BL0 and BL2 60 minutes prior to parameters reading were authentically higher than in the control group and authentically lower than in the intact group; they were also higher than in the group which was given Mexidol, one of the reference medications. Overshoot coefficient values in animals which were given the reference medications (Mexidol and Nic-

ergoline) tended to grow but didn't have any significant discrepancies from the control group parameters (Figure 1).

Auto-regulation power was equal to 0.61±0.041 in the control group which was authentically lower than in the intact group where this parameter amounted to 0.80±0.043. Auto-regulation parameters in animals which were given the examined substances BL0 and BL2, as well as Mexidol (one of the reference medications), didn't have any authentic discrepancies

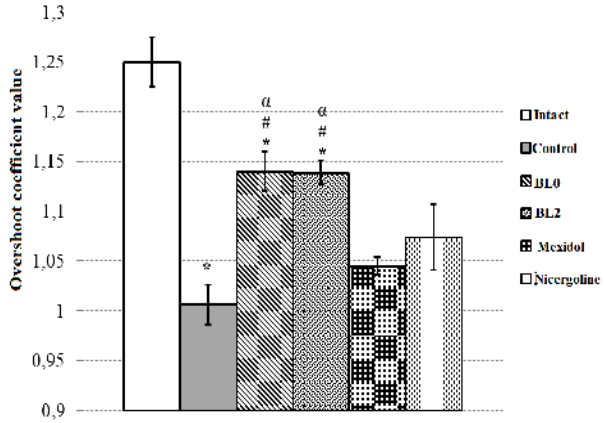

Figure 1. Overshoot coefficient value in the experimental groups.
Note: * means authentic against the intact group ($p<0.05$); # means authentic against the control group ($p<0.05$); α means authentic against the group which was given Mexidol ($P<0.05$)

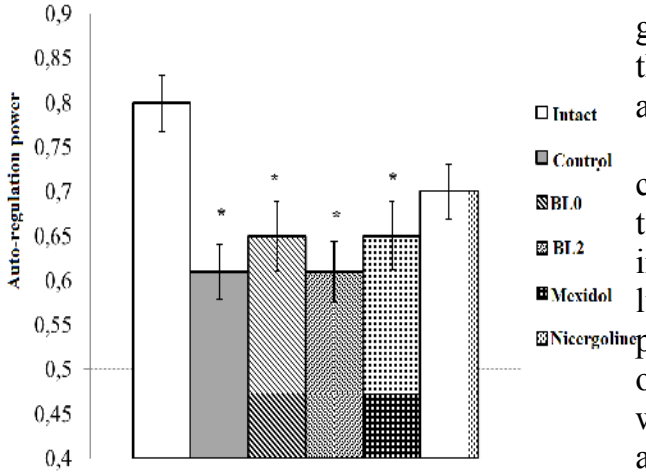

Figure 2. Values of cerebral hemodynamics auto-regulation power in the experimental groups.
Note: * means authentic against the intact group ($P<0.05$)

from the control group and were lower than the same parameter in the intact group. Auto-regulation power parameter in animals which were given Nicergoline (another reference medication) didn't have any authentic discrepancies either from the control group, or the intact group (Figure 2).

Research on brain vessels reactivity performed with ultrasound Doppler revealed that vasodilatation reaction to intravenous introduction of acetyl choline (0.1 mg/kg) was authentically lower in the control group than in the intact one and amounted to 12.7%±1.58, this parameter being equal to 23.7%±2.14 in the intact group. The examined new pyrimidine-4-on derivatives BL0 and BL2, as well as the reference medications Mexidol and Nicergoline, authentically enhanced vessels reaction to intravenous introduction of an endogenous nitrogen oxide modulator against the control group. We should note that growth in cerebral blood flow amounted to 35.2%±2.09 among animals which were given Mexidol, and it was authentically higher than the same parameter in the intact group. Vasodilatation reaction in rats which were given BL0 also tended to be higher than in the intact group, but this parameter didn't differ from that of the intact group authentically; however, it was lower than in the group which was given Mexidol and amounted to 28.0%±1.81.

A decrease in cerebral blood flow caused by intravenous L-NAME introduction (10 mg/kg) amounted to -11.5%±1.43, in the control group and it was authentically lower than in the intact group where this parameter amounted to -22.0%±1.44. Vasoconstriction reaction in animals which were given BL0, BL2, and Mexidol, was authentically lower that in the intact group and didn't have any authentic discrepancies from the control group. A reduction in cerebral blood flow speed among animals

which were given Nicergoline amounted to -21.0%±2.1 after e-NOS inhibitor intravenous introduction, which was authentically higher than in the control group and didn't have any discrepancies from the intact group (Figure 3).

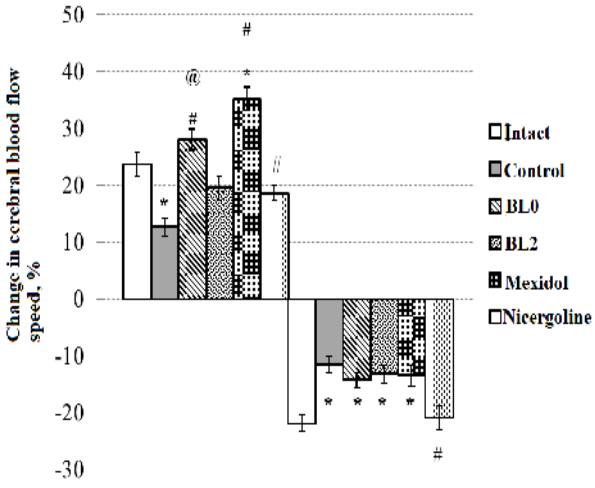

Figure 3. % of change in cerebral blood flow speed as a reaction to acetyl choline and L-NAME. Note: * means authentic against the intact group (P<0.05); # means authentic against the control group (P<0.05); @ means authenticc against the group which was given Mexidol (P<0.05).

A 50% decrease in vasodilatation reactions after acetyl choline was introduced intravenously, and vasoconstriction reaction, after L-NAME was introduced intravenously, in the control group against the intact group under chronic hemic ischemia proves there is a disorder in endothelium-mediated cerebral hemodynamics auto-regulation mechanisms allowing for an authentic reduction in overshoot coefficient and auto-regulation power.

New pyrimidine-4-on derivatives BL0 and BL2 to the same extent increase overshoot coefficient against the control group thus being more efficient than the reference medications. The examined substances and the reference medications didn't exert any positive influence on auto-regulation power. BL0, BL2, Mexidol and Nicergoline restored vasodilatating endothelium function after acetyl choline intravenous introduction in comparison with the control group, and in spite of Mexidol being more efficient, this new pyrimidine derivative, BL0, is not much inferior to it.

So, according to all the obtained data, new pyrimidine-4-on derivatives, BL0 and BL2, have positive influence on cerebral hemodynamics auto-regulation and endothelium vasodilatating function; they are more efficient than the reference medications as per some parameters, and it calls for their further examination in terms of health risk assessment and minimization.

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INTERDEPARTMENTAL INTERACTION ON PROVIDING BIOLOGICAL SAFE-TYON TATARSTAN REPUBLIC TERRITORY DURING PREPARATIONS FOR 2017 FIFA CONFEDERATIONS CUP IN KAZAN

M.A. Patyashina, M.V. Trofimova, L.G. Avdonina, L.T. Garaeva, G.R. Mansurova

Federal Service for Surveillance over Consumer Rights Protection and Human Well-being, Tatarstan Regional Office, 30 B. Krasnaya Str., Kazan', 420111, Russian Federation

Infectious agents collections used in practical work are to be securely protected as they can cause infections among people and animals; they are potential biological terrorism objects including periods when mass sport, political, or cultural events take place in the country. It made our research truly vital. Our research goal was to analyze an interdepartmental workgroup functioning aimed at inspecting objects located on areas where 2017 FIFA Confederations Cup and 2018 FIFA World Championship were to take place. This workgroup had to deal with biological substances, biological and microbiological organisms and infectious agents from II–IV pathogenicity groups. Its basic task was to minimize biological hazards during work with pathogenic biological agents. The research involved examination of legal documents (including international ones) which regulated biological safety requirements for work with pathogenic biological agents; consideration of joint work with the RF Federal Security Service, Tatarstan Regional Office, Tatarstan Anti-Terrorism Commission for providing anti-terroristic protection of organizations dealing with infectious agents, including those common for people and animals, on the example of Rospotrebnadzor Regional Office in Tatarstan; analysis of work performed by the interdepartmental workgroup.

It is shown that efficient interdepartmental interaction allowed to provide biological safety in Kazan and on adjoining territories, to prevent pathogen entering the environment and possibility to use pathogenic biological agents as biological terrorism objects during preparation for 2017 FIFA Confederation Cup and the event itself.

Key words: *anti-terroristic security, infectious diseases, biological safety, biological hazard, biological terrorism, biologically hazardous object.*

Rospotrebnadzor Regional Office in Tatarstan (hereinafter called "The Office") is to control biological safety provision in the Republic of Tatarstan [1, 2, 3]. Newly developed organizational procedures implemented in an interdepartmental workgroup functioning allowed to provide biological safety during preparations to 2017 FIFA Confederation Cup in Kazan and during the event.

In accordance with the federal legislation on obligatory licensing of specific activ-

Marina A. Patyashina – Doctor of Medical Sciences; Director (e-mail: org@16.rospotrebnadzor.ru; tel.: +7 (843) 238-98-54).

Marina V. Trofimova – Deputy Director (e-mail: org@16.rospotrebnadzor.ru; tel.: +7 (843) 238-98-54).

Lyubov' G. Avdonina – Deputy Director (e-mail: org@16.rospotrebnadzor.ru; tel.: +7 (843) 238-98-54).

Liliya T. Garaeva – Head of State Registrationand Licensing Department (e-mail: Garaeva.LT@tatar.ru; tel.: +7 (843) 238-53-28).

Guzel' R. Mansurova – expert-researcherat State Registrationand Licensing Department (e-mail: rpn.licenz@tatar.ru; tel.: +7 (843) 238-53-28).

ities[4] all the activities performed in closed systems in the sphere where agents of human and animals infectious diseases (excluding those activities which are performed in the medical sphere) and genetically modified organisms with III and IV potential hazard categories are applied are to be licensed. Such activities can cause a situation when there is a violation of citizens' rights, legitimate interests, lives or health, or there can be a damage to the environment, the defense and safety of the state. Starting from 1996 Rospotrebnadzor bears the full responsibility for the state regulation of licensing activities in the sphere where agents of human and animals infectious diseases are applied.

The state system for providing biological safety is an essential component in the RF national security system. It is a set of organizational and technical procedures aimed at preventing damage and providing protection of an individual, the society in general, and the state itself from potential and actual biological hazards. The latter can appear as a natural or deliberate lesion with such biological agents as bacteria, viruses, fungi, protozoa, or their toxins[5].

Collections of human and animals infectious diseases agents are regularly applied in practical work. Such collections are potential objects for biological terrorism and their protection is an essential part of the state policy aimed at providing sanitary-epidemiologic safety [1].

Anna Yu. Popova, the RF Chief Sanitary Inspector and the Head of Rospotrebnadzor, has repeatedly stressed the importance of the issue; she has reminded that there are events which usually cause biological risks. Such events are natural disasters during which biological pathogens transfer paths become extremely active; emergencies at potentially hazardous biological objects; biological terrorism acts; uncontrolled spread of genetically modified microorganisms; mass production and sales of genetically modified food products and agricultural products; development of biological weapons belonging to a new generation [2].

Moreover, there are situations when a pathogenic biological agent has been deliberately applied. The latest event of the kind was registered in the USA in 2015 when alive anthrax cultures were sent from a biological laboratory of the US Defense Ministry to dozens various organizations, including those located in 9 foreign countries in Europe and Asia [3].

International scientific society has developed a unified approach to providing

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public and individual safety during work with pathogens [4, 5], and a guidance on biological protection of laboratories [6, 7]; there are standards for managing laboratory biological risks [1, 8–10].

In December 2017 the member states of the Biological and Toxin Weapons Convention held a meeting in Geneva; they adopted a work program for 2018-2020 aimed at reducing risks for biological safety caused by a threat when bacteriological (biological) agents or toxins could be used as a weapon. The program includes the following basic subject: monitoring over scientific research in the biological sphere which could potentially have double application [11].

In 2008 new sanitary rules fixed the requirements to work with microorganisms from III – IV pathogenicity groups2; in 2013 the same was done for microorganisms from I - II pathogenicity groups3, and it made all the requirements to providing individual and public safety and environmental protection during work with pathogenic biological agents more strict.

Research goals and tasks. To analyze work done by the interdepartmental workgroup which was created to provide safe work with pathogenic biological agents (PBA). This team examined objects located on territories where 2017 FIFA Confederation Cup and 2018 FIFA World Championship were to take place. The objects under surveillance were those working with biological substances, biological and microbiological organisms, and infectious diseases agents from II-IV pathogenicity groups.

Data and methods. We examined legal documents, including international ones, which set forth the requirements to biological safety during work with PBA; considered how cooperation with RF Federal Security Service, Tatarstan Regional Office and Tatarstan Anti-Terrorism Commission was organized, its goals being to provide anti-terroristic safety of organizations dealing with infectious agents, including those common for people and animals on the example of Rospotrebnadzor Regional Office in Tatarstan; analyzed work performed by the interdepartmental workgroup.

Results and discussion. Safety precautions aimed at enhancing anti-terrorist protection and providing biological safety were adopted by The Office during preparation to 2017 FIFA Confederation Cup and the event itself.

In order to prevent biological terrorism, to enhance anti-terrorist protection, and to provide biological safety during 2018 FIFA World Championship, on December 24, 2015 the Head of the RF Federal Security Service, Tatarstan Regional Office major-general D.G. Khamitov [12] approved on the Register of industrial and infrastructural objects (hereinafter called "The Register") (critically essential, potentially hazardous and hazardous ones) located on territories where 2017 FIFA Confederation Cup and 2018 FIFA World Championship were to take place. Should such objects be put out of action (as a result of a subversive-terroristic act, or an emergency), it would threaten safety during these events (Figure1).

The Register was updated on the initiative of The Office by the EMERCOM of Russia, Tatarstan Regional Office (the RF Ministry on civil defense, emergencies, and elimination of natural disasters consequences). The Register included 40 laboratories (16 medical organizations, 9 communal objects, 7 food industry enterprises, 3 veterinary clinics, 3 industrial enterprises, and 2 scientific and educational institutions).

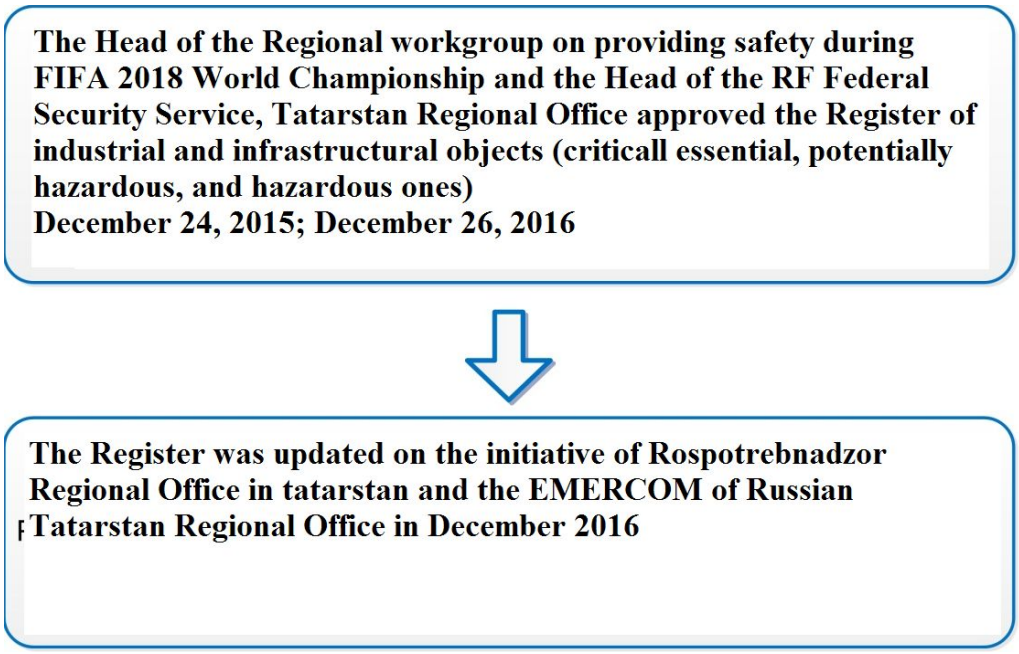

Figure.1. Interaction between controlling authorities

The Office drew up a map of Kazan city with adjoining territories; the map showed location of economic entities which dealt with biological substances, biological and microbiological organisms, and with infectious diseases agents from II – IV pathogenicity groups; it also showed sport objects where events of FIFA 2018 World Championship were to take place.

In November-December 2016 all the economic entities updated their documents which confirmed safety of a biologically hazardous object; their duplicates were sent to The Office [13].

In 2016 The Office sent 5 information letters to the Tatarstan Public healthcare Ministry stating that 4 medical organizations had problems in providing biological safety in their laboratories.

In the first half year 2017 the Tatarstan Public Healthcare Ministry, the Chief Veterinary Office at the Tatarstan Cabinet, and the Office held several meeting with heads and laboratory specialists from those economic entities which dealt with biological substances and infectious diseases agents; the meetings were organized to discuss issues related to providing biological safety and anti-terrorist protection of biologically hazardous objects.

The Tatarstan Minister for civil defense and emergencies (the Head of the EMERCOM of Russia, Regional Tatarstan Office) was sent some propositions to be included into a draft regulation by the Tatarstan Cabinet "on organizing radiation, chemical, and biological protection and control during preparations to FIFA 2017 Confederation Cup and the event itself in Kazan" [12].

In 2017 40 letters were sent to economic entities stating that they should implement additional measures on anti-terrorist protection. All the juridical persons had to confirm that they followed all the requirements to biological safety when dealing with pathogens providing this information to The Office (Figure 2).

The Office experts were members of the interdepartmental workgroup organized to examine objects located on territories where the FIFA 2017 Confederation Cup

and the FIFA 2018 world Championship (IWG for short). They inspected 29 juridical persons from October 2016 to May 2017 and controlled biological safety provision during work with pathogenic biological agents2,3 [14, 15] (Figure 3).

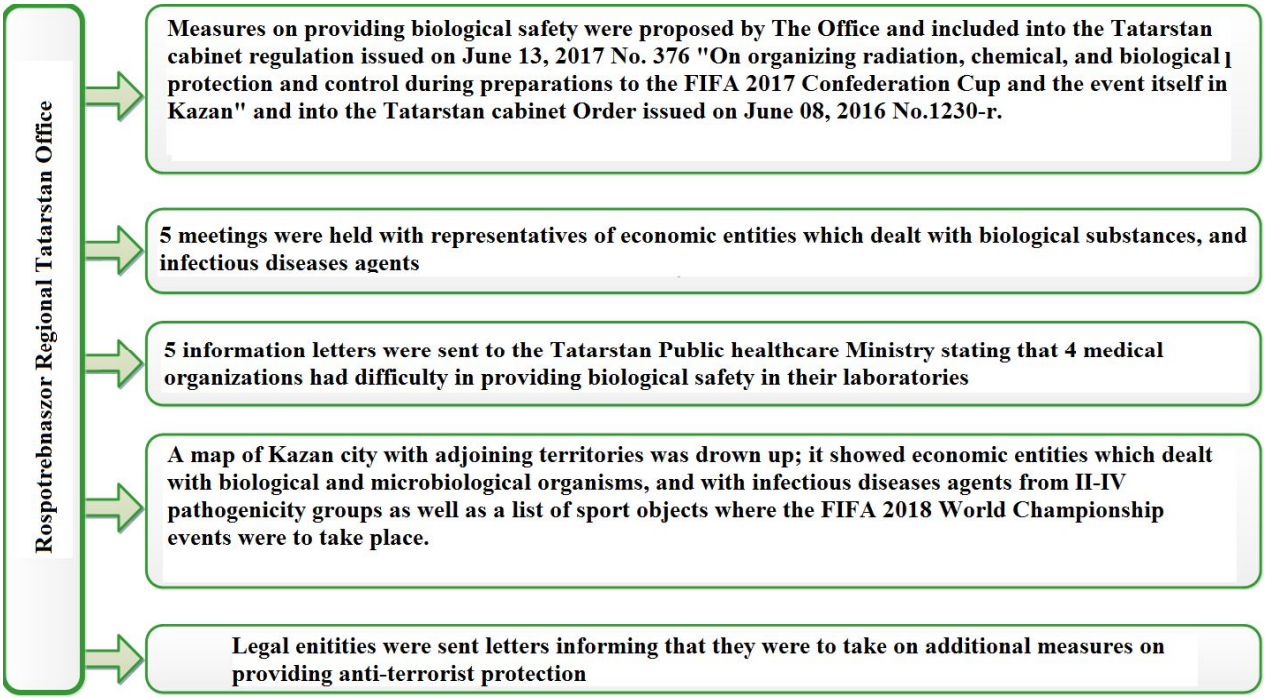

Figure 2. Activities performed by The Office during preparations to the FIFA 2017 Confederation Cup and the event itself.

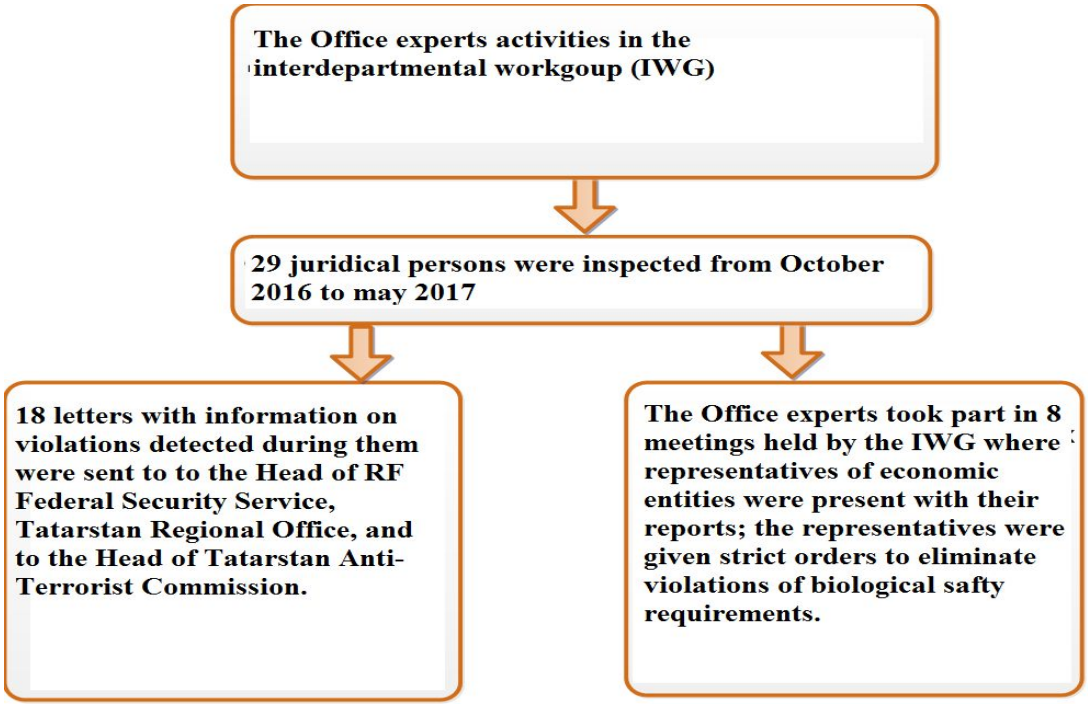

Figure 3. The Office experts activities in the interdepartmental workgroup.

As per inspections results 18 letters with information on violations detected during them were sent to the Head of the interdepartmental operating authority responsible for providing safety during the FIFA 2017 Confederation Cup and the FIFA 2018 World Championship events, to the Head of RF Federal Security Service, Tatarstan Regional Office, and to the Head of Tatarstan Anti-Terrorist Commission.

The RF Federals Security Service, Tatarstan Regional office, held 8 meetings where representatives of economic entities made their reports; the representatives were given strict orders to eliminate violations of biological safety requirements.

The IWG made a decision on its final meeting to stop work with biological substances, biological and microbiological organisms, and with infectious diseases agents in laboratories at 5 economic entities.

In order to provide execution of the RF Governmental Order issued on June 09, 2017 No. 689 "On certain measures aimed at implementing The RF President Order signed on may 09, 2017 No. 202 "On peculiarities of taking on enhanced safety precautions during the FIFA 2017 Confederation Cup and the FIFA 2018 World Championship in the Russian Federation" [16], the following measures were implemented concerning 40 juridical persons included in the Register (Figure 4):

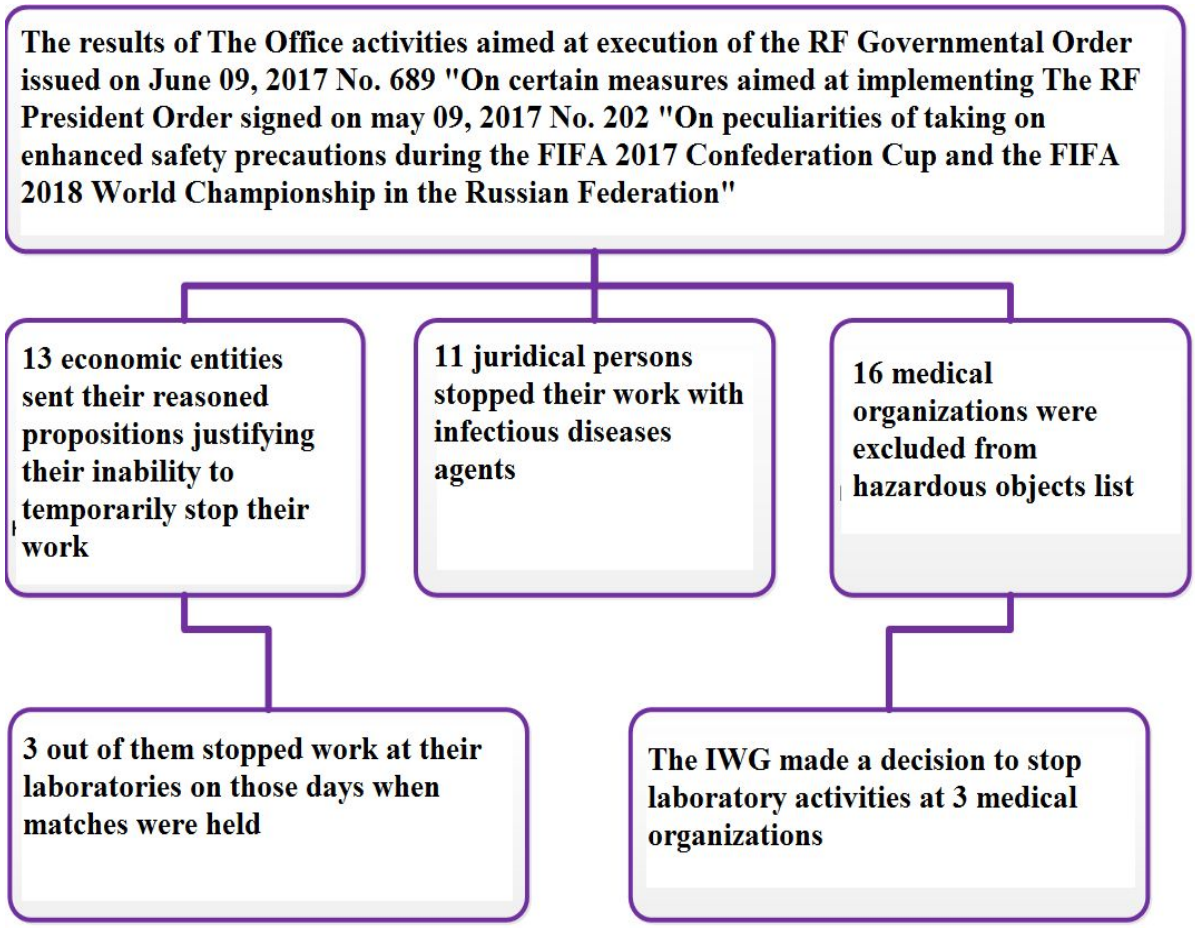

Figure 4. Execution of the RF Governmental Order issued on June 09, 2017 No. 689.

-13 economic entities sent their reasoned proposition to The Office and The Tatarstan Industry and Trade Ministry justifying their inability to temporarily stop their work with biological substances as such work was closely connected with surveillance and laboratory control over the environment, food products and water supply safety, and infectious diseases diagnostics among participants and visitors of the FIFA 2017 Confederation Cup. But at the same time 3 out of them made a break in their work on those days when matches were held;

-11 juridical persons stopped their work with infectious diseases agents for the whole period of the FIFA 2017 Confederation Cup;

-16 medical organizations were excluded from the list of hazardous objects approved by the RF Governmental Order dated June 09, 2017, No. 689. However, as the IWG detected violations of biological safety requirements, laboratory activities at 3 medical organizations were prohibited by its decision for the period when the FIFA 2017 Confederation Cup took place, namely, from June 12, 2017 to July 12, 2017.

Conclusions. Efficient interdepartmental interaction aimed at providing biological safety during preparation to the FIFA 2017 Confederation Cup and the event itself allowed to prevent pathogens entering the environment or possible PBA application as biological terrorism objects.

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RISK FACTORS WHICH CAUSE SENILE CATARACT EVOLVEMENT: OUTLINE

E.V. Bragin

Southern Urals Biophysics Institute of Federal Medical-Biological Agency, 19 Ozerskoe shosse, Ozersk, 456780, Russian Federation

Examination of natural ageing processes including those caused by multiple external factors has been attracting researchers' attention over the last years. Senile cataract is a multi-factor disease. Expenditure on cataract surgery remain one of the greatest expenses items in public health care. Age is a basic factor which causes senile cataract. Morbidity with cataract doubles each 10 years of life. This outline considers some literature sources which describe research results on influence exerted on cataract evolvement by such risk factors as age, sex, race, smoking, alcohol intake, pancreatic diabetes, intake of certain medications, a number of environmental factors including ultraviolet and ionizing radiation. mane of these factors are shown to increase or reduce senile cataract risk; there are conflicting data on certain factors. The outline also contains quantitative characteristics of cataract risks which are given via odds relation and evolve due to age parameters impacts, alcohol intake, ionizing radiation, etc. The authors also state that still there is no answer to the question whether dose-effect relationship for cataract evolvement is a threshold or non-threshold.

Key words: *multi-factor disease, senile cataract, risk factors, relative risk, odds relation, age parameters, dose-effect relationship.*

Cataract is any persistent opacity occurring in the lens substance or capsule. Cataract as a basic factor causing sight disorders and blindness (33%) in the world [1, 2] is a grave social, medical, and economic issue in many countries [1, 3, 4]; expenses on its surgery treatment contribute into overall public health care expenditure considerably.

Experts spot out senile, congenital, traumatic, complicated, and occupational cataract depending on reasons for its occurrence. Senile cataract (hereinafter called "cataract") is the most frequent. It evolves due to age-related changes in the lens, and morbidity with it grows with age.

There are three main cataract types determined as per clinical and anatomical features: nuclear, cortical, and back subcapsular one; they can occur both separately and in various combinations [5]. Nuclear cataract involves opacities in the lens central part (nucleus); the process is combined with lens fibers becoming sclerosed, with the nucleus color changing to yellowish or even brown, and with overall eyesight deterioration. Cortical cataract involves opacities evolvement in the lens periphery. Separate opacities appear in the cortex with age (they can be spoke-like or sectoral) and they usually don't lead to any clinical symptoms until the lens optical axis area is involved in the process. Back subcapsular cataract (BSC) is a compact opacity which is located in the posterior area of the central cortex under the capsule. It usually oc-

Evgeniy V. Bragin – Researcher at Clinical Department (e-mail: clinic@subi.su; tel.: +7 (35130) 2-93-20).

curs at younger ages and causes a considerable loss in the near vision activity.

Results obtained during multiple research on cataract evolvement reasons revealed that cataract was a multi-factor disease. Cataract evolvement depends on age, sex, race, concomitant somatic or eye pathology, bad habits (smoking or nutrition peculiarities), as well as environmental factors, such as ultraviolet radiation and ionizing radiation, and certain medications intake [4, 6].

Non-radiation factors causing cataract risks.

Age. Age is a basic factor causing cataract risk. Thus, cataract prevalence among people aged 52-62 amounts to 5% [7]; among people aged 60–69, 30%; and among people aged 70 and older, 64% [8]. The fact that morbidity with cataract doubles each 10 years of life after 40 means that practically all people aged 80-90 suffers from cataract [9]. Long-term impacts exerted by oxygen free radicals on the lens tissue are considered to be the main reason for opacities evolvement in the lens which are characteristic for senile cataract. A group of researchers revealed [10] that age had a statistically significant influence on all cataract types evolvement. Odds ratio (OR) per each 10 years of life amounted to 9.90 (95% CI: 8,20 – 11,90) for nuclear cataract; 3.06 (95% CI: 2,76 – 3,40)for cortical cataract; 3.09 (95% CI: 2.71 – 3.51) for back subcapsular cataract; and 6.62 (95% CI: 5.78 – 7.63) for all the cataract types.

Sex. A lot of epidemiologic researchers came to conclusions that cataract risk was a bit higher for women than for men; however, this dependence still remains unclear. Thus, for example, the following work [11] contains some data on OR for morbidity with cataract among women which amounted to 3.03 (95% CI: 1.83 – 5.00) against men. Other research [12] revealed that cataract frequency was a bit higher among women than among men, OR being equal to 1.55 (95% CI: 1.26 – 1.91), while at the same time another research performed as per "case - control" type revealed only a boundary dependence between cortical cataract and sex [13]. Some research contains data on protective effects of substitutive hormonotherapy for women during a period after their menopause [14, 15].

Race. Some researchers state there is a correlation between various cataract types and a patient's race. S.K. West, B. Munoz et al. [16] revealed that African Americans ran 4 times higher cortical cataract risk than White Americans while White Americans ran higher nuclear or back subcapsular cataract risks. Other research results show that cortical cataract prevailed among Latin Americans [17].

Smoking. Table 1 contains results of research related to cataract risk assessment depending on a patient' s smoking status.

Some research revealed a correlation between smoking and the lens nucleus sclerosis and detected a dose-effect dependence; people who gave up smoking ran lower cataract risk than those who continued to do it [18–21], so there was an apparent protective effect of giving up smoking.

Another research [10] revealed that smokers had higher morbidity with nuclear cataract (OR = 2.06; 95% CI: 1.46 – 2.98), with cortical cataract (OR = 1.33; 95% CI: 1.02 – 1.74), with back subcapsular cataract (OR = 1.39; 95% CI: 1.02 – 1.91), or with any cataract type (OR = 1.48; 95% CI: 1.10 – 1.99) after corrections as per age, sex, body mass index, arterial hypertension, and diabetes. At the same time another research [22] didn't contain any data on such dependence. Elementary

Table 1

Cataract risk depending on a patient's smoking status

Author(s), years	Participants number	Research results OR, 95% CI	Corrections
Delcourt et al. 2000	2584	Smoke at the moment: 2.34 (1.07 – 5.15) Former smokers: 3.75 (2.26 – 6.21)	Sex, age
Theodoropoulou et al. 2011	314, and 314 reference group	Smoke at the moment: 1.99 (1.23 – 3.23) Former smokers: 1.64 (1.02 – 2.70)	Sex, age
Renyi Wu et al. 2010	2927	Smoke at the moment	Sex, age, BMI, Hypertension, diabetes
		Nuclear cataract: 2.06 (1.46 – 2.98)	
		Cortical cataract:1.33 (1.02 – 1.74)	
		Back subcapsular cataract:1.39 (1.02 – 1.91)	
		All types 1.48 (1.10 – 1.99)	

or secondary education (OR = 1.67; 95% CI: 1.06 – 2.64) and low monthly income increased nuclear cataract risk while living in a small apartment increased back subcapsular cataract risks (OR = 1.70; 95% CI: 1.28 – 2.25). Smoking men run 17.9% risk of nuclear cataract evolvement and it was shown that a) smoking led to a statistically significant increased senile cataract risks (all its types) regardless of age, sex, body mass index, hypertension, and diabetes; b) morbidity with nuclear cataract depended on how many cigarettes a patient smoked a day, and it grew together with smoking index increasing.

Alcohol intake. An essence of influence exerted by alcohol on cataract genesis still remains unclear. The lens is sensitive both to oxidative stress induced by alcohol and to direct toxic effects exerted by alcohol and its metabolism products [23–25]. However, data on correlations between alcohol intake and senile cataract are controversial. "Case - control" research results revealed statistically significant increased cataract risks among beer abusers [26] and former alcoholics [27]. Two cohort examinations were conducted, the first among men only and it was based on questioning about cataract and its surgical treatment [28]; the second one was conducted among men and women and involved cataract type determination and surgical case histories [29]. These examinations revealed there was a positive but statistically insignificant correlation between alcohol intake and cataract evolvement. There was prospective research dedicated to assessing influences exerted by alcohol intake on cataract extraction among 77,466 women in the USA (1,468 cataract extractions) who drank more than 25 mg of alcohol a day and it didn't reveal an increased cataract extraction risk; relative risk (RR) amounted to 1.10; 95% CI: 0.90 – 1.35 [30]. Experts examining specific cataract types detected that strong spirits and wine intake was correlated to increased nuclear opacities risks (OR = 1.13; 95% CI: 1.02 – 1.26), while cortical opacities risks became lower when wine was consumed (OR = 0.88; 95% CI: 0.79 – 0.98) [31]. Population prospective cohort research [14] revealed a statistically significant positive correlation between alcohol intake and "operated" cataract risk; the risk grew with an increase in overall consumed alcohol volume; relative risk of "operated" cataract amounted to 1.11 (95% CI: 1.02 – 1.21) after corrections as per age and other potential risk factors. Multifactor analysis showed that an increase in alcohol intake equal to 13 grams a day (330 ml of beer, 150 ml of wine, or 45 ml of strong spirits correspondingly) caused a

7% growth in cataract extraction risk (RR = 1.07; 95% CI: 1.02 – 1.12).

Somatic pathology.

Pancreatic diabetes. Pancreatic diabetes of both 1st and 2nd types is one of the most significant somatic pathologies which cause higher cataract evolvement risks. Research [11] revealed that odds ratio for cataract evolvement in people suffering from pancreatic diabetes amounted to 2.72 (95% CI: 1.72 – 4.28) in comparison with people who didn't have such pathology. Another research [32] revealed that dextrose level in blood taken on an empty stomach being ≥ 6 mmol/l caused higher cataract risk (OR = 1.79; 95% CI: 1.25 – 2.57 against dextrose level being < 6 mmol/l). The same research also outlined that each 1 mmol/l increase in dextrose level in blood taken on an empty stomach was related to 5-year progress in back subcapsular cataract (OR = 1.25; 95% ДИСІ: 1.15 – 1.35) and to 10-year progress in cortical one (OR = 1.14; 95% CI: 1.01 – 1.27) and nuclear one (OR = 1.20; 95% CI: 1.01 – 1.43); and here no threshold was detected. Besides it was shown that cataract surgical treatment on patients with the 1st type pancreatic diabetes had to be performed 20 years earlier than in case of people who didn't have pancreatic diabetes [33].

Medications. A lot of research dwells on examining correlations between cataract evolvement and various medications intake.

Results obtained in research on correlations between cataract evolvement risk and glucocorticosteroids (GCS) intake are shown in Table 2.

Table 2

Correlation between cataract risk and GCS intake

Author(s), year	Participants number	Research results OR, 95% CI				
Smeeth et al., 2003	15476	Inhalation GCS	System parenteral steroids	System peroral steroids	Inhalation GCS > 1,600 mg/day	Eye drops with GCS
		1,15 (1,03–1,27)	1,56 (1,3–1,82)	1,59 (1,47–1,71)	1,69 (1,17–2,43)	2,12 (1,93–2,33)
Theodoropoulou et al., 2011	314 cases, 314 in reference group	Are taking GCS at the moment 2.59 (0.93 – 7.21)				
Delcourt et al., 2000	2584	GCS were taken orally during 5 and > years 3.25 (1.39 – 7.58)				

A correlation was detected between system corticosteroid intake, especially in high doses and during a long-term period, and cataract evolvement both in children [34] and adults [35]. We should note here that corticosteroids-induced cataracts are usually located in the back part of the lens (back subcapsular cataract). It was also detected that people who took GCS ran higher cataract risk than people who didn't take such medications [28, 36–40].

Statins have been widely used over the last decades to decrease cholesterol in blood plasma in order to prevent cardiovascular diseases. As statins are known to have antioxidant features their intake can lead to lower cataract risks. Research [41] revealed that 5-year morbidity with cataract among people who took statins was lower (12.2%) than among those who didn't take them (17.2%); OR amounted to 0.55 (95% CI: 0.36 – 0.84) allowing for age. When cataract evolvement risk was

assessed for non-smokers and people without pancreatic diabetes, OR amounted to 0.40 (95% CI: 0.18 – 0.90) with corrections as per sex, age, and lipids level in blood. It was shown that statins intake lowered senile cataract risk.

So, literature data prove that cataract evolvement risk depends on many factors, such as age, sex, race, smoking, alcohol intake, concomitant somatic or eye pathology, some medications intake etc.

Ionizing radiation as cataract risk factor. The lens is one of the most radiosensitive organs in a human body. It was detected that ionizing radiation impacts caused cataract evolvement [42, 43]. Ionizing radiation influences cubical epithelium cells which are located on the surface of the lens anterior capsule and damages them. After that damaged cells are differentiated and migrate consequently into the peripheral cortex and the lens back pole area and it causes opacities evolvement [43]. Latent period and effects intensity depend on age, sex, and also on a dose, dose intensity, and irradiation fractioning [44, 45]. Some long-term research allowed to make an assumption that radiation-induced cataracts were a determined long-term effect [46]. A lot of research revealed increased risks of morbidity with various cataract types among different people who were exposed to ionizing radiation impacts. Nowadays ionizing radiation impacts are assumed to cause higher risks of, first of all, back subcapsular cataracts, and, to a smaller extent, cortical cataracts. And it is also considered that nuclear cataracts are associated only with age and some other risk factors. However, evidences of this correlation are controversial enough as research was conducted in groups which included people with different irradiation scenarios and observation periods. So, risk assessment of morbidity with various cataract types among people exposed to long-term irradiation in small doses has been of great interest to researchers recently.

Irradiation during atomic bombing. Table 3 shows the results of research on cataract risk among a cohort made up of people who survived the atomic bombing.

In 2004 two works were published; they contained data on research performed on a cohort made up of people who had survived the atomic bombing in Japan. 55 years after the bombing Minamoto et al. examined eyes state in people who had survived in it and who had been younger than 13 at the moment they had been irradiated [47]. Odds ratios for cortical and subcapsular cataract at an irradiation dose being equal to 01 Gy amounted to 1.29 (95% CI: 1.22 – 1.49) and 1.41 (95% CI: 1.21 – 1.64), correspondingly. Authors didn't detect any statistically significant correlation between nuclear cataract and irradiation dose (odds ratio per 1 Gy amounted to 1.1; 95% CI: 0.9 – 1.3). Yamada et al. examined a wide range of non-tumor diseases in people who had survived the atomic bombing and had been observed by doctors for a long time (1958 - 1998), including 975 cataract cases in men and 2,509 ones in women [48]. This research results revealed there was a statistically significant positive correlation between morbidity with cataract and irradiation doses ($p = 0.026$). Morbidity with cataract among people who had been exposed to a dose higher than 1 Gy amounted to 7.98 (95% CI: 0.95 – 15.16) per 10,000 people annually; corresponding relative risk was equal to 1.06 (95% CI: 1.01 – 1.11). Relative risk of morbidity with cataract went down statistically significantly with a growth in age a person had managed to live to by the examination ($p < 0.001$) and with a growth in period of

Table 3

Cataract morbidity risk in a cohort made up of people who survived the atomic bombing

Author(s), year	Observation period	Irradiation dose, target organ	Research results	Corrections
Choshi et al., 1983	1978–1980	Dose on the lens: 0 – 600 rad	RR of BSC: 5.28 for people younger than 50 3.99 for people aged 50 – 59 2.34 for people older than 60 No dependence on a dose was revealed for nuclear or cortical cataract	City, age, sex
Minamoto et al., 2004	2000–2002	Dose on an eye: 0.005 – 2 Sv	OR per 1 Sv for: BSC = 1.41 (95% CI: 1.21 – 1.64) Cortical cataract = 1.29 (95% CI: 1.12 – 1.49) Nuclear cataract = 1.12 (95% CI: 0.94 – 1.30)	City, age, sex, smoking
Nakashima et al., 2006		Dose on an eye: 0 – 4.90 Sv	OR per 1 Sv for: BSC = 1.44 (95% CI: 1.19 – 1.73) Cortical cataract = 1.30 (95% CI: 1.10 – 1.53)	City, age, sex, smoking
Nakashima et al., 2013	1986–2005	Dose on the lens: 0 – 5.14 Gy	OR per 1 Gy for "operated" cataract = 1.33 (95% CI: 1.28 – 1.38)	
Neriishi et al., 2007	2000–2002	Dose on an eye: 0.005 – 4.90 Sv	OR per 1 Sv for "operated" cataract = 1.39 (95% CI: 1.24 – 1.55) Threshold dose = 0.1 Gy	City, age, sex, diabetes
Neriishi et al., 2012	1986–2005	Dose on the lens: 0 – 5.14 Gy Average: 0.54 Gy	Dose-effect linear dependence	Age, sex, social and medical factors
Yamada et al., 2004	1958–1998	Average weighted dose: 0.92 Sv	Cataract RR per 1 Sv = 1.11 (95% CI: 1.03 – 1.19)	City, age, sex, alcohol

time which had passed since the irradiation moment (p = 0.09).

In 2006 and 2013 Nakasima et al. published a reanalysis of data obtained on a cohort of people who had survived the atomic bombing in Japan and detected a statistically significant "dose - effect" relationship; cataract morbidity risk here went down with a growth in age a person had managed to live to [49, 50]. Odds ratio per 1 Sv amounted to 1.44 (95% CI: 1.19 – 1.73) for back subcapsular cataract and to 1.30 (95% CI: 1.10 – 1.53) for cortical cataract in people who had been 10 years old at the irradiation moment. Authors didn't reveal any statistically significant "dose - effect" relationships for nuclear cataract. Odds ratio grew with an increase in an irradiation dose for cortical and subcapsular cataract, a threshold dose was estimated to be equal to 0.6 Sv.

In 2007 and 2012 Neriishi et al. published results of their research on "dose - effect" relationship for clinically significant cataracts [51, 52]. The research included 3,791 people who had survived the bombing and 479 "operated" cataract cases; it detected some proves of a linear, and not a linear-quadratic, "dose - effect" dependence, and an estimated threshold irradiation dose amounted to 0.1 Gy.

Irradiation related to the Chernobyl' nuclear power plant disaster. In 2007 Worgul et al. published their analysis of cataracts frequency among Ukrainian liquidators of the Chernobyl' disaster consequences which was estimated 12-14 years after their irradiation. The model allowed for an age at the irradiation moment, sex, a dose with a 50 mGy interval, smoking status, diabetes, and some other potential mixing factors [53]. The authors revealed a statistically significant increase in non-nuclear (cortical and back subcapsular) cataracts: odds ratio per 1 Gy amounted to 1.65 (95% CI: 1.18 – 2.30), and a dose threshold for these cataracts was estimated to be equal to 0.50 (95% CI: 0.17 – 0.69) Gy. Odds ratio for all the cataract types amounted to 1.70 (95% CI: 1.22 – 2.38), and a threshold dose was equal to 1.50 (95% CI: 1.17 – 1.65) Gy.

Medical irradiation. In 1999 Hall et al. examined the lens opacities frequency among Sweden population who had been exposed to ionizing irradiation in their childhood as a results of skin hemangioma treatment [54]. The lens opacities frequency was shown to be higher in people who had undergone radiotherapy in their childhood against the reference group (37% and 20% correspondingly). After a correction per age at the examination moment odds ratio per 1 Gy was equal to 1.50 (95% CI: 1.15 – 1.95) for cortical cataract and to 1.49 (95% CI: 1.07 – 2.08) for bask subcapsular cataract.

Research on cataract risks among medical staff in the USA in 2008 [55] revealed that cataract evolvement risk grew by 15% annually. Female sex, smoking index being more than 15 packets/year, increased body mass index, diabetes, arterial hypertension, hypercholesterolemia, or arthritis increased cataract evolvement risk; at the same time, intake of 1 to 10 alcohol portions a week decreased cataract risk in comparison with those who drank less than 1 alcohol portion a week. The authors detected a statistically significant increase in cataract frequency in people who underwent a lot of diagnostic X-ray procedures (>25) against those who were exposed to a smaller number of such procedures (<5) with hazard ratio (HR) being equal to 1.4 (95% CI: 1.2 – 1.7). Hazard ratio (HR) for cataract extraction amounted to 1.50 (95% CI: 1.09 – 2.06) in this research. Hazard ratio per 1 Gy for people who underwent 3 and more X-ray diagnostic procedures on their faces and necks in comparison with those who didn't have to undergo any such procedures amounted to 1.25 (95% CI: 1.06 – 1.47); hazard ratio for cataract extraction amounted to 1.71 (95% CI: 1.09 – 2.68).

Cosmic radiation. Some research concentrated on the lens opacities frequency among aviation pilots and astronauts exposed to chronic occupational irradiation.

In 2001 Cucinotta et al. detected increased cataract evolvement risk in NASA astronauts [56]. A number of space flights being more than 2 against those who didn't have any or who participated in only one flight, astronauts' age, and a flight slope were statistically significant modifying factors. Hazard ratio (HR) for cataract evolvement at the age of 60 was estimated to be equal to 2.35 (95% CI: 1.01 – 5.51); and at the age of 65, 2.44 (95% CI: 1.20 – 4.98).

In 2005 Raffnson et al. applied "case - control" technique to examine whether the lens opacity frequency was related to an aviation pilot occupation [57]. The analysis allowed for a working period, flying hours per year, flight schedule and routes, and an accumulated irradiation dose calculated on the basis of the above mentioned data. Only nuclear cataract frequency (out of four cataract types - nuclear, cortical, central optical zoned and back subcapsular cata-

ract) was statistically higher in pilots who had regular flights in comparison with people who never worked as pilots with odds ratio being 3.02 (95% CI: 1.44 – 6.35). Age turned out to be a statistically significant factor. Thus, odds ratio for people aged 50 against people aged 40 amounted to 1.17 (95% CI: 1.12 – 1.22). Besides, research results revealed that pilots tended to have cataracts at younger ages. Research results on examining cataract evolvement risk under exposure to solar ionizing radiation are given in Table 4.

Table 4

Cataract evolvement risk among astronauts and pilots

Author(s), Year	Observation period	Irradiation dose	Research results	Corrections
Chylack et al., 2009	2004–2006	Median dose on the lens 12.9 mSv	OR for BSC= 2.33 (95% CI: 1.16 – 4.26)	Age, solar ultraviolet radiation, place of residence, nutrition peculiarities
Chylack et al., 2012	2004–2006	Median dose on the lens 12.9 mSv	Cosmic ionizing irradiation is related to greater BSC size and is not related to nuclear cataract	Age, solar radiation, place of residence, nutrition peculiarities
Cucinotta et al., 2001	1977–1988	Dose on the lens 0.2 – 91.0 mSv	Hazard ratio = 2.6 (95% CI: 1.5 – 4.8)	Diabetes, renal failure, steroids intake, eyes diseases
Rafnsson et al., 2005	1996–2001	1–48 мЗв	Increased nuclear cataract risk in pilots	Age, smoking, a habit to go sunbathing

Table 5

Cataract evolvement risk for intervention surgery staff

Author(s), year	Research model	Results, back subcapsular opacities HR per 1 Gy	
		Cardiosurgeons	Nurses
Ciraj-Bjelac O., 2012	Case - control	2.6 (95% CI: 1.2 – 5.4)	2.2 (95% CI: 0.98 – 4.9)
Vano E., 2010	Case - control	3.2 (95% CI: 1.7 – 6.1)	1.7 (95% CI: 0.8 – 3.7)

Occupational irradiation. Over the last years some data on cataract risks for workers exposed to occupational long-term irradiation have been collected [58]. A statistically significant linear correlation between morbidity with cataract and a total external gamma-irradiation dose was detected; excessive relative risk (ERR/Gy) was equal to 0.28 (95% CI: 0.20 – 0.37). Risk assessment varied insignificantly when additional correlations per various non-radiation factors (smoking status and alcohol intake, smoking index, arterial hypertension, body mass index, and diagnosed "grave myopia") were included. Introduction of correction per a neutron irradiation dose caused a significant increase in external gamma-irradiation ERR/Gy for morbidity with cataract (Err/Gy = 0.31; 95 % CI: 0.22 – 0.40).

Cataract risk assessment for intervention surgeons has been of great interest recently as they are usually exposed to long-term occupational irradiation. Re-

search [59, 60] contains some data on statistically significant increased risk of back subcapsular opacities evolvement in intervention cardiosurgeons. Cataract evolvement risk for auxiliary medical staff was statistically insignificant. The research results are given in Table 5.

So, literature data show that senile cataract is a multi-factor disease. The following cataract risk factors are proved to be significant: sex, age, smoking, alcohol intake, concomitant ophthalmologic pathology, certain somatic diseases (pancreatic diabetes, for example), certain medications intake, exposure to ultraviolet radiation etc.

Over the last years researchers have detected increased risk of specific cataract types under exposure to ionizing radiation as well as made some attempts to estimate a threshold external gamma-radiation dose for various cataract types evolvement. As a result of the research [53] a threshold external gamma-radiation dose amounted to 0.35 (95% CI: 0.19 – 0.66) Gy for back subcapsular cataract; and to 0.34 (95% CI: 0.18 – 0.51) for cortical cataract. Research performed on cohorts made up of people who had survived the atomic bombing [40] revealed that a threshold dose for BSC amounted to 0.7 (95% CI: 0.0 – 2.9) Gy; and to 0.6 (95% CI: 0.0 – 1.4) Gy for cortical cataract. According to different research results a threshold dose for "operated" cataract amounted to 0.50 (95% CI: 0.17 – 0,65) Gy [59]; 0.41 (95% CI: 0.04 – 1.03) Gy [14]; and 0.50 (95% CI: 0.10 – 0.95) Gy [41].

However, a question whether a "dose - effect" relationship is a threshold or a non-threshold one for cataract evolvement still remains open.

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MONITORING OF LEGAL AND REGULATORY DOCUMENTS IN THE SPHERE OF PUBLIC HEALTH AND SANITARY-EPIDEMIOLOGIC WELFARE

January-March 2018

The Decision by The Board of the Eurasian Economic Commission dated January 16, 2018 No. 1 "On making alterations into the Appendix 19 to Section 22 Chapter II of the Unified Sanitary-Epidemiologic and Hygienic Requirements to products (goods) which are subject to sanitary-epidemiologic surveillance (control)"

1-Phenylpropan-2-on is excluded from the list of flavor aromatic chemicals which are permitted to be used in food flavoring agents production.

The Decision by The Board of the Eurasian Economic Commission dated January 23, 2018 No. 12 " On making alterations into the Section 13 Chapter II of the Unified Sanitary-Epidemiologic and Hygienic Requirements to products (goods) which are subject to sanitary-epidemiologic surveillance (control)"

The Section 13 "Requirements to cigarettes and tobacco raw materials" is given in new edition. This section is now called "Requirements to non-smoking tobacco products, non-smoking tobacco goods, and tobacco raw materials such products and goods are made of". The section fixes the requirements to non-smoking tobacco products, non-smoking tobacco goods (including chewing tobacco, snuff tobacco, and sucking tobacco (snus)) and tobacco raw materials applied in production of them and classified in goods items 2401 and 2403 in CU CNFEA.

The Decision by The Board of the Eurasian Economic Commission dated February 07, 2018 No. 22 "On the list of international and regional (inter-country) standards, and in case of their absence, national (state) standards, the application of which results in voluntary compliance with the requirements set forth in the EEU Technical Regulations "On safety of equipment installed on children playgrounds" (TR EEU 042/2017) and… the EEU Technical Regulations "On safety of equipment installed on children playgrounds" (TR EEU 042/2017) and assessing compliance of objects which are subject to technical regulation"

The Decision establishes a list of standards which are necessary to provide compliance with the requirements fixed in the EEU Technical Regulations "On safety of equipment installed on children playgrounds" (TR EEU 042/2017). It contains the list of international and regional (inter-country) standards, and in case of their absence, national standards, the application of which provides voluntary compliance with the requirements set forth in the technical regulations. It also approves on the list of international and regional (inter-country) standards, and in case of their absence, national standards, which contain rules and procedures for examinations (tests) and measurements, and rules for sampling, which are necessary for proper fulfillment of the requirements set forth in the above mentioned Technical Regulations "On safety of equipment installed on children playgrounds" (TR EEU 042/2017) and assessment of compliance of objects which are subject to technical regulation".

The Decision by The Council of the Eurasian Economic Commission dated February 16, 2018 No. 5 "On making alterations into the Decision by the Customs Union Commission dated May 8, 2010 No. 299"

Amendments are made into the procedures for accomplishing sanitary-epidemiologic surveillance (control) over people, vehicles, products (goods) under control moving across the EEU customs border. Conceptual tools are adjusted, and updates are made in the list of documents (data) applied as a confirmation that goods under control were registered by state officials according to the established order. Some appendixes to the above mentioned procedures are given in new edition.

The Decision by The Board of the Eurasian Economic Commission dated March 06, 2018 No. 37 " On making alterations into the Decision by the Customs Union Commission dated December 7, 2011 No. 878"

The Decision contains new editions of the lists of standards and documents on standardization necessary for compliance with and proper applica-

tion of the Customs Union Technical Regulations "On safety of individual protection means" (TR CU 019/2011). It has a list of standards (stating their validity term) the application of which results in voluntary compliance with the requirements set forth in the above mentioned technical regulations, as well as a list of documents on standardization which contain rules and procedures for examinations (tests) and measurements which are necessary for assessing compliance of objects which are subject to technical regulation".

The RF President Decree signed on January 11, 2018 No. 12 "On approval of the Russian Federation State Policy in the sphere of protecting population and territories from emergencies for the period up to 2030"

The Decree states basic principles of the country policy in the sphere of protecting people and territories from emergencies for the period up to 2030; these principles, among other things, imply higher efficiency of managing risks which occur in case of an emergency allowing for contemporary natural technogenic and other threats; development of systems for early detection of rapidly evolving dangerous natural phenomena and processes; creation of universal light-weighted individual protection means as well as improvement of organizational procedures for individual protection means storage and provision of population with such means; organization of mass events (trainings, lectures, meetings with citizens etc.) aimed at life safety culture creation and development; implementation of risk-oriented approach into organization and implementation of state surveillance in the sphere of protecting population and territories from emergencies.

The RF Presidential Message to the Federal Assembly dated March 01, 2018

The RF President mentioned in his message, among other things, such issues as demography, ecology, education, public healthcare, social sphere, development of the country economy, and international relations. He highlighted the most vital ones: preservation of the RF population; providing welfare for the citizens; providing sustained natural growth of the RF population.

The most important tasks in the public healthcare are to provide easy access to primary public healthcare institutions, to create a unified "circuit" of medical and prevention organizations at various levels in order to combine efforts by the whole national public healthcare system to help each person in need; implementation of a specialized national program aimed at fighting against oncologic diseases which is supported by science, up-to-date complex diagnostics, treatment, and prevention, including large-scale inter-subject projects in the sphere of genome research.

As for urban development, there are vital issues related to industrial and communal wastes dumps and recultivation of places where wastes were stored. A goal was set to achieve substantial increase in drinking water quality.

It was noted that risk-oriented approach should be implemented into the overall system of state surveillance and control over business during the next two years.

The RF Governmental Regulation dated January 19, 2018 No. 31 "On making alterations into the unified list of products the conformity of which is to be confirmed by declaration of conformity"

Sections which classify fish and products made of fish are excluded from the list of products subject to declaration of conformity. It is fixed that validity terms of declarations of conformity which were approved prior to the date when the EEU Technical Regulations "On fish and fish products safety" (TR EEU 040/2016) came into force, as well as procedures for manufacturing and distributing products as per the above mentioned declarations, are to be fixed in accordance with the Decisions by the Boards of the Eurasian Economic Commission dated April 24, 2017 No. 40 "On transient provisions of the EUU Technical Regulations "On fish and fish products safety" (TR EEU 040/2016). Products and (or) package distributed on the RF territory as per the above mentioned declarations are not subject to being re-labeled with the compliance mark.

The RF Governmental Regulation dated January 24, 2018 No. 52 "On making alterations into the list of workplaces in organizations performing specific activities which are subject to specialized working conditions assessment allowing for peculiarities approved by an authorized federal executive body"

The Regulations make additions to a list of working places which require a specialized working conditions assessment performed according to specific procedures. The above mentioned list approved by the RF Governmental regulations dated April 14, 2014 No. 290 includes the following: working places directly related to design, manufacturing, pro-

cessing, testing, utilization, and inter-operation storage of explosives, pyrotechnic compounds, gunpowder, propellants, detonating agents, and products made of them, in organizations dealing with radiation- and nuclear-dangerous productions (objects) and organizations manufacturing ammunition and specialized chemicals. Specific peculiarities of assessment procedures in relations to the above mentioned working places are to be fixed by the RF Labor Ministry by July 1, 2018.

The RF Governmental Regulation dated January 25, 2018 No. 84-p «On approval of Production Development Strategy for processing, utilization, and neutralization of industrial and consumption wastes for the period to 2030

The Regulation approved a strategy aimed at developing new industrial branch in the RF. The branch is going to deal with processing, utilization, and neutralization of wastes. This new branch should combine the following: economic entities which design, manufacture, and sell technical equipment, technologies, production units, and equipment for processing, utilization, and neutralization of wastes; scientific-research and research and development organizations and establishments engaged in developing innovating resource-saving technologies, processing, utilization, and neutralization of wastes; economic entities in one or several economic branches which deal with processing, utilization, and neutralization of wastes and production of goods from secondary raw materials.

Innovative development of the branch is a top priority and it implies that development should be complex, balanced, and efficient; conditions for innovations should be created; all the necessary and sufficient funding should be provided.

The appendixes to the strategy contain the following: the list of main industrial objects the activity of which leads to formation of wastes and which apply processed secondary raw materials in their production; the strategy targets for the period up to 2030; the strategy parameters for the period up to 2030 which determine resource potential as per specific types of wastes.

The RF Government Regulation dated January 29, 2018 No. 81 "On making alterations into the RF Government Regulation dated September 23, 2013 г. No. 839"

The precise definition is given to the rules on the state registration of genetically modified organisms (GMO) which are to be distributed on the market, and products which contain such organisms or are manufactured via application of such organisms. It is fixed that if the state registration of such products, regardless of their declared end use, began prior to July 1, 2017, or if molecular-genetic research, medical-biological assessment, sanitary-epidemiologic inspection, and research on biological safety of these products are initiated, then the state registration of modified organisms which were applied and (or) are contained in the products is not required.

A registering body makes its decision on registering these products basing on the application which was accepted prior to July 1, 2017, and on reports with results of research, assessment, and inspection which were initiated prior to the above mentioned date.

The RF Government Regulation dated March 03, 2018 No. 222 "On approval of Rules for sanitary hygienic zones establishment and use of ground areas located within the boundaries of sanitary hygienic zones"

The Regulation fixes the procedures for establishment, alterations, and cessation of sanitary-hygienic zones. It enlists objects in case of which sanitary-hygienic zones are to be established; it describes the procedures and grounds for making a decision on a sanitary hygienic zone establishment, alteration, or cessation; it fixes permissible use of ground areas which are located within a sanitary hygienic zone. The Regulation sets forth the requirements to a form of an application on establishment, alteration, or cessation of a sanitary-hygienic zone, a list of documents which should be attached to it, and who can submit the above mentioned application; the requirements to the content of a decision on establishment, alteration, or cessation of a sanitary-hygienic zone; it also clarifies the grounds for refusal to establish a sanitary hygienic zone.

It is also fixed that data on a sanitary-hygienic zone establishment are to be put into The Unified State Register of Real Estate and a sanitary hygienic zone itself is considered to be established since the date the corresponding data have been put into the Register.

Since the date of a sanitary hygienic zone establishment it is prohibited to build or reconstruct any object of capital construction on ground areas within it the end purpose of which is beyond the limitations imposed on the use of ground areas by a decision on a sanitary protection zone establish-

ment; use of ground areas which is beyond the above mentioned limitations is also prohibited.

The program "Epidemiologic surveillance and prevention of enterovirus (non-polio) infections for 2018-2022". Approved by the head of the Federal Service for Surveillance over Consumer Rights protection and Human Well-being on January 18, 2018

The purpose of the program is to improve monitoring of morbidity with enterovirus (non-polio) infection, circulation of non-poliomyelitis enterovirus strains, and to reduce risks of niduses development and formation.

The program sets the following tasks: to examine epidemic process of the infection; to determine regularities of epidemic rises in morbidity; to provide early detection of epidemic strains; to improve laboratory diagnostics of the infection; to train qualified personnel in the spheres of the infection diagnostics, epidemiology, and prevention.

The expected results are: lower morbidity with the infection; a decrease in number of disability outcomes and prevention of death cases; a decrease in infectious episodes number.

The Letter by Rospotrebnadzor dated January 23, 2018 "On standardization of fat acids trans-isomers contents in food products "

A new standard which regulates contents of fat acids trans-isomers in butter and fat products came into force on January 1, 2018, after the transition period ended. This standard is the Customs Union Technical Regulation CU TR 024/2011 called "Technical Regulation for butter and fat products" approved by the Customs Union Commission on December 09, 2011 No. 883. Contents of fat acids trans isomers in solid margarines, soft and liquid margarines, milk fat substitutes, and specialized fats should not exceed 2.0% of the overall fat contents in a product.

Additional data on maximum content of saturated fat acids and fat acids trans-isomers in a product fat phase (given in % from the overall fat content in a product) should be given on a consumer package of margarines, vegetative-creamy and vegetative-fat spreads, vegetative-creamy and vegetative-fat melted mixtures, specialized fats including cooking fats, confectionary fats, bakery fats, milk fat substitutes, and other products which contain trans-fats.

The Letter by Rospotrebnadzor dated February 14, 2018 Nj. PH-04-03-27/2839 "On state registration of objects which exert negative influence on the environment"

The Letter states that an object which exerts negative influence on the environment (NIOE) is a capital construction object and (or) other object, as well as a set of objects which have the same purpose and (or) are inseparably linked physically or technologically and located with one or several ground areas. Only NIOE objects which correspond to the Criteria for determining a category of NIOE object fixed in the RF Government Regulation dated September 28, 2015 No. 1029 are subject to the state registration.

Juridical persons and private entrepreneurs are to register a garage as an object which can exert negative influence on the environment if any activity which can cause such influence is performed in it. Should any such activity be performed in garages equipped with exhaust ventilation, an exhaust ventilation pipe should be considered a stationary source of the environmental contamination. In this case a juridical person or a private entrepreneur is to register operating NIOE objects, work out standards for MPE, and to obtain a permission to emit hazardous (polluting) substances into the atmospheric air.

The Letter by Federal Service for Accreditation dated January 25, 2018 No. 1681/05-CM "On application of standards"

The Federal Service for Accreditation informs all the lower organizations on a list of standards which have been adopted instead of previously existing ones. New standards included into the list can be applied by test laboratories (centers) without any additional test equipment or measurement tools, without skills development for their staff, without any changes in test procedures, and without extension of the accreditation sphere of juridical persons and private entrepreneurs who assess conformity.

The list includes 81 standards. The denomination and other essentials of a previously existing state standard, as well as the denomination and the essential of a standard which is valid now, are given for each of them.

The Letter by the RF Labor Ministry dated January 26, 2018 «On organization of labor during cold season of the year on an open territory or in closed spaces without any heating"

The RF Labor Ministry reminds that only workers without any medical contraindications can be admitted for work in cold. They should be

equipped with a set of individual protection means which correspond to the existing climatic conditions. Time which a worker can spend in cold is to be determined in conformity with a permissible chilling of a human body according to Methodical Guidelines 2.2.7.2129-06 "Regimes of work and rest in cold season on an open territory or in rooms without heating". When workers perform their job tasks during cold season on open air or in rooms without heating, they should be granted additional specialized breaks for heating; these breaks are to be included into their work hours and are to be paid for. Breaks number and duration depends not only on air temperature, but also on wind force and speed.

Methodical Guidelines 1.1.0120-18 «Quick technique for toxicological hygienic assessment of perfumes and cosmetics with luminous bacterial test (with application of a "Biotoks-10" type luminometer measuring device)" Approved by the Head of the Federal Service for Surveillance over Consumer Rights protection and Human Well-being, the RF Chief Sanitary Inspector on February 13, 2018.

The guidelines contain the description of a technique for toxicological testing of perfumes and cosmetics when a reagent of 'Ecolum" luminous bacteria, or any other bacterial luciferase preparation, is applied as a test-object (biosensor). They also give the outline of the testing procedure.

Methodical Guidelines 1.1.0121-18 "Assessment of general toxic effects by perfumes and cosmetics via in vitro technique (on mobile cells culture)" Approved by the Head of the Federal Service for Surveillance over Consumer Rights protection and Human Well-being, the RF Chief Sanitary Inspector on February 13, 2018.

The guidelines contain the description of a technique for testing perfumes and cosmetics with application of a short-term suspension mobile cells culture (a bull's sperm) and give the outline of the testing procedure.