Founder: Federal Scientific Center
for Medical and Preventive
Health Risk Management
Technologies Federal Service
for Surveillance on Consumer
Rights Protection and
Human Wellbeing

Contact Information:
82 Monastyrskaya Str.,
Perm, 614045, Russia
Tel/Fax: +7 (342) 237-25-34
E-mail: journal@fcrisk.ru
Site: journal.fcrisk.ru/eng

Editor and corrector – M.N. Afanaseva
Technical Editor – A.A. Nizhegorodova
Translator – N.V. Dubrovskaya

The publication 30.06.2020.
Format 90×60/8.
Order No. 68/2020.
Edition is 500 copies.
The price is free.

The Journal is registered by The Federal
Service For Supervision Of Communications,
Information Technology, And Mass Media
(Roscomnadzor). Register certificate
СМИ – ПИ No. ФС 77-52552
issued on January 21, 2013

Address of the publisher and printing house:
29 Komsomolsky ave., Perm, 614990,
Russia, tel.: +7 (342) 219-80-33

Printed by the Publishing House of
Perm National Research Polytechnic
University (29 Komsomolsky ave.,
Perm, 614990, Russia,
tel.: +7 (342) 219-80-33)

Subscription number:
catalog "Russian Post"
annual subscription – 04153
semi-annual subscription – 83927

ISSN (Print) 2308-1155
ISSN (Online) 2308-1163
ISSN (Eng-online) 2542-2308

HEALTH RISK ANALYSIS

Theoretical and practical journal. Start of publication: 2013.

4 issues per year

2

April 2020 June

СОДЕРЖАНИЕ

PREVENTIVE HEALTHCARE: TOPICAL ISSUES OF HEALTH RISK ANALYSIS

UDC 614.7
DOI: 10.21668/health.risk/2020.2.01.eng

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NEW MECHANISMS FOR REGULATION OF INDUSTRIAL EMISSIONS INTO THE ATMOSPHERE: A CONCEPTUAL LOOK AT PROSPECTS AND PROBLEMS FROM SANITARY-EPIDEMIOLOGICAL POINT OF VIEW

N.V. Zaitseva, I.V. May

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

The article considers the main aspects of environmental regulation of chemicals emissions into the atmosphere, based on the principles of quotas for individual business entities. It is shown that new approaches to establishing permissible emissions are an important step towards taking into account human health indicators while limiting the negative impact of all types of emission sources. The main positive innovations are the consideration of long-term pollution indicators, verification of calculated data by field measurements and the use of risk assessment methodology when choosing priority substances.

A comparative analysis of the results of emissions despersion simulating and instrumental data (at the environmental monitoring observation points) showed the need to adjust the consolidated databases of emission sources in the territories of the federal "Clean Air" project.

A conceptual scheme is proposed for establishing limits for permissible emissions from the standpoint of ensuring the sanitary and epidemiological well-being of the population.

It is proposed to supplement the normatively fixed algorithm with a number of steps that will ensure not only compliance with established hygienic standards for air quality, but also take into account the consequences of multicomponent pollution specific to each city. Such steps include identifying unacceptable risk zones in the territories, assessing the contribution of each business entities to health risks and assessing the residual risk after the implementation of separate environmental protection measures and the totality of comprehensive plans measures.

The authors indicate that achieving acceptable risk should be supported by epidemiological data on the territory and the results of in-depth biomedical research. The purpose of such studies is to form a reliable evidence base of absence or preservation of public health harm in the conditions of reducing emissions to level of environmental standards.

Keywords: *emission sources, summary databases, emission quotas, atmosphere air, risk, health harm.*

On November 01, 2019 the Federal Law No. 195-FZ «On performing an experiment on quoting emissions of pollutants and making alterations into some legislative acts existing in the Russian Federation as regards reduction in ambient air pollution»[1] came into force. 12 cities are planned as experimental grounds; they are included into «Clean air» Federal project that is a part of «Ecology» National project. Norilsk, Bratsk, Krasnoyarsk, Magnitogorsk, Chita, and other cities are territories with the highest ambient air contamination; population and authorities there pay a lot of social attention to environmental issues, including ambient air contamination. A task a new quoting mechanism has to solve is to achieve an actual decrease in ambient air contamination in these cities during implementa-

Nina V. Zaitseva – Academician of the Russian Academy of Sciences, Doctor of Medical Sciences, Professor, Scientific Director (e-mail: znv@fcrisk.ru; tel.: +7 (342) 237-25-34; ORCID: https://orcid.org/0000-0003-2356-1145).

Irina V. May – Doctor of Biological Sciences, Professor, Deputy Director responsible for research work (e-mail: may@fcrisk.ru; tel.: +7 (342) 237-25-47; ORCID: https://orcid.org/0000-0003-0976-7016).

[1] On performing an experiment on quoting emissions of pollutants and making alterations into some legislative acts existing in the Russian Federation as regards reduction in ambient air pollution: The RF Federal Law No. 195-FZ. *KonsultantPlus*. Available at: http: //www.consultant.ru/document/cons_doc_LAW_329955/ (10.05.2020) (in Russian).

tion of «Clean air» Federal project as a part of «Ecology» National project.

Successful accomplishment of the above experiment seems to probably provide grounds for emissions quoting to be applied in all the regions in the country. Given that, it seems vital to consider all aspects of new approaches bearing in mind providing sanitary-epidemiologic welfare of the population.

The Federal Law stipulates implementing the following stage-by-stage algorithm aimed at fundamental improvement of ambient air quality in cities included into the Federal project:

– the 1st stage: (till May 01, 2020) is consolidated calculations of ambient air contamination;

– the 2nd stage (till August 01, 2020) is calculating and assessing health risks caused by exposure to chemicals contained in emissions;

– the 3rd stage (till November 1, 2020) is stipulating a list of economic entities that are to allow any emissions in strict conformity with directive quotas and to perform compensatory activities;

– the 4th stage (till March 01, 2021) is making alterations into complex activity programs aimed at reducing contaminants emissions into ambient air.

Including a stage that involves health risk assessment is the most significant innovation in the new mechanism as it will allow providing sanitary-epidemiologic welfare of the population. On one hand, it will provide a tool for determining and imposing limits on emissions that are responsible for the greatest medical and demographic losses among population; on the other hand, it will secure harmonization of approaches to fixing quotas on emissions and give grounds for determining sanitary protection zones. The latter involves health risk assessment fixed in the regulatory documents[2, 3] and has been successfully applied in practice for many years [1–3].

But still, each element in this new system has its significance and each stage makes its contribution into the ultimate result of standardizing.

When we consider consolidated calculations as the first stage in our experiment, we should note that after the Order by the RF State Ecological Committee No. 66 was issued in 1999, many cities in the country (Perm, Voronezh, Lipetsk, Kazan, Nizhnekams, and some others) created and have been keeping consolidated databases; experts there have been performing consolidated dispersion calculations and their results have been applied to solve variable tasks, for example, in the spheres of city development, monitoring, or giving predictions [4–6], including new standards for emissions into ambient air[4, 5] [6–8].

However, practical work revealed that creation of a consolidate database requires extremely thorough formation, system verification, and constant actualization of all data that are put into it. There are several reasons for that.

An economic entity bears full responsibility for making an inventory list of sources that emit hazardous substances into ambient air; according to the existing regulations, in usual situations such a procedure should be accomplished every five years[6]. Even bearing in

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[2] On approval of Rules for sanitary hygienic zones establishment and use of ground areas located within the boundaries of sanitary hygienic zones. The RF Government Regulation issued on March 03, 2018 No 222 (last edited on December 21, 2018). *KonsultantPlus*. Available at: http: //www.consultant.ru/document/cons_doc_LAW_292487/ (10.05.2020) (in Russian).

[3] On validating the last edition of sanitary-epidemiologic rules and standards 2.2.1/2.1.1.1200-03. Sanitary protection zones and sanitary classification of enterprises, buildings, and other objects: The Order by the RF Chief Sanitary Inspector issued on September 25, 2007 No. 74. Registered in the RF Ministry of Justice on January 25, 2008 No. 10995 (last edited on April 25, 2014). *KonsultantPlus*. Available at: http: //www.consultant.ru/document/cons_doc_LAW_74669/ (30.04.2020) (in Russian).

[4] On applying a system of consolidated calculations when standardizing emissions: The Order by the RF State Ecological Committee issued on February 16, 1999 No. 66. *KODEKS: an electronic fund for legal and reference information*. Available at: http: //docs.cntd.ru/document/901729767 (30.04.2020) (in Russian).

[5] Completion of the consolidated database on maximum permissible emissions into ambient air in Naberezhnye Chelny for implementing a system aimed at determining calculated background contamination in the city. The report on fulfilling The State Contract No. 14 ME-8c signed on March 25, 2014. IPEN AS RT. Kazan, 2014, 218 p. (in Russian).

[6] On Approval on the procedure for inventories of stationary sources and emissions of hazardous (contaminating) substances into the atmosphere, adjustment, documenting and storage of data obtained during such inventories: the Order by the RF Ministry of national Resources and the Environment issued on August 7, 2018 No. 353. *KonsultantPlus*. Available at: http: //www.consultant.ru/document/cons_doc_LAW_309693/ (30.04.2020) (in Russian).

mind maximum objectivity presumption and ecological responsibility of an economic entity, one should also take into account that:

– those who use natural resources are not obliged to make inventory lists at the same moment; that is, a database is always somewhat different from the actual situation;

– when making inventory lists, economic entities apply different calculation procedures; some of them, even being included into a list of procedures considered to be valid at the moment[7], are based on parameters and models that were created 10, 15, or even 20 years ago. For example, *Methodical guidelines on calculating gross emissions of hazardous chemicals into ambient air for oil processing and petrochemical enterprises (1990); Methodical guidelines on calculating quantitative properties of contaminants emissions into ambient air from basic technological equipment installed at enterprises that manufacture concentrated food… (1987); Specialized procedure for determining quantities of contaminants that are emitted into ambient air due to technological equipment operating at printing enterprises (1990).*

As a result, inventory lists created by economic entities can differ significantly from the actual situation; first of all, it comes to a structure of chemical admixtures that are emitted into ambient air. There is practically no document that stipulates spotting out PM10 and PM2.5 fine-dispersed fractions in solid emissions. And at the same time there are data both in domestic and foreign literature sources on occurrence of PM10 and PM2.5 fine-dispersed fractions in emissions from multiple productions [9–12] and on substantial health risks caused by particles with their size being less than 10 μm [13–15];

– most procedures are rather poor tools for approximating emissions from non-standard emission sources; admixtures emitted from such sources are often encoded differently and their types fixed for each particular source also differ from each other;

– taking autonomous heating sources into account is also a tedious, complicated and labor-consuming task that requires a lot of organizational efforts and patience. As a rule, these emission sources are stoves and boilers installed in private houses. Data on fuel that is used in households and periods of stove and boilers functioning can be provided only by citizens who are not obliged to submit them and do not bear any responsibility for their correctness;

– when a consolidate database on emissions sources is being created, emissions from motor transport become another problem as their emissions are not stationary in time and correct calculating in this case depends on how precisely intensity and structure of traffic flows on specific sections in traffic networks have been taken into account and what fuels are commonly used in this or that city [16, 17]. This component requires constant interaction between consolidated database keepers and local authorities bearing in mind that the latter should be genuinely interested in constant and qualitative data exchange.

Section No. 3 in the Rules for accomplishing consolidated calculations[8] (hereinafter called the Rules) stipulates that there can be a limitation imposed on including data on contaminants emissions into a database. It is envisaged that not less than 95 % of the total emissions from objects included into the state register that keeps records on emissions sources should be considered. But sometimes emissions that are insignificant in their mass can be emitted from sources that are located in close proximity to residential areas; they can exert more significant impacts on the quality of the environment and population health than more powerful but at the same time more distant emission sources. This fact is unfortunately neglected.

[7] A list of procedures applied in 2020 to calculate, standardize, and control contaminants emissions into ambient air. Approved by A.O. Martsinovskiy, the MD of «Atmosfera» Scientific Research Institute (Joint-stock company). Saint Petersburg, 2019, 11 p. (in Russian).

[8] Rules for accomplishing consolidated calculations of ambient air contamination including their actualization / approved by the Order of the RF Ministry of Natural Resources and the Environment issued on November 26, 2019 No. 813. *Konsultant-Plus*. Available at: www.consultant.ru/document/cons_doc_LAW_341489/ (30.11.2020) (in Russian).

Thus, for example, when a consolidated database was created for Bratsk, there were emissions sources included into it that caused 95.2 % of the total emitted contaminants in the city; but still, it didn't include such sources as «Karat» LLC, «Atlanta» Ltd, «Timoks» LLC, «Alyans» LLC, «Irkustliy vtormet» LLC, «Vostochnosibiskiy vtorchermet» LLC, «Sanitary-technical and electrical mounting plant» joint-stock company, «Bratskiy benzin» LLC, and almost 60 other economic entities that totally emitted almost 6.3 tons per year! And industrial grounds belonging to these economic entities are located directly next to residential areas (Figure 1).

Point 5. «Karat» LLC (15.98 tons/year); point 10. «Alyans» LLC (3.4 tons/year); point 11. JSC tons/year, point 47. «Union Trade» LLC (22.07 tons/year); point 52. MP «DGI»; MO (7.72 tons/year); point 66. «Universal Eco» LLC (6.10 tons/year).

Probably, if we treat a system for ecological standardizing as being fiscal only and primarily oriented at fixing environmental charges, then taking into account economic entities with insignificant emissions is too labor-consuming and not «beneficial» at all. But if we are preoccupied with providing safety and sanitary-epidemiologic welfare of the population, then excessive data including «insignificant» small emission sources should not a priori be excluded from a consolidated database before consolidated calculations are completed. It can be done only as per results of reconnaissance calculations, ground concentrations, and individual and population risks being taken into account basing on a maximally complete database on emission sources.

Quality of a created database on emission sources guarantees that all the subsequent steps are correct; these steps are determining ground concentrations of contaminants; assessing population exposure; assessing and characterizing health risks; selecting priority chemicals and objects for quoting; fixing quotas for specific economic entities; working out activities aimed at reducing emissions. Incorrect or just not very precise assessment of environmental contamination and contributions made by specific emission sources into this contamination can result in inadequate managerial decisions and risks of financial and time losses borne by economic entities or authorities[9] [18].

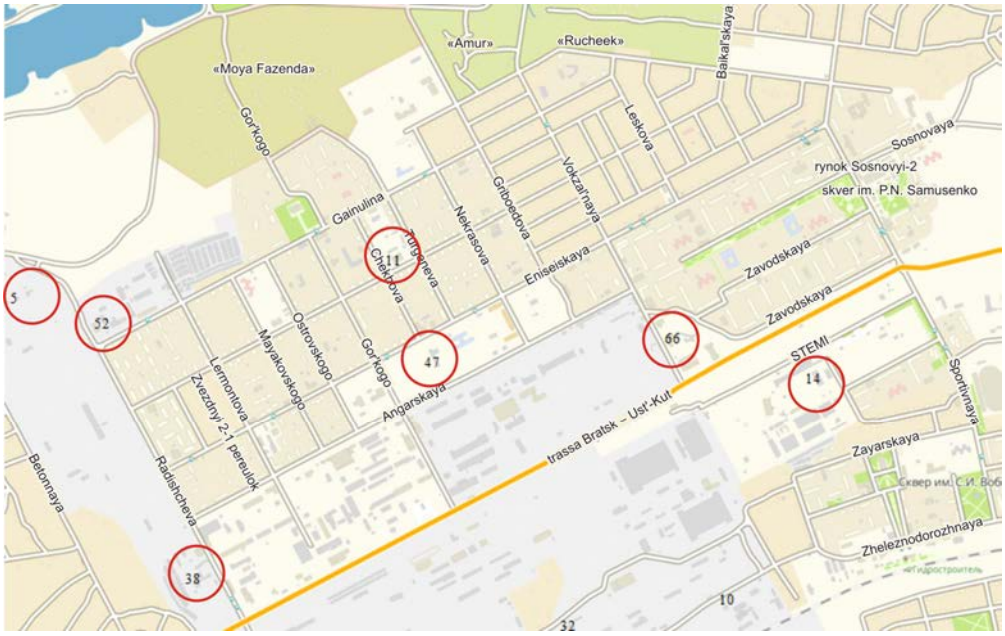

Figure 1. An example showing location of economic entities that were not included into the consolidated database in Bratsk

[9] HB 436: 2004. Risk Management Guidelines Companion to AS/NZS 4360. Jointly published by Standards Australia International Ltd. and Standards New Zealand, 2004, 11 p. (in Russian).

Verification of calculation results with data obtained via instrumental research is certainly a way to overcome uncertainties in creation of inventory lists and a consolidated database (Section 7 in the Rules)[7], and it was first stipulated in a system for fixing maximum permissible emissions. It is assumed that if a database is correct, then dispersion results will satisfactorily coincide with data obtained via ecological monitoring systems. According to items 45–50 in the Rules, 98-th percentile in the distribution function of a measured substance $q_{98,j}$ and single ground concentrations calculated for a point where a monitoring post is located are to be compared as per each contaminant included into conjugated analysis (when short-term concentrations are calculated). When contamination levels are calculated, average annual or average seasonal background concentrations $C_r j$ are to be compared with similar calculated values.

Difference between measured and calculated values is determined (1).

$$\Delta c_j = q_{98,j} - c_j. \quad (1)$$

The following condition is checked at each monitoring post as per each substance (2):

$$\Delta c_j > 0,25 q_{98,j}. \quad (2)$$

When the condition (2) is met, it is necessary to analyze why there is this significant difference in values including obtaining more accurate inventory lists, detecting new sources that were probably neglected etc.

Should data correction not result in eliminating significant Δc_j difference, then values are considered to be authentic, and difference is considered to be due to contaminants being transferred from sources located beyond a territory for which consolidated calculations have been accomplished. In case a value of ΔC difference is negative, it is fixed as equal to 0. The same approaches are applied when verifying averaged data over a year (a season).

Practical work on implementing the 1st stage in the experiment has revealed that overall convergence between calculated and field data is not satisfactory.

Tables 1 and 2[10] give examples of conjugated analysis performed on calculated and instrumental data and conclusions on necessity to make adjustments into initial databases substantiated according to the Rules.

As we can see from the given data, calculated single concentrations of sulfur dioxide are systematically higher than actual contamination (from 2 to 90 times). It is most likely due to drawbacks intrinsic to calculation procedures that are applied to determine emissions, first of all, from energy sources.

Table 1

Instrumental (C_{measd}) and calculated (C_{calcd}) ground concentrations (98-th percentile) of nitrogen dioxide at points where ecological monitoring posts are located

Post No.	Territory	C_{measd}	C_{calcd}	C_{measd}/C_{calcd}	C_{measd}-C_{calcd}	ΔC	Necessity to make data more precise
7	Bratsk	0.009	0.26	0.03	-0.251	0	no (?)
8	Bratsk	0.012	0.171	0.07	-0.159	0	no (?)
11	Bratsk	0.007	0.055	0.13	-0.048	0	no (?)
1	Krasnoyarsk	0.009	0.095	0.09	-0.086	0	no (?)
2	Krasnoyarsk	0.009	0.114	0.08	-0.105	0	no (?)
5	Krasnoyarsk	0.022	0.223	0.10	-0.201	0	no (?)
7	Krasnoyarsk	0.016	0.108	0.15	-0.092	0	no (?)
9	Krasnoyarsk	0.024	0.117	0.21	-0.093	0	no (?)
2	Chita	0.048	0.102	0.47	-0.054	0	no (?)

[10] As per data taken from the Report on accomplishing the following activities: Consolidated calculations of ambient air contamination in Bratsk, Krasnoyarsk, Lipetsk, Magnitogorsk, Mednogorsk, Nizhniy Tagil, Novokuznetsk, Norilsk, Omsk, Chelyabinsk, Cherepovets, and Chita, including instrumental research on ambient air contamination. Analyzing representativeness of the existing system for instrumental observations over ambient air quality and ways to improve it. Saint Petersburg: «Atmosfera» Scientific Research Institute (Joint-stock company), 2020 (in Russian).

Post No.	Territory	C_{measd}	C_{calcd}	C_{measd}/C_{calcd}	$C_{measd}-C_{calcd}$	ΔC	Necessity to make data more precise
3	Chita	0.047	0.139	0.34	–0.092	0	no (?)
4	Chita	0.066	0.094	0.70	–0.028	0	no (?)
5	Chita	0.049	0.196	0.25	–0.147	0	no (?)
6	Chita	0.043	0.124	0.35	–0.081	0	no (?)
1	Cherepovets	0.006	0.251	0.02	–0.245	0	no (?)
2	Cherepovets	0.034	0.254	0.13	–0.220	0	no (?)
31	Magnitogorsk	0.079	0.09	0.88	–0.011	0	no (?)
33	Magnitogorsk	0.03	0.06	0.50	–0.030	0	no (?)
34	Magnitogorsk	0.077	0.16	0.48	–0.083	0	no (?)
35	Magnitogorsk	0.087	0.08	1.09	0.007	0	no (?)
36	Magnitogorsk	0.092	0.13	0.71	–0.038	0	no (?)
2	Novokuznetsk	0.075	0.179	0.42	–0.104	0	no (?)
9	Novokuznetsk	0.023	0.207	0.11	–0.184	0	no (?)
10	Novokuznetsk	0.049	0.345	0.14	–0.296	0	no (?)
19	Novokuznetsk	0.094	0.276	0.34	–0.182	0	no (?)
2	Omsk	0.008	0.224	0.04	–0.216	0	no (?)
5	Omsk	0.013	0.225	0.06	–0.212	0	no (?)
7	Omsk	0.010	0.368	0.03	–0.358	0	no (?)
26	Omsk	0.100	0.162	0.62	–0.062	0	no (?)
27	Omsk	0.020	0.295	0.07	–0.275	0	no (?)
29	Omsk	0.009	0.835	0.01	–0.826	0	no (?)
3	Norilsk	1.04	5.53	0.19	–4.490	0	no (?)
4	Norilsk	0.770	5.90	0.13	–5.130	0	no (?)
11	Norilsk	0.720	4.89	0.15	–4.170	0	no (?)

Table 2

Instrumental (C_{measd}) and calculated (C_{calcd}) ground concentrations (98-th percentile) of hydrogen sulfide at points where ecological monitoring posts are located

Post No.	Territory	C_{measd}	C_{calcd}	C_{measd}/C_{calcd}	$C_{measd}-C_{calcd}$	ΔC	Necessity to make data more precise
2	Bratsk	0.0060	0.0001	60.00	0.0059	0.0015	yes
3	Bratsk	0.0060	0.0022	2.73	0.0038	0.0015	yes
7	Bratsk	0.0060	0.0001	66.67	0.0059	0.0015	yes
8	Chita	0.0220	0.000003	733.33	0.0220	0.0055	yes
11	Chita	0.0170	0.0001	340.00	0.0170	0.0043	yes
1	Cherepovets	0.0060	0.0060	1.00	0.0000	0.0015	no
2	Cherepovets	0.0060	0.0022	2.73	0.0038	0.0015	yes
5	Cherepovets	0.0060	0.0012	5.13	0.0048	0.0015	yes
7	Cherepovets	0.0060	0.0024	2.50	0.0036	0.0015	yes
9	Magnitogorsk	0.0080	0.0009	9.09	0.0071	0.0020	yes
8	Magnitogorsk	0.0080	0.0005	16.00	0.0075	0.0020	yes
2	Magnitogorsk	0.0090	0.0008	11.11	0.0082	0.0023	yes
3	Magnitogorsk	0.0370	0.0011	33.64	0.0359	0.0093	yes
4	Novokuznetsk	0.0060	0.0017	3.53	0.0043	0.0015	yes
5	Novokuznetsk	0.1560	0.1080	1.44	0.0480	0.0390	yes
6	Omsk	0.0060	0.0017	3.53	0.0043	0.0015	yes
1	Omsk	0.0060	0.0060	1.00	0.0000	0.0015	no
2	Omsk	0.0060	0.0023	2.61	0.0037	0.0015	yes
3	Omsk	0.0060	0.0040	1.50	0.0020	0.0015	yes
5	Omsk	0.0060	0.0011	5.45	0.0049	0.0015	yes
31	Norilsk	0.0700	0.0370	1.89	0.0330	0.0175	yes
33	Norilsk	0.0700	0.0340	2.06	0.0360	0.0175	yes
34	Norilsk	0.0700	0.0400	1.75	0.0300	0.0175	yes

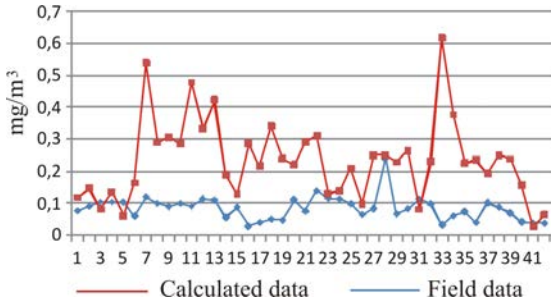

Figure 2. Compared data on calculated and measured single (q98) concentrations of nitrogen dioxide at points where Rosgidromet's monitoring posts are located in cities included into «Clean air» Federal project

However, according to approaches fixed in the regulatory document[7] this situation doesn't require any adjustments made into initial data. But at the same time, if calculated data are applied as an information basis for assessing exposure and health risks, we can be sure there will be substantial «overestimating» and risks levels will be overstated. The latter will be used for determining unacceptable risk levels and will unavoidably result in making recommendations on reducing ecological burdens for populations and implementing additional air protecting activities by industrial enterprises. In this case, financial costs will hardly be justified bearing in mind potentially prevented damage to health. Assessing correctness of calculated data as per C_{measd}/C_{calcd} ratio seems easier to understand and more informative and can be used as an additional parameter when making decisions on further actions required to correct inventory lists.

We should note that the same trend («overstated» calculated levels as compared with actual measured ones) is detected via conjugated analysis of air contamination with nitrogen dioxide (Figure 2). In spite of overall data convergence being rather satisfactory (difference varies from 1.1 to 20 times at some monitoring posts), potential risks aggravation can still be expected.

Even more alerting is a situation when calculated data are substantially lower than measured ones. It was detected for carbon oxide in Chita (measured concentrations are up to 11.5 times higher than calculated ones), Omsk (up to 9 times higher), and Novokuznetsk (up to 6 times higher).

Calculated and field data on dusts (particulate matter) are practically beyond any comparison (Figure 3).

High convergence of the results in this case could hardly be expected to due peculiarities intrinsic to differentiated coding applied for solid emissions during inventories and practically complete absence of differentiated instrumental measuring applied to solid substances in monitoring systems.

The existing situation requires fundamental revision of approaches to taking into account solid components in emissions; it is obligatory to identify and quantitatively determine fine-dispersed PM10 and PM2.5 fractions during inventories as they are the most hazardous for human health.

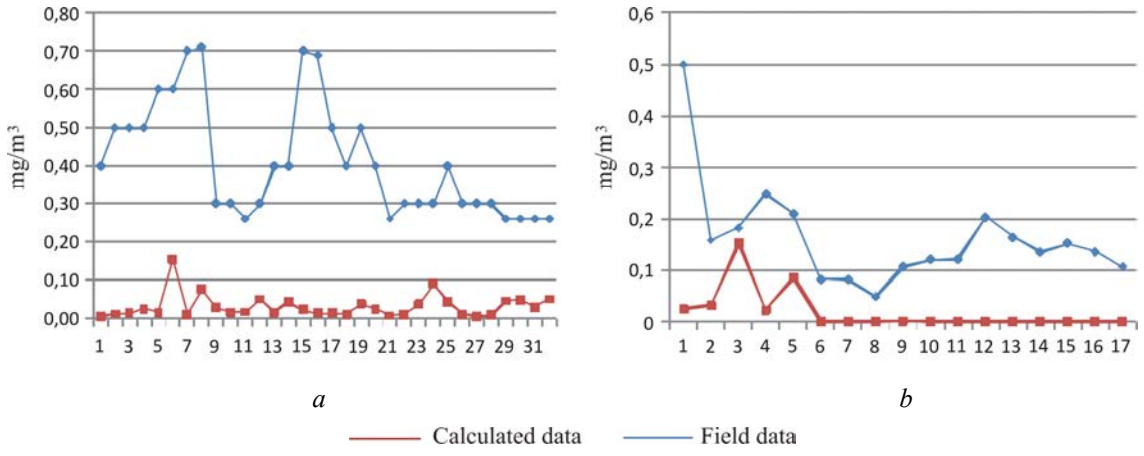

Figure 3. Compared data on calculated and measured single (a) and average annual (b) concentrations of particulate matter at points where Rosgidromet's monitoring posts are located in cities included into «Clean air» Federal project

Even more significant differences between calculated and field data were detected for specific contaminants. Measured single concentrations were extremely higher than calculated ones at some monitoring posts; for example, hydrogen sulfide concentration was up to 700 times higher (Table 2); hydrogen chloride, up to 180 times higher; phenol, up to 6,000 times higher, etc.

Average annual calculated concentrations of specific chemicals were also lower (by several times) than measured ones practically at all monitoring posts.

Should calculated data be applied to assess population health risks in this situation, it will unavoidably result in inadequate decisions on emission quoting.

But still, making adjustments into inventory lists and improving initial databases applied for calculations seems to be merely a technical and/or organizational task. As certain experience has been accumulated in creating consolidated databases, these problems can be and most likely will be eliminated or minimized.

Involving a greater number of points where field data are collected for further verification of calculated ones can be an instrument for improving initial data quality. It will allow more rapid and precise identification of reasons for data not being convergent and will help making proper corrections into parameters of sources. To solve these tasks, it seems advisable to use not only data obtained via ecological monitoring systems but also data collected within social and hygienic monitoring systems.

Therefore, creation of a complete and correct database on parameters of emissions sources that influence ambient air quality on a given territory is the first and the most significant step in implementing the whole new system for emission quoting.

The next significant step in fixing standards for permissible emissions is selecting priority contaminants, objects for quoting, and control points for emission quoting.

Priority substances that are subject to quoting are *contaminants that, when emitted into the atmosphere, influence violation of hygienic standards for ambient air quality and create health risks on territories included into the experiment* (item 1 in Clause 3 of the Federal Law 194-FZ)[1].

It is for the first time when risk assessment results are fixed in legislation as an element in a system for standardizing emissions. At the same time, a dozen or even more admixtures can make their contributions into health risks and shares belonging to some can be really insignificant. It seems relevant to provide precise criteria for fixing a minimal contribution made by a contaminant into unacceptable health risks; any quoting below this minimum level seems unadvisable and, consequently, inefficient. Due to determination of priority contaminant lists being a responsibility borne by the Federal Service for Surveillance over Consumer Rights Protection and Human Well-being (item 4 in Clause 4 of the Federal Law 194-FZ)[1] it seems important to provide scientific substantiation and methodical support for clear and unified procedures and criteria applied to select priority substances for further accounting. And when substantiating a list of priority contaminants, it is advisable to take into account not only calculated risks but also results obtained via epidemiologic research, and in some cases also evidence proving that damage has been done to human health. A methodical document provided by Rospotrebnadzor is truly significant due to priority contaminants selection being directly related to calculating contributions made by specific economic entities into occurring health risks; it can be used as grounds for creating a list of objects that are subject for quoting (item 5.2 in the Rules).

Unfortunately, the most significant components in the quoting system, namely selecting criteria for standardizing and control points parameters of which are used as a toll to substantiate quoting, do not take into account health risk parameters. According to item 3.2 in the Rules, *«control points are points… where long-term… or single maximum calculated concentrations of priority contaminants… violate the standards fixed for ambient air quality (hereinafter called MPC)».* According to item 4.2, *«To assess whether ambient air contamination*

complies… one should use maximum permissible concentrations of contaminants in ambient air…». Therefore, risk assessment results are just abandoned since a target criterion in quoting is compliance with MPC and not achieving acceptable health risk levels.

The Rules do not stipulate any procedure for assessing residual health risks after emission quotas have been fixed. Accordingly, obtained results will not stimulate economic entities to reduce contamination down to acceptable risk levels. And we should note that if there is long-term multi-components contamination, health risks and additional mortality and morbidity among population can occur even in case a concentration of each specific component doesn't violate hygienic standards; therefore, socially significant results may not be achieved.

Bearing in mind strategic goals set by the RF President and the Government that clearly define population health and an increase in life expectancy as top state priorities, it seems extremely vital to be guided exactly by criteria related to population health, health risks or damage parameters, when fixing standards for hazardous impacts exerted on the environment. Such criteria can provide a clearer idea of potential medical and demographic losses than MPC.

The Figure 4 shows a conceptual scheme that can be applied to fix standards for permissible emissions bearing in mind providing sanitary-epidemiologic welfare of the population. All the basic components in the system that is fixed in the Federal Law on quoting are preserved.

But still, we recommend adding several steps into the fixed algorithm; they will allow not only providing compliance with the hygienic standards fixed for ambient air quality but also taking into account effects produced on population health by multi-component contaminations that is specific for each given city. These steps are:

– spotting out zones where health risks are unacceptable on each territory. Such zones do not always coincide with zones where ground concentrations of certain contaminants are the highest hence risk assessment usually takes into account aggregated impacts exerted by all the substances that influence the same organs and systems and reference levels of each component;

– assessing contributions made by specific economic entities into health risks. This additional criterion can be taken into account when priority objects for quoting are being determined. Primarily, it is necessary to reduce emissions from objects that create the highest health risks; it will allow reliable achieving acceptable risk levels using an optimal set of activities;

– assessing residual risks after accomplishing either specific environmental activities or a whole set of measures stipulated in complex programs. The step will allow assessing whether activates have been productive and efficient as per acceptable risk criteria;

– accomplishing profound epidemiologic and medical-biological research, with its aim being creation of a reliable evidential database proving absence or occurrence of damage to population health including a situation when emissions have been reduced to acceptable levels fixed in ecological standards.

The step seems truly vital due to risks being a calculated and predictive value in spite of the whole system being guided by the health risks assessment methodology. Reference concentrations that are safety criteria for a given admixture are not always adequate to specific conditions occurring due to multi-component and long-term contamination. Socioeconomic conditions, peculiarities related to population genotypes, etc., also make their adjustments into actual exposure levels.

To make calculation estimates more precise, it is advisable to perform epidemiologic and profound medical research in order to assess actual realization of risks and creation of evidential databases that prove there has been damage to health caused by combined aerogenic exposure [19–21], In some cases specific research can detect risk factors that are typical for a given territory only and can't be revealed via calculations [22]. It is extremely important for decision-makers at all management levels as it allows them to avoid situations in which risks aggravation leads to unnecessary expenses on air-protecting activities and risks underestimation results in absence of positive effects for population health expected due to the Federal project implementation.

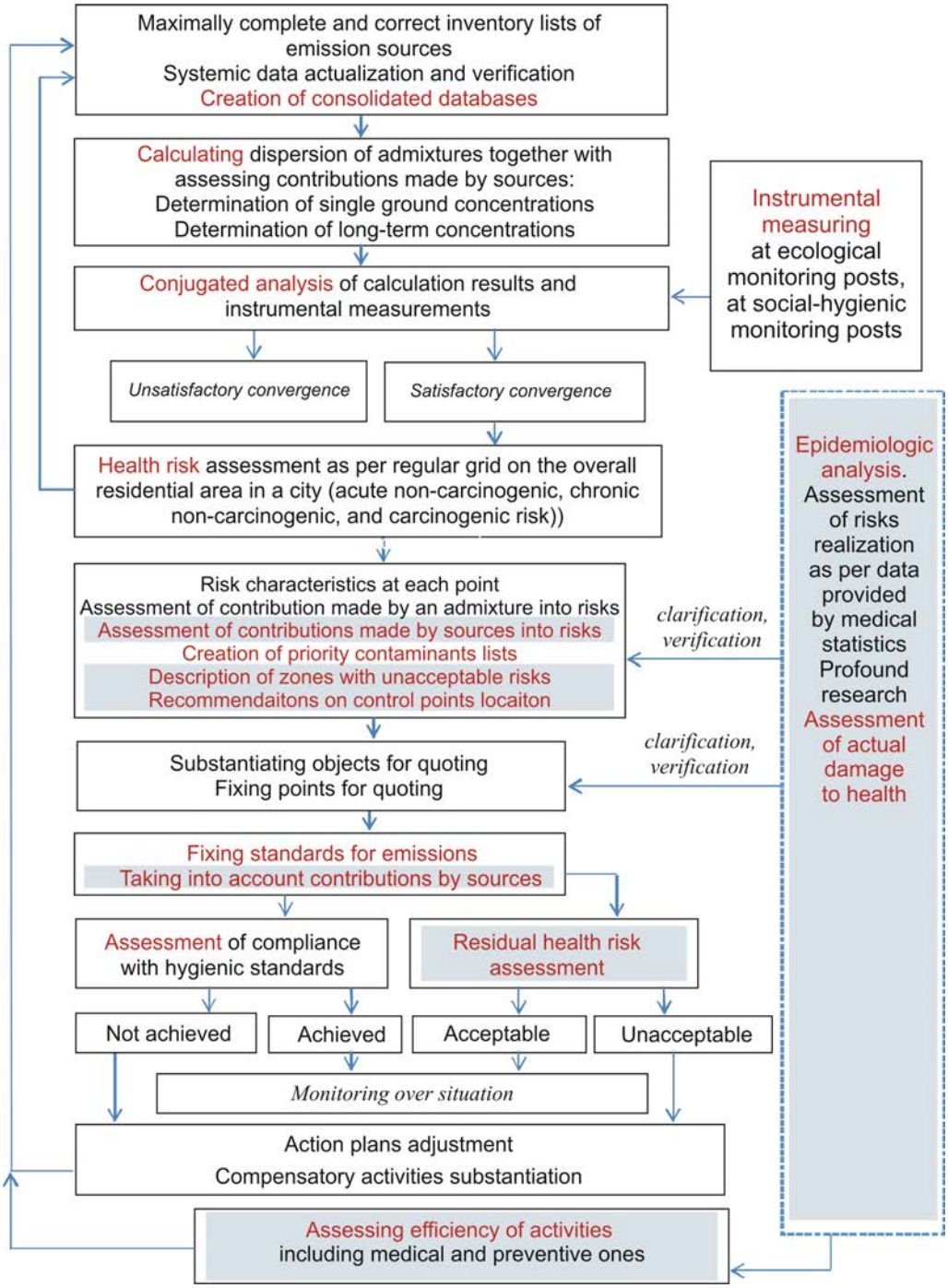

Figure 4. Conceptual diagram. Fixing standards for permissible emissions bearing in mind providing sanitary-epidemiologic welfare of the population

Elements that are not included into a conventional standardizing procedure are shaded

Conclusion. New approaches to standardizing contaminants emissions into ambient air are undoubtedly a significant step towards taking population health into account when imposing limits on negative impacts exerted by emission sources of any type. Basic positive innovations are taking into account long-term contamination and applying risk assessment methodology when selecting priority contaminants.

According to the Federal Law 195-FZ quotas are to be fixed for substances that are considered «priority» ones; given that, it is necessary to scientifically substantiate and methodically determine clear and unified methods and criteria for selecting priority substances for further ac-

counting, including those based on risk assessment, epidemiologic research, and an evidential base proving detected damage to health.

Creation consolidated databases for a whole territory should be thorough and a process should be controlled by both authorized Rospotrebnadzor bodies that verify parameters of emissions sources located at industrial objects and by local authorities that verify parameters of emissions from mobile sources and emissions from private households (stoves and boilers). Besides qualitative collection of initial data, it is also necessary to organize work on systematic and persistent actualization of a database and on verifying parameters of emissions sources with data obtained via field observations.

Differentiation of solid components with spotting out PM10 and PM2.5 fine-dispersed fractions as the most hazardous ones should become the most significant element in emissions accounting.

Substantiating the selection of control points for emissions quoting seems to be the most vital task. Prior to any selection, admixtures dispersion should be calculated and all variants of unfavorable meteorological conditions should be taken into account; these conditions should be preset for sources with different heights; it is also necessary to perform spatial assessment of health risks distribution, both individual and population ones.

Within the experiment it seems vital to test both the algorithm and criteria for substantiating priority object for quoting taking into account detected zones with unacceptable risks on a given territory and assessing contributions made by economic entities into occurring health risks.

Assessment of residual risks after either specific environmental activates or an overall set of them stipulated in complex programs have been accomplished should become an obligatory element in a system used for standardizing permissible emissions.

Achieving acceptable risks should be supported by epidemiologic data collected on a given territory and results obtained via profound medical and biological examinations aimed at creating a reliable evidential base that proves absence or persistence of damage to health after emissions have been reduced down to acceptable target levels fixed in ecological standards.

Funding. The paper has been accomplished within the fulfillment of tasks set by «Clean air» federal project as a part of «Ecology» national project.

Conflict of interests. The authors state that there is no any conflict of interest.

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Received: 03.05.2020
Accepted: 13.06.2020
Published: 30.06.2020

UDC 504.75
DOI: 10.21668/health.risk/2020.2.02.eng

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SELECTED HEALTH PARAMETERS OF PEOPLE LIVING IN CITIES INCLUDED INTO «CLEAN AIR» FEDERAL PROJECT

B.A. Revich[1], T.L. Kharkova[1,2], E.A. Kvasha[2]

[1]Institute of Economic Forecasting of the Russian Academy of Sciences, 47 Nakhimovskii Ave., Moscow, 117418, Russian Federation
[2]Institute of Demography of National Research University Higher School of Economics, 3 Bolshoi Trekhsvyatitel'skii lane, Moscow, 109028, Russian Federation

Our research goal was to assess expected efficiency of «Clean air» Federal project with its activities aimed at reducing ambient air contamination and population health risks.

We revealed that finding solutions to the project tasks on emissions reduction that had been set without taking into account peculiarities of city design, development, landscapes, meteorological conditions, and other factors, would not result in improved ambient air quality. Road and transport systems are to be modernized basing on transport flows modeling and application of calculations taking into account transport flows structure, speed, and intensity as well as some other parameters. Analysis of standardized death rate (SDR) in 2000–2018 revealed the highest total mortality in Chita against a reference city, Lipetsk; mortality due to respiratory diseases was higher in Bratsk, Krasnoyarsk, Magnitogorsk, Nizhniy Tagil, Novokuznetsk, Omsk, Chelyabinsk, Cherepovets, and Chita. Mortality caused by these diseases has been going down since 2007; starting from 2013, the highest mortality due to respiratory diseases has been registered in Krasnoyarsk. Long-term annual average SDR due to neoplasms is rather chaotic in most cities but it is persistently higher than in Lipetsk, the reference city; asymptomatic parameter ($p<0.001$) indicates discrepancies are valid. In some years, the highest SDR due to lung cancer among men was detected in cities with aluminum productions, such as Krasnoyarsk, Bratsk, Novokuznetsk, as well as in Chita. To assess efficiency of environmental policy aimed at improving ambient air quality in cities, it is necessary to perform epidemiologic activities, including assessment of asthma-like symptoms and bronchial asthma prevalence among children using an international standardized questionnaire and analysis of neoplasms frequency among various population groups.

Key words: *ambient air, emissions, «Clean air» Federal project, monitoring, population health, health risk assessment, mortality, bronchial asthma, malignant neoplasms, environmental policy.*

In 2018, the Russian Federation Government approved National Project «Ecology», which includes the Federal Project «Clean air», aimed at improving the environmental situation and reducing by 20% the total emission of all pollutants into the air in 12 cities: Bratsk, Krasnoyarsk, Lipetsk, Magnitogorsk, Mednogorsk, Novosibirsk, N. Tagil, Novokuznetsk, Norilsk, Omsk, Chelyabinsk, Cherepovets and Chita by 2024; reducing the number of cities with high and very high levels of air pollution, assessed by the pollution index; at creating an effective air quality monitoring and control system, as well as, which is very important, to track the level of satisfaction of the population with the quality of atmospheric air through sociological surveys. The project developers chose these cities from a formal rather than a substantive position, i.e. based only on the pollutant emissions mass without taking into account their dispersion in the air and public health. The announced project's goal of reducing the total pollutant emissions by 20 percent by 2024 seems to be highly urgent, but the main question arises: can such a factor as reducing emissions really improve air

Boris A. Revich – Doctor of Medical Sciences, Professor, Head of Laboratory for Environment Quality Prediction and Population Health (e-mail: brevich@yandex.ru; tel.: +7 (499) 129-36-33; ORCID: https://orcid.org/0000-0002-7528-6643).

Tatiana L. Kharkova – Candidate of Economic Sciences, Senior researcher at Laboratory for Environment Quality Prediction and Population Health; Senior researcher Institute of Demography of National Research University Higher School of Economics (e-mail: tatkharkova@mail.ru; tel.: +7 (910) 479-69-84; OPCID: https://orcid.org/0000-0001-7460-1966).

Ekaterina A. Kvasha – Candidate of Economic Sciences, Senior researcher Institute of Demography of National Research University Higher School of Economics (e-mail: keapost@mail.ru; tel.: +7 (916) 811-19-52; ORCID: https://orcid.org/0000-0002-2003-5484).

quality, as well as what models this has been proven on, and what positive impact it will have on the health of citizens. The 12 selected cities vary considerably in terms of natural conditions, frequency and severity of adverse weather conditions, planned concepts, type of buildings and urban density, chemical composition of emissions, height of pipes and many other factors that determine the level of air pollution. In previous years, sizable environmental protection actions were taken in Krasnoyarsk, Norilsk and other cities from the above list, but the pollution level is still high, which causes additional health risks. Our critical assessment of a number of provisions of the project [1] coincided partially with the report of the Russian Federation Accounts Chamber[1], stating the unlikelihood of radical reduction in air pollution. Our work confirms this ultimate conclusion.

Data and methods. Based on Rosstat data, we calculated the age-specific and standardized death rates (SDR) for the main causes of death, which can be attributed to environmentally dependent diseases. For two cities of the «Clean air» project – Norilsk and Mednogorsk, which are included in the list of cities with the air pollution highest level, Rosstat does not have long series of data by different causes of death so these cities were excluded from the analysis. To eliminate the influence of differences in the population age composition, a comparative regional analysis of mortality due to causes of death was conducted on the basis of the calculation standardized death rate, according to ICD-10. The European Standard of 1976, widely used by WHO and Rosstat, was taken as reference. The comparison of these indicators was carried out in relation to Lipetsk – the city with the lowest level of pollution in this group of cities and the absence of significant health risks of the population from emissions from industrial enterprises of the city [2, 3].

Linear regression analysis was used to estimate the mortality dynamics (trends). The generally accepted level of $p = 0.05$ was taken as a threshold value when deciding on statistically significant difference between trends. Statistical evaluation of SMR differences for 9 cities was determined in relation to the city of comparison – Lipetsk. Chita was excluded from this analysis because of extremely high variation in SMR values. The estimation of SMR differences between the cities was obtained by comparing their median in relation to Lipetsk using the asymptotic significance «p». The hypothesis of inequality was confirmed for most of the indicators, except for all the causes, as well as for cardiovascular diseases (CVD) in men.

Brief description of atmospheric air quality in cities of the Federal Project.

The state control over the air pollution in residential areas is exercised by RosHydroMet (Russian Federal Service for Hydrometeorology and Environmental Monitoring), its territorial subdivisions at stationary observation units, local sanitary and epidemiological supervision bodies, small laboratories of RosPrirodNadzor (Russian Federal Service for Surveillance over Nature Resources), systems for environmental monitoring of Moscow, St. Petersburg, Krasnoyarsk local administrations, and a number of other cities. Unfortunately, the activities of these units are not coordinated due to different estimation methods with different equipment being applied in the process, so it is difficult to obtain reliable data on the pollution level for such a variable environment such as atmospheric air. Based on the data of pollutants in the air, RosHydroMet annually publishes a list of cities with the highest levels of pollution. This list may be changed without explaining the reasons, which may be due not only to the actual improvement in air quality, but also to the peculiarities of the location of stationary posts of the Roshydromet network, the use of archaic equipment, technical malfunctions and others.

[1] Report on the results of the expert and analytical event «Monitoring the progress of the national project «Ecology», including expedience of their financial support, achieving goals and objectives, benchmarks, as well as management quality». Accounts Chamber of the Russian Federation, 2020, 41 p. (in Russian).

The studies cities, given the dominance of the type of industry or fuel used, can be divided into several groups, although most cities have different sources of industrial and energy emissions: non-ferrous metallurgy in Bratsk, Mednogorsk and Norilsk; ferrous metallurgy in Cherepovets, Magnitogorsk, Novokuznetsk, N. Tagil, Chelyabinsk and Lipetsk; large pollution sources of various industries using coal – Krasnoyarsk, Omsk. The particularly unfavorable landscape conditions, which prevent pollutants dispersion in the air, are typical for Chita due to power plants operating on lignite coal. Only three cities of the Federal Project are located in the European part of Russia, the rest are in Siberia, where climate conditions are much more unfavorable, and where coal is mainly used as fuel. In Chita, for example, this fuel accounts for 95% in the combustibles balance. Depending on air pollution level in the last 5 years (2014–2018), the cities may be divided into several categories: with a constantly high pollution level: Bratsk, Krasnoyarsk, Norilsk and Chita; with a high level of pollution in some years: Magnitogorsk, Novokuznetsk, Chelyabinsk; with least high pollution level in these years: Lipetsk, Mednogorsk, N. Tagil, Omsk, Cherepovets. As a rule, in all these cities the increased level of air pollution with the most common substances, such as suspended particles (fine dust), sulfur dioxides and nitrogen, carcinogenic benzene (pyrene) was registered for many years. Cities which have metallurgical industry are also characterized by the presence of a wide range of toxic metals in the air: zinc, lead, copper; provided smelting aluminum in Bratsk, Krasnoyarsk, Novokuznetsk, fluorine hydride is observed. Among these cities, the most unfavorable environmental situation is in Krasnoyarsk, where such major emission sources as aluminum smelter (JSC «RUSAL Krasnoyarsk»), non-ferrous metals plant, cement plant, machine-building plants, tire plant, thermal power plant and many other enterprises are located. In this city, the population health risk from exposure to a complex of carcinogenic substances in the air (hexavalent chromium, benzene, formaldehyde, benz(a)pyrene) resulted in 12 cases of malignant neoplasms per year [4]. Our calculation, carried out in collaboration with Prof. Avaliani S.L., showed that the proportion of additional deaths only from exposure to RM10 reaches 9.3–21.9% per year from all causes except for the external ones.

The urban population health status in the cities of the «Clean air» project can be assessed based on the most accurate and verified indicator such as mortality. This indicator can be used to assess the impact of polluted air on health along with the assessment of the prevalence of bronchial asthma, congenital malformations among children; analytical epidemiological studies of cancer, etc.

Dynamics of urban mortality in 2000–2018. In all Federal Project cities, there was a gradual decrease in mortality, the rate of which varied depending on the level of mortality in the early 2000s. Figures 1–3 show the differences between cities, in terms of both the level and dynamics of SDR, the similar trend in total mortality, and the differences from the city of Chita, where a much higher mortality rate was registered over the 11 years (2000–2010). However, a relatively significant decrease in mortality in Chita in 2011 compared to 2010 and previous years may be the result of an incorrect correlation between the collected data on the number of deaths and the population estimates used in calculating mortality rates. Thus, in 2011, due to administrative reforms, the population of this city increased by 5.2%. Besides, such a difficult situation in Chita is, of course, related not only to the high level of air pollution, but also to the socio-economic situation. According to the indices of sustainable development, the Chita Region, which became the Transbaikal Territory in 2008 due to its merger with Aginskiy Buryat Autonomous District, was in the lower quartile of this indicator.

The second group in terms of increased total mortality compared to the «conditional control» Lipetsk are cities with aluminum industry enterprises – Bratsk, Novokuznetsk, Krasnoyarsk.

Then follows the group of cities with ferrous metallurgy enterprises: N. Tagil, Magni-

togorsk, Cherepovets, and also cities with the minimum level: Lipetsk and Omsk.

Mortality by selected causes of death. Using the indicator of asymptotic significance «p» for 12 causes of death separately for the male and female population allowed to identify eight groups of causes for which all cities, except Chita, reliably significantly differed from the corresponding data for Lipetsk.

For Chita, due to significant fluctuations in SDR from selected causes of death, the calculation of this indicator was not carried out. Reliable differences did not appear only in the 3 groups of death causes – all causes (men and women) and cardiovascular diseases (CVD) among women. The reason for the absence of differences in the group «all causes» is due to the presence of external causes of death, the share of which traditionally ranks third in the structure of mortality of men, and fourth to fifth – in the mortality structure of women. At the same time, among the external causes for men and women, injury with unknown intent, suicides and homicides are leading, accounting for 40–60% of all external causes. The share of transport accidents is also quite significant, and it is higher among women than among men (10–20 and 7–12% of all external causes, respectively).

Respiratory diseases (RD) and, to a lesser extent, malignant neoplasms may be associated with the negative impact of air pollution. This is shown by many epidemiological studies of Russian and foreign authors based on both meta-analysis of a large array of data from hundreds of cities and clinical and

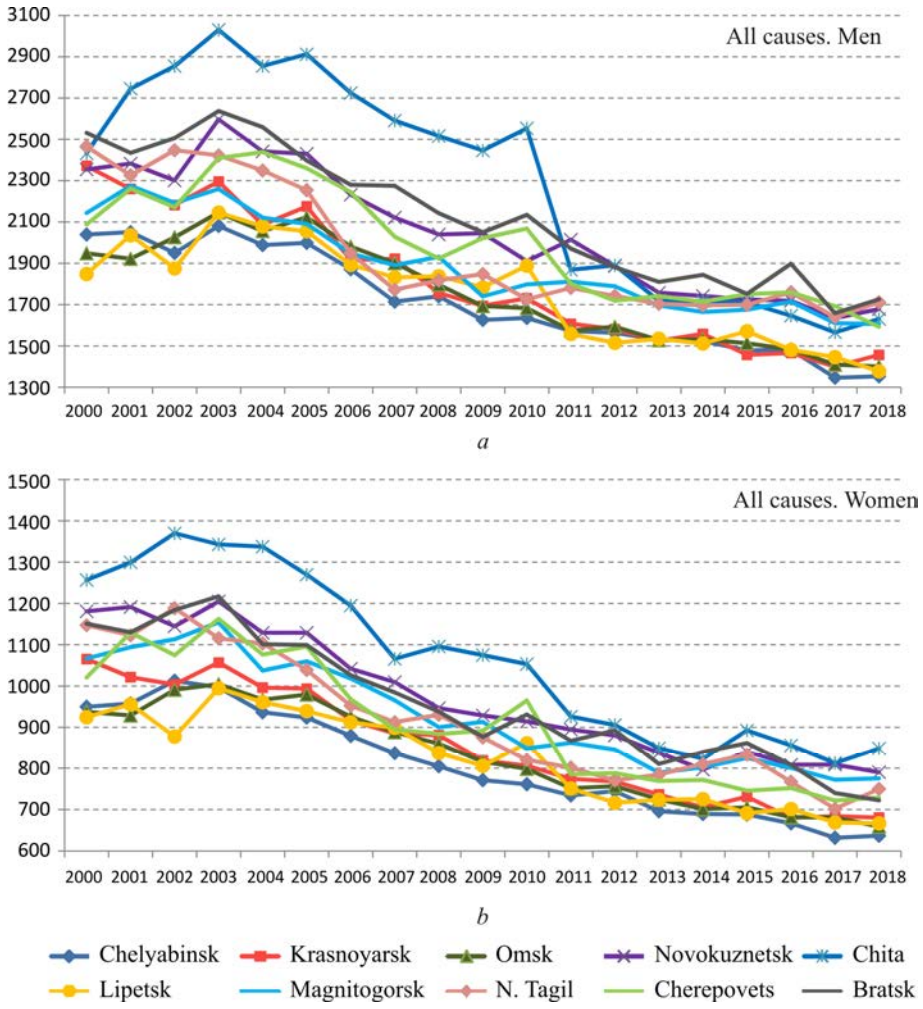

Figure 1. Standardized death rates from all causes in cities with different levels of air pollution, 2000–2018, per 100,000 of population (*a* – men, *b* – women)

epidemiological studies in the most ecologically problematic cities. SDR of RD in cities with different levels of atmospheric air pollution are varying more significantly than the total mortality. They are the highest among the Chita population and the lowest – in Lipetsk and Omsk. In the period since 2007 mortality from RD has started to decrease more intensively than in previous years, the fluctuations of the average annual values for the last 5 years (2014–2018) are in a very large range – from 50 to 100 cases per 100,000 (Figure 2). Mortality of both male and female population due to RD in Krasnoyarsk is constantly above the upper boundary of this interval since 2013. In this city, as in Chelyabinsk and Magnitogorsk, high risks of respiratory diseases are revealed due to air pollution[2] [5]. Whether it is connected with deterioration of the atmospheric air quality in Krasnoyarsk and the regular phenomena of «black sky» is not yet established. The possible reason for this phenomenon – the accumulated long-term influence of the polluting substances the negative effect of which is already manifested in childhood.

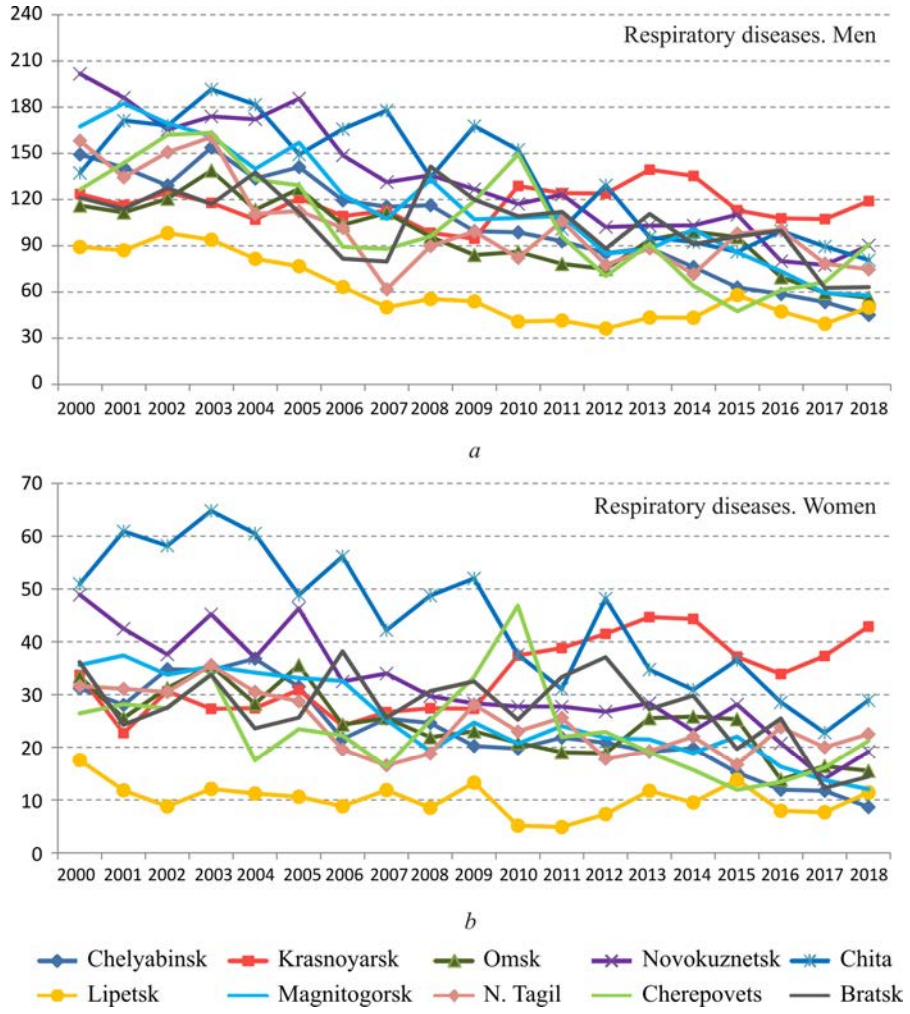

Figure 2 Standardized death rate from respiratory diseases in cities with different levels of air pollution, 2000–2018, per 100,000 of population (*a* – men, *b* – women)

[2] On the state of sanitary and epidemiological well-being of the population in Krasnoyarsk Krai in 2017: State report. Krasnoyarsk, 2018, 301 p. (in Russian).

Neoplasms. Estimating the impact of air pollution on cancer morbidity and mortality is a very difficult task, and it can only be solved using modern analytical epidemiological methods. However, this use may become a certain indicator for the cancer situation. The long-term average annual SDR from these diseases in most cities is very chaotic (Figure 3), but constantly higher than in the city of reference – Lipetsk, and asymptotic indicator ($p < 0.001$) shows the difference reliability.

It is known that, the main cause of men's death from malignant neoplasms is tracheal, bronchial and lung cancer. Despite the fact that the mortality level from this cause has some chaotic annual changes, we can still talk about the emerging trend of declining male mortality from his cause, while for women it remains relatively stable. At the same time, throughout the whole period, the mortality rate from tracheal, bronchial and lung cancer was higher in the cities, while in the reference city Lipetsk it was lower than the rates calculated for Russia as a whole. In some years, Novokuznetsk, Chita, Krasnoyarsk and Bratsk had the highest SDR rates of lung cancer for men.

Ecologically dependent changes in population health. After the second year of the Federal Project «Clean air», we were tasked to assess, using the standardized rate, such basic public health indicators, as mortality. In these most ecologically problematic cities, the mortality rate is much higher in all major disease groups, and there is not such a smooth decline in SDR than in such megacities as Moscow, St. Petersburg, Rostov-on-Don, which

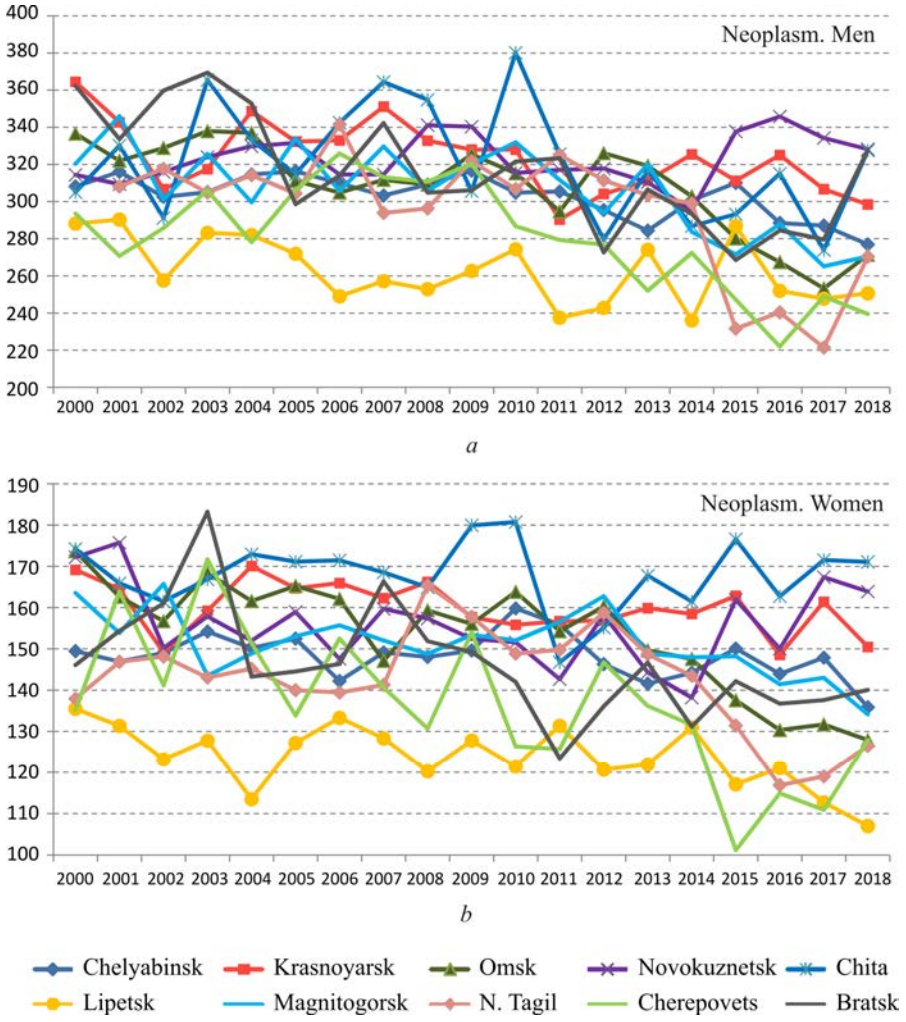

Figure 3. Standardized death rate from neoplasm in cities with different levels of air pollution, 2000–2018, per 100,000 of population (*a* – men, *b* – women))

we conducted a similar analysis earlier for [6]. Comparing the structures of mortality by causes of death reveals both their similarities and differences: in the early 2000s, more than 70–80%, and in 2018, more than 60–70% of the causes of death of men and women are due to cardiovascular diseases (CVD), neoplasms and external causes. At the same time, the share of CVD everywhere takes the first place, although it is gradually decreasing, and women's share is more significant than men's. In the early 2000s, men's share is second in all cities except for Omsk and Lipetsk, for external causes, and neoplasms – taking third place. However, in the following years, as a result of a significant decrease in mortality from external causes, they moved to the third place, giving way to neoplasms, the proportion of which was almost twice as high as in external causes.Women had a slightly different picture: if in 2000, the external causes took ranked third place in the structure of mortality, in 2018, in most cities they moved to the fourth place, and in Omsk, Magnitogorsk, N. Tagil and Bratsk – even the fifth, ahead of respiratory and digestive diseases.

SDR, assessed by the median criterion, showed significant differences (less than 0.001) in comparison with the city of Lipetsk on cardiovascular diseases in men, neoplasms, respiratory diseases and cerebrovascular diseases. No differences significant at the level of 0.05 were found for other indicators.

Let's review the planned and partially implemented activities of «Clean air» project from the perspective of their effectiveness in improving the health of residents of the cities under consideration. The first results of the health risk assessment for emission reduction in Krasnoyarsk showed extremely low efficiency of the implemented emission reduction measures, the risk was reduced only for the group of 4.8 thousand people [7] that in a city with a population of 1.1 million may be useful only for 0.4 percent of residents.

The estimation of mortality data for cities with the most polluted air is consistent with previous studies on the health effects of carcinogens and other substances. Thus, in Norilsk, the population carcinogenic health risk is described as unacceptable. It is possible that it is the increased level of air pollution by carcinogens that has caused the high level of cancer incidence. Standardized incidence rates of lung cancer men were significantly higher compared to that of the region [8]. The authors of this study believe that such high rates as in Norilsk have no parallel in other regions of the country. Another epidemiological work published 5 years later, in 1992, reported a high incidence of lung cancer not only in men, but also in women [9], and a subsequent publication 10 years later reported a rising trend in cancer incidence, including young ages [10]. Carcinogenic risk assessment of atmospheric air is also given for Chita, where the population risk is characterized as elevated and makes 56.6 cases/year. The growth rate of cancer incidence is higher than in the country as a whole[3].

Two cities in the Chelyabinsk region, included in the Federal project – Chelyabinsk and Magnitogorsk are constantly included in the list of cities with the highest level of air pollution with carcinogenic substances. This is due to the increased level of benz(a)pyrene in the air and the presence of other carcinogenic substances in metallurgical emissions [11]. Apparently, this is the reason for the higher standardised incidence of lung cancer and other population localizations in the left-bank part of the city where the smelter is located. In this part of the city similar indices were reliably ($p < 0,05$) exceeded for the right bank district: for men – lung cancer 1.7 times, stomach cancer – 1.5 times, skin cancer – 2.3 times, for women – 1.2 times; 1.4 and 1.6 times respectively [12]. However, it should be noted that the author of this work does not specify whether the metallurgical plant em-

[3] Mikhailova L.A. Hygienic analysis of the urban environment impact on the oncologic morbidity of the population (on the example of the industrial centre of Siberia): author's abstract, Cand. of Medical Sciences. Irkutsk, 2009, 139 p. (in Russian).

ployees, including those who have professional contact with carcinogenic substances, have been excluded from the mortality analysis. In Chelyabinsk, the carcinogenic risk from exposure to contaminated air is also assessed as unacceptable in result of exposure to benzene, formaldehyde and chromium. The total carcinogenic population risk for 646,000 people made 297.4 additional cancer cases during 70 years of life [13]. There is an increase in carcinogenic risk indicators in comparison with previous years in the Orenburg region cities [14].

Use of health risk assessment methods, including carcinogenic risk, makes it possible to estimate hypothetical risks with a definite uncertainty degree, and it is very important for assessing the environmental situation in cities to identify the specific emissions sources of carcinogenic substances, in particular, develop measures to reduce them, improve methods for air pollution monitoring. However, from the point of the evidence-based medicine, techniques of analytical epidemiology are needed to prove carcinogenic effects. Anyway, they are very rarely used in the Russian studies to meet environmental and epidemiological challenges, and only two such works can be mentioned: on the assessment of workers exposure to lead at Moscow print shops in contact with lead-containing font [15] and on the assessment of dioxins impact on breast cancer incidence in women living near a chemical plant producing chlorinated pesticides [16].

A much higher number of publications are devoted to research on respiratory diseases, including those children. For the period from 2001 to 2011, according to official data, the total morbidity of children with bronchial asthma has increased from 971.2 to 1171.0 [17], as well as allergic diseases of the respiratory tract [18]. This applies not only to children, but also to adults in Krasnoyarsk[4]. Some Russian industrial cities (Novokuznetsk, Orenburg) have higher prevalence of respiratory diseases, including bronchial asthma in children, compared to other more environmentally friendly residential areas[5, 6]. Almost all researchers reported higher prevalence of asthma-like symptoms and of bronchial asthma using an internationally standardized questionnaire. The survey results of 1,518 people aged 18–44 in Chelyabinsk city showed that the bronchial asthma prevalence is 3 times higher than official data [19].

As stated in the National program «Bronchial Asthma in Children. Treatment strategy and prevention», the current genetic studies have proven the role of hereditary predisposition to bronchial asthma development, but the endotype implementation is associated with environmental factors[7]. Indeed, fine particles present in the ambient air of any residential area, and especially of the industrial cities under consideration, are the risk factors for respiratory diseases development in children. For example, in Bratsk, the aluminium industry emissions and other sources of pollution have created such an unfavourable situation that respiratory diseases in children, including bronchial asthma, are registered more often than the regional average. A survey of children in the area affected by emissions from the aluminium smelter in Bratsk revealed an increased level of chronic respiratory diseases (2.9 times higher than in the comparison group), 5.5 times higher than functional disorders of autonomic and central nervous systems [20].

Results and discussion. For the first time in the recent decades, the Federal project «Clean air» has been developed, and substan-

[4] Gordeeva N.V. Structure of bronchial asthma incidence in Krasnoyarsk. Pharmacoepidemiology. Symptoms control: autoref. disk. Cand. of Medical Sciences. Krasnoyarsk, 2010, 120 p. (in Russian).

[5] Kurilova T.N. Clinical-epidemiological characteristics of bronchial asthma and allergy in schoolchildren of Novokuznetsk: author's abstract. Cand. of Medical Sciences. Novokuznetsk, 2003, 127 p. (in Russian).

[6] Skachkova M.A. Recidivating respiratory diseases in children in the industrial city: Cand. of Medical sciences. Orenburg, 2004, 270 p. (in Russian).

[7] Bronchial asthma in children. Treatment strategy and prevention: National program. 5th Edition. Moscow, Original-maket, 2017, 160 p. (in Russian).

tial funding has been allocated for its implementation to improve air quality. However, both in selecting cities to be included in the project, and in determining the necessary actions, the results of many years of research into public health carried out by various scientific and educational organizations, including the Kemerovo, Krasnoyarsk, Omsk, Novokuznetsk, Novosibirsk and other medical universities and medical research institutes, were not used. The lack of proper professional interaction with physicians will be the reason why the formally stated goals of reducing the number of cities with high and very high levels of air pollution and increasing the share of citizens satisfied with the air quality in large industrial centers will not be achieved, and the financial cost of 500 billion rubles will not lead to the result expected. It should be noted that this amount also includes considerable costs to reduce air pollution from motor vehicles, but there is no substantiation for the proposed solutions, no developed models for optimizing transport flows, taking into account pollutant emissions and health risks assessment. In 2020, with COVID-19 pandemic, this epidemiological aspect of research became particularly crucial, given also some similarities between exposure to airborne fine particles smaller than 2.5 and 0.1 μm and the COVID-19 virus. Fine particles absorb various toxic substances on their surface, penetrate bronchial tree and accumulate in lung tissues; smaller particles of less than 2.5 μm in diameter ($PM_{2.5}$) reach bronchial tubes and alveole, and penetrate the bloodstream. Long-term exposure to high concentrations of these particles increases mortality from respiratory and cardiovascular diseases (myocardial infarction, stroke, coronary heart disease and other diseases).

In early April 2020, Harvard School of Public Health published the results of the pilot study to estimate mortality from this disease in the United States localities, where 90% of the population of this country lives, showing the correlation between an increase in mortality from COVID-19 and concentration of RM2.5 in ambient air, i.e. with an increase in the concentration of these particles by 1 μ/m^3 there is a 15% increase in mortality. The mathematical model here took into account the population density, the number of hospital beds, socio-economic, behavioral and other factors [21].

Health assessment in 12 cities of the Federal project is carried out by Rospotrebnadzor scientific institutes based on the use of risk assessment methodology. Such studies are usually conducted to identify the priority pollutants with the highest risks to public health, to justify the necessary measures to reduce emissions of specific toxicants, as well as the size of sanitary protection zones and other environmental issues. However, the indicators for urban population health associated with air pollution are not only the modeling estimates, but also the natural indices – mortality, morbidity, prevalence, including children's bronchial asthma, presence of malignant neoplasm locuses, results of studies on children's health, reproductive health, data from various registers, including congenital malformations. For 12 cities of the Federal project, it is necessary to analyze the prevalence of asthma-like symptoms and bronchial asthma among children using the international standardized questionnaire ISAAC. The results of this study for 17 regional centers, including Novokuznetsk and the Chelyabinsk region, allowed to determine the prevalence of the verified diagnosis of bronchial asthma based on meta-analysis, and compare it with European indices [22]. Application of this method makes it possible to trace the dynamics of the disease prevalence and evaluate the effectiveness of activities to improve ambient air quality, as well as preventive measures by the public health authorities. The pilot project in this direction can be carried out in Krasnoyarsk, especially considering the experience of the Department of Pediatrics of the Krasnoyarsk State Medical Institute named after Prof. V.F. Voyno-Yasenetsky[8]. In this

[8] Stepanova L.V. Clinical and organizational problems of bronchial asthma in children of Krasnoyarsk and their solution: Author's abstract. Candidate of Medical sciences. Krasnoyarsk, 2009, 207 p. (in Russian).

city, as well as in Bratsk and Novokuznetsk, oncoepidemiological studies are needed, given the high carcinogenic risk of exposure to contaminated air. The presence of this risk may justify the additional funding for early cancer diagnostics, oncological prevention and evidence-based oncoepidemiological studies. We believe that in Siberian cities radical changes in air quality and improvement of public health are possible only after reduction of coal use or modernization of power plants with reduction of particulate emissions.

To better assess the impact of various environmental and lifestyle factors on the health of urban populations in New York, London, Berlin, Singapore and other capitals, other indicators and for this purpose, scientific organizations or health authorities have established special units [23]. Urban health has become a subject of discussion in our country, for example, at annual international Urbanist forums in Moscow.

An effective environmental policy to reduce the emission of suspended particles has resulted in not only a reduction in the concentrations of these particles in the air of cities in Europe, the United States and other countries of the Organization for Economic Development and Cooperation, but also to a reduction in additional mortality rates. As a consequence, life expectancy at birth in the USA increased by 0.61/year from 1980 to 1990 (this calculation naturally also took into account the impact of socio-economic factors) [24]. Thus, the benefits of reducing ambient air pollution could lead to the achievement of both national demographic and health project objectives, provided adequate interaction with these projects and medical community.

Funding. The research was carried out within the framework of the state task of IEF RAS «Formation and adjustment of the short-, medium- and long-term forecasts for the development of the social sector of economy».

Conflict of interests. The authors state that there is no any conflict of interest.

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Received: 09.06.2020
Accepted: 23.06.2020
Published: 30.06.2020

UDC 628.194: 628.1
DOI: 10.21668/health.risk/2020.2.03.eng

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HYGIENIC ASSESSMENT OF DRINKING WATER FROM UNDERGROUND WATER SOURCES TAKEN FROM CENTRALIZED WATER SUPPLY SYSTEMS ON ISLAND RUSSKIY

V.D. Bogdanova[1,2], P.F. Kiku[1], L.V. Kislitsyna[2]

[1]School of Biomedicine of Far Eastern Federal University, Bld. 25, FEFU Campus, Ajax Bay, Russkiy Island, 690922, Russian Federation
[2]Center for Hygiene and Epidemiology in Primorye, 36 Utkinskaya Str., Vladivostok, 690091, Russian Federation

Drinking water is a leading environmental and hygienic factor that influences population health as it tends to contain a lot of chemicals, both natural and anthropogenic in their origin.

Our research goal was to hygienically assess drinking water from underground water sources taken from centralized water supply systems on Island Russiky.

Research object. We hygienically assessed quality of water supply on Island Russkiy (Primorye) in 2017–2019 as per 33 sanitary-chemical and 3 microbiological parameters at three stages: water from underground sources (120 samples); water at pump stations (138 samples); water taken from distribution network (204 samples).

Data and methods. The first stage in hygienic assessment of drinking water was performed as per methodical guidelines provided by F.F. Erisman's Federal Scientific Center for Hygiene «Assessment of sanitary-epidemiologic reliability of centralized drinking water supply systems» (MG 2.1.4-2370-08). The second stage involved calculating reflex-olfactor, chronic non-carcinogenic and carcinogenic effects and integral assessment of drinking water taken from centralized water supply systems as per chemical safety parameters (MG 2.1.4.0032-11).

Basic results. We detected that drinking water quality most significantly deteriorated as per its microbiological and organoleptic parameters during transportation, and it made the greatest contribution into sanitary-epidemiologic ill-being of centralized drinking water supply systems. We revealed that non-carcinogenic risks and reflex-olfactor impacts exceeded their acceptable levels. Our analysis also revealed that physiologically insufficient iron contents and water turbidity were priority factors that predetermined poor quality of drinking water. Chemical structure of drinking water didn't cause any significant threats for population health; however, it is necessary to reconstruct water supply systems and eliminate deficiency of macro- and micro-elements in drinking water due to additional sources of their supply.

Key words: *underground source, pump stations, distribution network, iron, turbidity, reliability of water supply systems, Island Russkiy, risk assessment.*

The impact of environmental and hygienic factors of habitat on population health in the current conditions of the society development governs the need to improve the forms and methods of risk assessment [1]. Establishing causal links between public health and exposure to environmental factors is the basis for social and hygienic monitoring (SHM) – a system of continuous monitoring and assessment of environmental factors, forecasting the development of adverse effects and decision-making to reduce risks to public health [2]. Identification of patterns in distributing the resulting risk by time and territory gives an opportunity to accumulate preventive activities before the rise of morbidity in the terri-

Valeriya D. Bogdanova – post-graduate student at the Department for Public Health and Prevention Medicine, biologist at the Social and Hygienic Monitoring Department (e-mail: ha-lera@mail.ru; tel.: +7 (423) 240-21-85; ORCID: https://orcid.org/0000-0002-5580-5442).

Pavel F. Kiku – Doctor of Medical Sciences, Candidate of Technical Sciences, Director of the Department for Public Health and Prevention Medicine (e-mail: lme@list.ru; tel.: +7 (423) 265-24-24; ORCID: https://orcid.org/0000-0003-3536-8617).

Lidiya V. Kislitsyna – Head of the Social and Hygienic Monitoring Department (e-mail: sgm@fguzpk.ru; tel.: +7 (423) 240-21-85; ORCID: https://orcid.org/0000-0002-4172-609X).

tory where its occurrence probability is the highest [3, 4]. At present, such patterns are outlined in the methodology of risk assessment for public health[1].

The importance of groundwater as a source of drinking water supply has increased in recent years, due to its several advantages over surface sources. Groundwater is not subject to seasonal changes and is reliably protected from pollution in case of anthropogenic disasters. Data from the state report «On the state of sanitary and epidemiological well-being in the Russian Federation in 2018» also confirm the high quality of groundwater in comparison with surface sources[2]. During 2013–2018, the share of surface sources in the Russian Federation that do not meet sanitary and epidemiological requirements is at least twice as high as the share of underground sources.

Comparative analysis of water quality from groundwater and surface sources based on microbiological parameters both in the Russian Federation (RF) and in the territory of the Primorskiy Krai (PK), in particular, confirms the best protection of groundwater from living organisms' penetration[3]. However, in terms of sanitary and chemical parameters, the share of unsatisfactory samples taken from the underground sources is higher (2018: RF – 25.8 %; PK – 18.2 %) than from the surface sources (2018: RF – 21.6 %; PK – 1.1 %).

The list of sanitary and chemical parameters for drinking water that have a significant impact on public health includes chemicals of both natural and anthropogenic origin. In order to assess the risk of their presence with respect to drinking water, an oral route associated with water supply as drinking water should be chosen as the priority exposure scenario. Methodical guidelines MG 2.1.4.0032-11 serve as a supporting methodology for assessing the risk of chemicals in drinking water to public health[4]. They supplement the guidelines with the criteria for the acceptable risk levels and an algorithm for the formation of an overall or integral assessment of its harmlessness.

Environmental problems are more often addressed in large cities [5]. At the same time, small settlements on the island territories that are part of an urban district, but are remote from the major water supply networks have specific issues, often unrelated to the industrial load, but having a significant impact on public health [6–8]. For example, water supply on Island Russkiy is carried out from the deep well-water intakes, which provide drinking water to small settlements (settlements of Ekipajniy, KET, Shigino, Rynda, Voyevoda, Melkvodniy, Paris, Podnozhye, Tserkovnaya Pad'). The rest of the settlements and objects located on the island are supplied with water from the surface sources. Ekipajniy, KET, Shigino, Rynda are under surveillance within the system of SHM.

Only half of the wells (8 out of 16), where water is taken for Island Russkiy, are not subject to surface contamination. Water distribution networks are 59 % worn- out, their condition requires technical improvement, the condition of water pumping stations – operational[5].

The purpose of the study is hygienic assessment of drinking water from the under-

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[1] R 2.1.10.1920-04. Guidance on Health Risk Assessment under the Exposure of Chemicals Polluting the Environment. In: Yu.A. Rachmanin, G.G. Onishchenko, A.V. Kiselev [et al.] eds. Moscow, Federal Centre of the State Sanitary and Epidemiological Surveillance of the Ministry of Health of Russia, 2004, 143 p. (in Russian).

[2] On the State of Sanitary and Epidemiological Well-being in the Russian Federation in 2018: State report. Moscow, Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2019, 254 p. (in Russian).

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ground sources of the centralized water supply systems in Island Russkiy.

To meet this purpose, we set and solved the following tasks:

– to assess drinking water quality and water physiological adequacy (the full-value condition) at all stages of water supply in terms of maximum concentrations of substances divided by the limiting harmful indices;

– to give a qualitative assessment for the ill-being degree of each block on a 4-rank scale with the definition of priority elements characterizing the sanitary-epidemiological reliability of the centralized water supply systems[6];

– to calculate and assess risks at oral intake of chemicals with drinking water characterized by olfactory-reflexive (organoleptic), non-cancerogenic and carcinogenic effects.

Data and methods. To assess sanitary-epidemiological reliability of the centralized water supply systems, 28 sanitary-chemical and 3 microbiological parameters of drinking water for 2017–2019 were analyzed. Qualitative assessment of the ill-being degree for each block on a 4-rank scale was carried out with the determination of priority elements on the basis of MR 2.1.4.2370-08. Individual factors that form sanitary and epidemiological reliability of the water supply system were identified through W index. The assessment was carried out by 8 blocks (factors).

Samples were taken at different stages of the water treatment system: in wells, at the outlet of water pumping stations and from the water stand-pipes in Island Russkiy in 4 settlements (Shigino, Rynda, Ekipajniy, KET). Chemical substances concentrations in drinking water taken from the wells and at the outlet of stations were determined by KSUE «Primorskiy Vodokanal» (46 % of samples). The enterprise collects, stores, treats and supplies drinking water in the surveyed settlements. Data on the drinking water quality taken from the external water collection facilities (standpipes) at the monitoring points were determined by FSUE «Center for Hygiene and Epidemiology in Primorskiy Krai» (44 % of samples). The results of 462 drinking water samples were analyzed using the following techniques: microbiological, atomic absorption with flame atomization, gravimetry, titrimetry, potentiometry, fluorimetry, photometry and gas chromatography.

The studied parameters are divided by the Limiting Harmful Index (LHI) according to GN 2.1.5.1315-03[7]. Epidemiological parameters include total microbial number, total coliform bacteria and thermotolerant coliform bacteria). Sanitary and toxicological indices include nitrates, fluoride ion, arsenic, nickel, lead, cobalt and cadmium. The organoleptic ones include total iron, total manganese, magnesium, color index, turbidity, copper and aluminium. Iron and manganese affect the color of water, magnesium, copper – the off-flavour, aluminum – the turbidity. The list of composite indices includes: permanganate oxidation, hydrogen index, total hardness, dry residue, multi-sulfur oil, surfactants, phenolic index, zinc, calcium (optimal value: 60 mg/l)[8].

Carcinogenic, non-carcinogenic and organoleptic risks at the stage of water consumption were calculated to obtain an integral assessment of eventual negative impact of water on public health using MG 2.1.4.0032-11.2.1.4. For the calculation of non-carcinogenic risk from chemical exposure, 18 indices were selected, for carcinogenic risk calculation – 7 indices. The initial sampling was added with the

[6] MR 2.1.4.2370-08. Drinking water and water supply for residential areas. Assessment of the sanitary-epidemiological reliability of the centralized drinking water supply systems. Approved by the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, Chief State Sanitary Doctor of RF June 16, 2008. *CODEX: electronic fund of legal and normative and technical documentation*. Available at: http://docs.cntd.ru/document/1200077721 (11.03.2020) (in Russian).

[7] GN 2.1.5.1315-03. Maximum Permissible Concentrations (MPC) of Chemicals in Water of Water Objects of Drinking and Household and Cultural and Social Water Use. *CODEX: electronic fund of legal and normative and technical documentation*. Available at: http://docs.cntd.ru/document/901862249 (11.03.2020) (in Russian).

[8] Gildenskiold R.S., Yastrebov G.G., Vinokur I.L. Integrated determination of anthropogenic load on water bodies, soil, atmospheric air in residential areas: Methodical guidelines of the State Committee for Environmental Protection of Russia. Moscow, 1996, 35 p. (in Russian).

substances of Hazard Class 1: chloroform (MPC: 0.06 mg/l), tetrachloromethane (MPC: 0.002 mg/l), bromdichloromethane (MPC: 0.03 mg/l), tetrachloroethylene (MPC: 0.005 mg/l), and substance of Hazard Class 2: strontium (MPC: 7 mg/l). The choice of additional indices is made based on the class of hazard and carcinogenicity, and is relevant for Class 2 water bodies of economic and drinking water supply in the Primorskiy Krai, where disinfection is carried out by chlorination.

Maximum actual concentrations of substances were used to assess the reliability of centralized water supply systems as well as the physiological full-value condition of drinking water. For the integral assessment of water organoleptic properties the maximum parameters of 98 % probability were taken, for the assessment of expected non-cancerogenic and carcinogenic effects – the average annual concentrations of 95 % probability were used.

Carcinogenic risk assessment was performed using the standard values: daily consumption of 2 liters for exposure duration of 30 years and the average human weight in a population of 70 kg.

Results and discussion. Population coverage with the centralized water supply in the settlements of Island Russkiy, according to the data of the last population census in 2010 and the annual data on population using piped water provided by KSUE «Primorskiy Vodokanal» for 2019, is estimated as insufficient (92 % for permanent residents of the whole Island Russkiy). As a result, the general characteristics of these settlements are estimated as moderate by the scale of sanitary-epidemiological reliability of drinking water supply to population, considering the absence of facts of exceeding the design capacity of water pumping stations and interruptions in drinking water supply ($W_1 = 0.3$).

The water intake facilities studied are operated under the conditions of compliance with the mode of source water sanitary protection zones according to SanPiN 2.1.4.1110-02 (assessed 'satisfactory' for all settlements by the relevant scale, $W_2 = 0$)[9]. Laboratory control of drinking water conditions is carried out in accordance with SanPiN 2.1.4.1074-01 (assessed 'satisfactory' for all residential locations by the relevant scale, $W_7 = 0$)[10].

For ranking the residential settlements, we used rating scales for sanitary-epidemiological condition of underground water supply sources (W_3), reliability of water treatment (W_5) and drinking water transportation in centralized water supply systems (W_6), as well as quality of drinking water from a water-dispensing unit (W_8) by LHI and physiological full-value condition. The assessment results for sanitary and epidemiological ill-being are presented in points (Table 1).

The assessment of water quality from the underground water supply sources showed that there were no the above-limit values in terms of hygienic standards for sanitary, chemical and epidemiological parameters. All samples were in line with the maximum permissible values. The qualitative characteristics (W_3) of the assessment scale corresponded to the first rank (permissible level).

The drinking water in all settlements had a lower content of calcium, magnesium and fluoride salts, and was characterized by low mineralization and hardness. All parameters of the drinking water physiological full-value condition were below the optimal values. Consumption of too «soft» drinking water without taking the additional sources of calcium and magnesium may be one of the risk factors for cardiovascular diseases [9–11].

Despite the fact that fluorine is one of the priority components of natural origin with a high probability of detecting the MPCs excess in the territory of the Primorskiy Krai, according to SP 2.1.5.1059-01, the opposite phenomenon was observed in the locations studied. Low fluoride concentrations in drinking

[9] SanPiN 2.1.4.1110-02. Sanitary protection zones of water supply sources and drinking water pipelines. Moscow, 2002, 11 p. (in Russian).

[10] SanPiN 2.1.4.1074-01. Drinking water. Hygienic requirements for water quality of centralized drinking water supply systems. Quality control. Moscow, 2001, 62 p. (in Russian).

Table 1

Assessment of sanitary-epidemiological reliability of centralized drinking water supply systems and indices of physiological full-value condition of water mineral composition

Residential settlement	Stage	Sanitary and epidemiological reliability (score in points)			Physiological full-value condition of water mineral composition (Cmax, mg/l)					Ca^{2+}/Mg^{2+} mmole-eqv/l
		Water quality at certain stages	W_6	W_{ov}	TH	TDS	F^-,	Mg^{2+}	Ca^{2+}	
KET	W_3	0 (Permissible)	1.05 (0.75+0.3)**	0.84	2.2	211.0	0.5	18.2	16.6	0.8
	W_5	0 (Permissible)			2.0	205.0	0.3	10.9	21.3	1.2
	W_8	1.65 (0.3+0.3+1.05)*			1.2	94.1	0.1	9.6	25.5	2.0
Rynda	W_3	0 (Permissible)	1.05 (0.75+0.3)**	0.83	2.1	221.0	0.4	13.4	18.7	1.2
	W_5	0 (Permissible)			1.8	207.0	0.2	6.1	21.6	2.6
	W_8	1.6 (0.3+0.25+1.05)*			1.1	105.5	0.2	3.8	21.3	5.4
Ekipajniy	W_3	0 (Permissible)	1.05 (0.75+0.3)**	0.83	2.2	187.0	0.4	14.6	17.8	1.0
	W_5	0 (Permissible)			2.2	208.0	0.3	10.3	18.0	1.5
	W_8	1.6 (0.3+0.25+1.05)*			1.1	106.3	0.2	10.1	20.0	1.7
Shigino	W_3	0 (Permissible)	0.95 (0.75+0.2)**	0.79	1.3	105.0	0.2	4.3	18.0	2.7
	W_5	0 (Permissible)			1.6	202.0	0.2	4.9	7.5	1.0
	W_8	1.5 (0.1+0.35+1.05)*			0.9	90.5	0.2	3.6	14.5	5.0
Optimal value: MR 2.1.4.2370-08 (TH, TDS, F^-), SanPiN 2.1.4.1116-02[11] (Ca^{2+},Mg^{2+})					1.5–7	200–500	0.8–1.5	5–65	25–130	–

Note:
* – organoleptic + physiological full-value condition + microbiological;
** – microbiological + organoleptic (sum of points in terms of LHI);
*** – W_6 – transportation;
W_3 – water source quality;
W_5 – water treatment (water quality at the pumping station outlet);
W_8 – water quality from the distribution network;
W_{ov} – overall composite index;
TH – total hardness;
TDS – total dissolved solids.

water increase the risk of caries development. Calcium along with fluorides is an important protective factor against caries. Their combined protective effect has been proven in several analytical studies[12] [12, 13].

In the studied drinking water samples taken from wells, the ratio of Ca^{2+} and Mg^{2+} ion concentrations (expressed in mmol-eq./l) was significantly lower in the three settlements than in drinking water passing through the water supply network. This was due to an increase in soluble calcium compounds and a decrease in the number of magnesium ions during the transportation of water to consumer.

[11] SanPiN 2.1.4.1116-02. Drinking water. Hygienic requirements for the quality of water packaged in containers. Quality control. Moscow, 2002, 22 p. (in Russian).

[12] SanPin 2.1.5.1059-01. Hygienic requirements for groundwater protection against pollution. Moscow, 2001, 14 p. (in Russian).

In terms of such indices, as total hardness, total mineralization and fluorine, there was a tendency to decreasing concentrations during transportation through water supply network.

At the water pumping stations outlet, the analysis results for the drinking water samples (W_5) met hygienic standards which speaks of the proper water treatment and consistency of drinking water composition on the way from the water supply source to the pumping stations and before entering the distribution network. Water treatment improves drinking water quality in terms of such organoleptic indices, as iron and turbidity.

The analysis results for the quality of drinking water taken from the distribution network (stand-pipes) occasionally did not meet hygienic standards for microbiological and organoleptic parameters (in Table 1 these indices are included in the assessment of water quality from the distribution network – W_8). Physiological deficiency of water, in terms of general mineralization («extremely high» ill-being degree for all locations), overall mineralization and fluoride concentrations («moderate» for one third of locations and «high» – for Shigino settlement) contributed to the sanitary ill-being of the drinking water.

The ill-being degree in terms of microbiological parameters by the scale of sanitary-epidemiological reliability of drinking water transportation in the centralized water supply systems was assessed as «extremely unsatisfactory» (>10 % of unsatisfactory samples) for all networks studied. According to organoleptic indices, when calculating the above-limit MPC's values multiplicity factor of the maximum concentrations, the qualitative assessment was defined as «extremely unsatisfactory» for one third of settlements and «moderate» – for Shigino settlement.

The quality parameter of the drinking water from the distribution network (W_8) by the scale of sanitary and epidemiological ill-being for water was closer to the «high» pollution characteristics (rank 3rd out of 4 possible ones), taking into account the contribution coefficients of each limiting index (overall, organoleptic, sanitary-toxicological, epidemiological and physiological full-value condition of mineral composition).

Having assessed the sanitary and epidemiological reliability of the drinking water transportation (W_6), we can speak about the increase in the share of non-standard samples in terms of organoleptic and microbiological LHI. According to the scale of sanitary-epidemiological ill-being of drinking water transportation, the qualitative characteristic of pollution was defined as «moderate» in all residential settlements.

It should be noted a significant increase in maximum concentrations of iron and turbidity of water in the distribution network due to its transportation from the pumping station to the water stand-pipe (Figure).

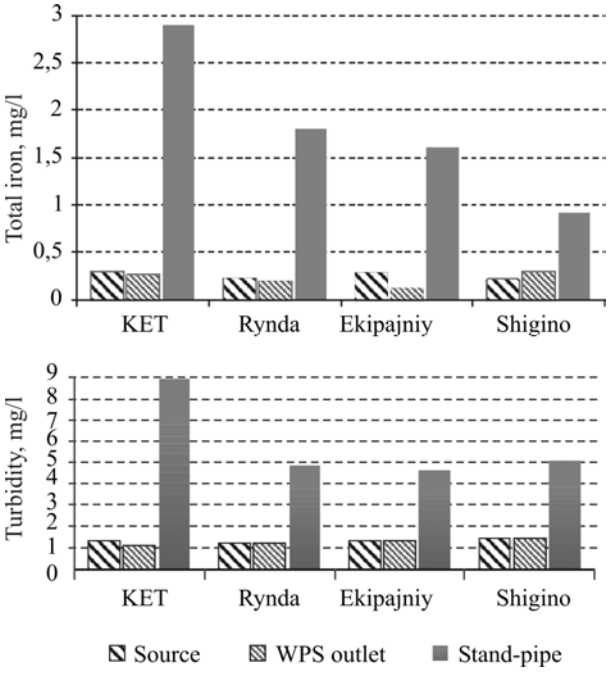

Figure. Concentration of total iron and turbidity in drinking water of the centralized water supply taken from underground sources, at a pumping station and from a distribution network

This pattern was observed not only in the studied locations of the Island Russkiy, but also on other territories of the region, the Russian Federation subjects and beyond [14–18]. Iron content above 1 mg/l deteriorates organoleptic properties of water, it becomes turbid, colored in yellow-brown color, it has a characteristic metallic flavor, mucus is formed

on the pipes walls, typical for iron bacteria. Such water has an adverse effect on skin, causing dryness and itching.

In terms of the overall composite index (W_{ov}), the ill-being degree of drinking water supply can be considered as «moderate» ($0 < W_{ov} < 1$) in all settlements.

The overall index defined the network in Shigino settlement as the most satisfactory drinking water supply system, despite the fact that drinking water there is the least physiologically full-valued by its mineral composition. As the research results show, microbiological and organoleptic indices make the most significant contribution to the assessment of sanitary-epidemiological reliability of water supply systems in these settlements. As a result, the share of non-standard samples in the distribution network increased compared to those registered at the outlet of the pumping station.

The priority type of impact, when calculating the integral health risk for the population consuming drinking water from the distribution network, is the olfactory-reflex effect, which prevails in all water supply systems under study (Table 2). The leading indicator in assessing the organoleptic effects of exposure to maximum concentrations of 98 % probability of such water consumption is iron in three settlements, and turbidity (Shigino settlement).

The intrinsic uncertainty responsible for reliability and validity of risk assessments at the dose-effect stage is the lack of sensitivity in laboratory techniques for such indicators as aluminium, zinc, multi-sulfur oil, nickel, tetrachloroethylene, tetrachloromethane, arsenic and cadmium. Due to the fact that it was not possible to determine the exact data on these substances actual concentration taking into account the methods used, and thus did not guarantee the calculations objectivity for non-carcinogenic and carcinogenic risks, it was decided not to use them for risk assessment. It should be noted that the established concentrations of these substances at the lower limit of methods sensitivity were the values from 0.001 MPC – for zinc to 0.3 MPC – for tetrachloromethane. According to the uncertainty analysis, the final list of criteria considered in risk assessment is given in Table 3.

Non-cancerogenic risks did not exceed the acceptable value for certain selected parameters. The total non-cancerogenic risk in drinking water consumption exceeded the permissible level (0.05) in KET settlement due to the unacceptably high concentration of total iron. In the concentrations detected, iron can have an irritating effect on mucous membranes, cause changes in skin, affect hematopoietic and immune systems and peripheral blood parameters.

Table 2

Overall indices for the quality of drinking water from the distribution network

Residential settlement	Risk type	Value by total score	Risk to acceptable value	Overall index
KET	OR	0.70	7.04	8.60
	NCR	0.06	1.12	
	CR	0.000004	0.45	
Rynda	OR	0.40	3.99	5.13
	NCR	0.04	0.76	
	CR	0.000004	0.38	
Ekipajniy	OR	0.38	3.76	5.06
	NCR	0.04	0.82	
	CR	0.000005	0.47	
Shigino	OR	0.13	1.25	2.42
	NCR	0.03	0.61	
	CR	0.000006	0.56	

Notes:
OR – organoleptic risk;
NCR – non-carcinogenic risk;
CR – carcinogenic risk.

Table 3

Results of risk assessment by criteria taken into account

Non-cancerogenic risk assessment results								
Criteria taken into account	$C_{95\,\%}$	HP	$C_{95\,\%}$	HP	$C_{95\,\%}$	HP	$C_{95\,\%}$	HP
Iron, mg/l	0.75	0.04	0.43	0.02	0.26	0.02	0.46	0.03
Manganese, mg/l	0.02	0.003	0,02	0.004	0.02	0.003	0.03	0.01
Nitrates, mg/l	3.58	0.001	3,36	0.001	5.38	0.002	4.90	0.002
Cobalt, mg/l	0.02	0.003	0.02	0.004	0.02	0.003	–	–
Magnesium, mg/l	10.08	0.004	13.22	0.01	3.88	0.001	4.74	0.002
Copper, mg/l	0.02	0.003	0.02	0.003	0.011	0.002	0.04	0.006
Fluorine, mg/l	0.16	0.001	0.17	0,002	0.17	0.002	0.17	0.002
Lead, mg/l	0.002	0.004	0.004	0.001	0.002	0.003	0.001	0.002
Chloroform, mg/l	0.012	0.004	0.01	0.003	0.03	0.008	0.01	0.003
Bromdichloromethane, mg/l	0.003	0.002	0.002	$1.3\cdot10^{-4}$	0.004	0.002	0.003	0.002
Strontium	0.3	$7.5\cdot10^{-5}$	0.280	$7.0\cdot10^{-5}$	0.010	$2.5\cdot10^{-6}$	0.180	$4.5\cdot10^{-5}$
Results of organoleptic risk assessment								
Criteria taken into account	C_{m98}	OP	C_{m98}	OP	C_{m98}	OP	C_{m98}	OP
Color,°	14.4	0.01	11.5	0.01	14.1	0.01	15.9	0.01
Turbidity, mg/l	7.76	0.14	3.15	0.01	4.0	0.02	3.92	0.02
pH, unit	7.71*	0.005	7.55*	0.003	7.0*	0.001	7.31*	0.001
Iron, mg/l	1.74	0.7	0.97	0.38	0.5	0.13	1.01	0.4
Manganese, mg/l	0.02	$1.9\cdot10^{-5}$	0.05	$2.0\cdot10^{-3}$	0.04	$7.9\cdot10^{-4}$	0.06	$3.6\cdot10^{-3}$
Cancerogenic risk assessment results								
Criteria taken into account	$C_{95\,\%}$	KP	$C_{95\,\%}$	KP	$C_{95\,\%}$	KP	$C_{95\,\%}$	KP
Lead, mg/l	0.002	$1.2\cdot10^{-6}$	0.004	$2.2\cdot10^{-6}$	0.002	$8.7\cdot10^{-7}$	0.001	$7.4\cdot10^{-7}$
Chloroform, mg/l	0.01	$9.2\cdot10^{-7}$	0.01	$7.7\cdot10^{-7}$	0.03	$1.9\cdot10^{-6}$	0.01	$8.1\cdot10^{-7}$
Bromdichloromethane, mg/l	0.003	$2.4\cdot10^{-6}$	0.002	$1.8\cdot10^{-6}$	0.004	$2.8\cdot10^{-6}$	0.003	$2.2\cdot10^{-6}$

N o t e s:
C_{m98} – maximum concentrations of 98 % probability;
$C_{95\,\%}$ – average annual concentrations of 95 % probability;
«–» – cobalt concentration less than test sensitivity threshold (less than 0.01 mg/l);
* – average value for hydrogen indicator is taken.

Carcinogenic risks to public health from exposure to chemicals from the drinking water supplied to the distribution network did not exceed the acceptable level (0.00001) both for the indices considered separately and for their cumulative effect.

According to the data of the integrated assessment for the drinking water quality from the distribution network, it was found that for all objects the overall indices did not correspond to the permissible value, which is associated with exceeding the levels of acceptable risk for olfactor-reflex effects (for all residential settlements) and non-carcinogenic risk (for KET).

The deterioration pattern of the drinking water quality from the centralized water supply systems for population, is caused by the chemical composition, affecting mainly its organoleptic properties and is widespread [19, 20]. In general, the chemical composition of the drinking water studied does not pose a threat to public health, however, it is necessary to reconstruct water supply systems and correct the lack of macro- and microelements in drinking water through additional sources of their supply, including food and food additives.

Conclusions:

– the sanitary-epidemiological assessment of water from the centralized household and drinking water supply systems on the Island Russkiy showed that the highest contribution to the water quality is made by the non-

compliance with hygienic norms for organoleptic parameters in terms of iron and turbidity, as well as microbiological indices;

– it was shown that deterioration of the drinking water quality occurs in the process of its transportation from water pumping station to disposable device;

– calculation of an overall index for the drinking water of the centralized household and drinking water supply systems in terms of chemical harmlessness allowed for differentiation the water hygienic quality by settlements;

– the non-carcinogenic risks from total exposure to substances exceeded the permissible values in one of the centralized water supply systems owing to total iron;

– the carcinogenic health risks for population from the exposure to chemicals from the drinking water supplied to the distribution network did not exceed the permissible level both for certain indices considered separately, as well as for their total impact;

– in order to improve the sanitary reliability of the centralized water supply systems, it is necessary to reconstruct water supply systems in the Island Russkiy, which will give an opportunity to preserve the composition consistency of the natural water from the source to the point of consumption;

– physiological ill-being of water detected should be adjusted with food and nutritional additives to meet the average daily requirement of a body for macro- and microelements.

Funding. The research was not granted any sponsor support.

Conflict of interests. The authors declare there is no any conflict of interests.

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Received: 18.03.2020
Accepted: 02.06.2020
Published: 30.06.2020

UDC 613.24: 613.99
DOI: 10.21668/health.risk/2020.2.04.eng

Read online

ASSESSING RISK FACTORS THAT CAN CAUSE OVERWEIGHT AND OBESITY IN WOMEN OF REPRODUCTIVE AGE

E.L. Makarova[1], A.A. Olina[2], M.M. Padrul'[3]

[1]M.A. Tver'ye's Municipal Clinical Hospital, 2 Brat'ev Ignatovykh Str., Perm, 614600, Russian Federation
[2]D.O. Ott's Scientific and Research Institute for Obstetrics, Gynecology, and Reproductology, 3 Mendeleevskaya line, Saint Petersburg, 199034, Russian Federation
[3]Perm State Medical University named after E.A. Wagner, 26 Petropavlovskaya Str., Perm, 614000, Russian Federation

We examined 226 women of reproductive age who permanently resided in Perm. Our research goal was to examine certain risk factors and assess their effects on overweight and obesity in women of reproductive age.

All the patients were divided into 2 groups; the reference one was made up of 123 women with normal body weight; the test one included 103 women with overweight and obesity. We determined body mass index (BMI) of each woman; obesity type (in case BMI was higher than 25 kg/m^2, namely android or gynoid one; physical activity; nutrition stereotypes; smoking status (more than 5 cigarettes a day daily for not less than 1 months); sleeping disorders; research season; concomitant gastrointestinal diseases and liver diseases. We calculated relative risk of obesity and BMI predictors.

The research revealed a significant correlation between overweight and obesity and elevated risks of unhealthy nutrition stereotypes (RR=3.3); low physical activity (RR=2.6); age exceeding 35 (RR=2.1); smoking (RR=1.8); gastrointestinal diseases and liver diseases (RR=1.5); sleeping disorders (RR=1.5). Women from the test group had improper eating habits and nutrition behavior as opposed to their counterparts from the reference group. Each second patient who suffered from android obesity was also a smoker. Winter season didn't turn out to be a predictor of fat metabolism disorders.

Therefore, having analyzed pre-obesity and obesity risk, we recommend efficient activities performed in public healthcare and personal adherence to healthy lifestyle as it will allow reducing body weight of fertile Russian women. Doctors of any specialty should share the responsibility for preserving health of future parents and generations.

Key words: *risk factors, obesity, overweight, physical activity, season, nutrition stereotype, smoking, sleeping disorders.*

«Overweight epidemic» is now spreading fast both in developed and developing countries. More than 500 million people worldwide have overweight as their body mass index (BMI) varies from 25 to 29.9 kg/m^2. 250 million people suffer from obesity (their BMI exceeds 30 kg/m^2) [1, 2]. The mankind can't cope with obesity; everybody seems to know how to lose weight but nobody actually manages to do it. Since 90ties last century people in Russia «have put on considerable weight». Obesity, both in the country and in Perm region, has grown by 4.8 times over the last 15 years [3]. According to official statistic data (2017), in Russia 29 % women aged 18–45 have obesity; in Perm region – 13 %. According to the Statistic Report Form No. 12 (official statistical data collected in Perm region), in 2018 «obesity» (E.66 as per ICD-10) was diagnosed in 9 % of cases when people older than 18 applied for medical health. And still, results of periodical medical examinations performed among working population and students in Perm revealed even higher figures. Obesity was diagnosed in 15 %; «morbid obesity» was detected in 5 % cases (BMI exceeded 40 kg/m^2); overweight (pre-obesity) was diagnosed in each 6th examined person [3]. We should note that official statistical data can't be a basic data source for determining actual prevalence of diseases associated with lipid metabolism disorders as people rarely apply for medical health due to having overweight. So, it is truly vital to examine actual prevalence of such diseases in various age groups as well as their contemporary etiological and pathogenetic aspects.

Elena L. Makarova – Candidate of Medical Sciences, obstetrician-gynecologist at the Municipal Perinatal Center (e-mail: makarova_803@mail.ru; tel.: +7 (904) 849-37-70; ORCID: https://orcid.org/0000-0002-1330-8341).

Anna A. Olina – Doctor of Medical Sciences, Professor, First Deputy Director (e-mail: olina29@mail.ru; tel.: +7 (922) 329-53-62; ORCID: http://orcid.org/0000-0001-9101-7569).

Mikhail M. Padrul' – Doctor of Medical Sciences, Professor, Head of the Obstetrics and Gynecology Department (e-mail: rector@psma.ru; tel.: +7 (342) 217-20-21; ORCID: http://orcid.org/0000-0002-6111-5093).

Fat accumulation is hazardous for people of any sex and age. However, bearing in mind the latest demographic trends in the RF (negative natural growth, ageing, and first-time mothers becoming older) it is necessary to pay more attention to young women of reproductive age as they secure reproductive potential in the country. Future mothers with overweight trigger transformation of genes that are responsible for metabolic processes in lipocytes thus creating a so called «protected fat tissues» in their children [4]. A number of fat cells multiplies during fetal development [5]. This genetically determined obesity will become hardly curable in future.

«Obesity» as a diagnosis is not registered by doctors who treat related pathologies. For example, a young woman doesn't come to a gynecologist-obstetrician because she has overweight; instead she comes to treat menorrhalgia or infertility, that is, reproductive disorders related to fat metabolism disorders. Even if she manages to get pregnant, an imbalance in fat tissue hormones can cause certain complications, both for a mother (miscarriage, gestational pancreatic diabetes, preeclampsia, fetoplacental failure, etc.) and for a fetus (hypersomia, birth traumas, carbohydrates metabolism disorders etc.) [6–12]. At present, a wide range of research works are concentrating on prenatal programming of obesity. As a result, experts have managed to reveal an adaptation reaction in a fetus as a response to nutrition factors and its ability to provide survival via epigenetic modification of genes that participate in multiple key regulatory cycles [4]. Clinically significant adaptation to changes in nutrition that takes place during fetal development is able to become apparent as a primary component in a metabolic syndrome. Consequently, obesity in an adult person is not only a result of an unhealthy lifestyle but also a disease predetermined at early stages of development and not genetic in its essence.

Evolution biology implies that a living individual should strive for food in order to survive as it allows renewing energy resources that are stored in a body as fat tissues. Traditionally, starvation was much more hazardous for life than overeating. However, overall economic progress has resulted in food becoming much more available for people; huge variety of tasty and high-calorie food doesn't require great physical efforts to obtain it and issues related to starvation are now replaced with excess consumption. Food industry is ready to provide high-calorie products that are easy to assimilate, have minimal nutrition value and a lot of calories, and contain taste enhancers. It makes a person to consume them more and more without any feeling of satiation.

Obesity can develop due to multiple factors that can produce their effects both together and separately. The most widely spread factors are genetic predisposition, lifestyle (overeating and hypodynamia), and endocrine systems dysfunctions [13]. Since researchers on genome became possible, a lot of genes have been identified that code functions of various sections in body mass regulation and metabolism. However, identified locuses predetermine less than 5 % of discrepancies in BMI [4]. Disputable issues related to impacts exerted on excess fat occurrence in a body by intoxications, sleep deprivation, water metabolism disorders, and microbiota require further investigation.

«Obesity» epidemic will only develop more rapidly due to scientific and technical progress; therefore, it will still be vital to examine behavioral peculiarities (lifestyle) of patients with overweight and obesity.

Our research goal was to examine certain risk factors and estimate their effects on overweight and obesity occurrence among women of reproductive age.

Data and methods. The research was accomplished in a clinic belonging to E.A. Vagner's Perm State Medical University, and a perinatal center of M.A. Tver'ye Municipal Hospital. Overall, we examined 226 women of reproductive age permanently residing in Perm. The patients were divided into 2 groups according to their BMI; group A (n = 123) was made up of women with normal body weight (reference group); group B (n = 103) included women with fat metabolism disorders (test group).

We determined the following parameters for each woman:

1. BMI as the body weight in kilos (kg) divided by the square of the body height in meters (m^2). BMI equal to 25–29.9 kg/m^2 meant a woman had overweight; BMI being 30 kg/m^2

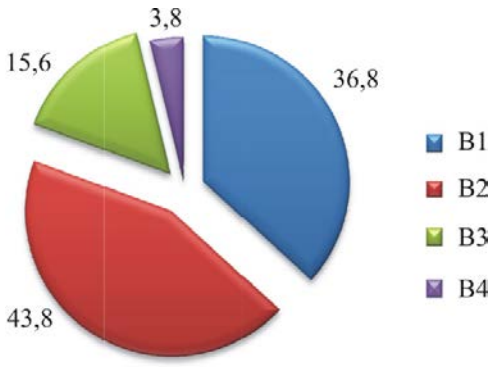

Figure 1. Test group structure depending on BMI (in %)

and higher meant she had obesity. The test group was divided into subgroups (Figure 1): women in subgroup B1 had BMI varying from 25.0 to 29.9 (overweight); subgroup B2, BMI = 30.0–34.9 (class 1 obesity); subgroup B3, BMI = 35.0–39.9 (class 2 obesity); subgroup B4, BMI exceeding 40.0 kg/m^2 (class 3 obesity).

2. Obesity type, android or gynoid. To determine it, we calculated (K) coefficient as waist circumference (WC) divided by thigh circumference (TC). In case K = 0.8 and lower, obesity was considered gynoid (GO); in case K = 0.81 and higher, obesity was android (AO) (Table 1).

3. Physical activity (PA). In the given work, we applied a population technique for assessing PA (a questionnaire recommended by the WHO); the examined cohort was divided into two categories basing on the results. The 1st category were sufficiently active women, their energy costs reaching recommended levels and being not less than 500 MET/min per week. The 2nd category included women who were not physically active (less than 500 MET/min per week) [14]. GPAQ (Global Physical Activity Questionnaire) contains questions aimed at determining amounts of time spent on three types of PA: at work, during travelling from place to place, and at leisure. «Sufficient» PA was taken as per levels recommended by the WHO for adults, 150 min moderately intense PA or 75 min intense PA per week, or an equivalent combination of moderately intense and intense PA. Additionally, we calculated individual energy costs borne by a respondent. When calculating overall energy costs in MET with the use of GRAP data, we took 1 minute of moderate PA as being equal to 4 MET; 1 minute of intense PA, 8 MET. Accordingly, energy costs being 600 MET per week or more were considered sufficient [15]. GPAQ has been validated multiple times, tested in terms of reproducibility, and recommended as a tool for estimating PA with the STEPS international system for monitoring over risk factors causing non-communicable diseases.

4. Adherence to nutrition stereotypes. The factor was assessed via 24-hour observation over a daily ration together with analyzing its structure as per specific food products; to do that, all the female participants were offered to fill in relevant questionnaires. A list of products recommended by the Institute for Obstetrics and Gynecology of the RAS was taken as a criterion for assessing an average daily ration consumed by women. Adherence was considered satisfactory if a ration and the list were similar; otherwise, it was considered unsatisfactory[1] [16].

Table 1

Characteristics of the examined groups

Group	Age, years	Weight, kg	BMI, kg/m^2	GO (from as group as per a row)	AO (from as group as per a row)
Group A (n = 123)	23.6 ± 0.15	63.8 ± 1.29	21.5 ± 0.37	–	–
Group B (n = 103)	24.6 ± 0.37	78.8 ± 2.59	28.9 ± 0.43	62.1 %	37.9 %
Subgroup B1 (n = 38)	23.6 ± 0.51	72.4 ± 1.83	26.6 ± 0.31	76.3 %	23.7 %
Subgroup B2 (n = 45)	24.1 ± 0.49	88.4 ± 1.10	32.5 ± 0.38	62.2 %	37.8 %
Subgroup B3 (n = 16)	24.7 ± 0.31	98.3 ± 2.11	36.8 ± 0.55	37.5 %	62.5 %
Subgroup B4 (n = 4)	24.0 ± 0.61	107.6 ± 1.6	41.5 ± 0.57	25.0 %	75.0 %

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5. Smoking (more than 5 cigarettes a day daily for not less than 1 month).

6. An examination taking place during a specific season. Women were selected for examination during a cold season (from October 01 to April 30) and a warm one (from May 01 to September 30) in a city located at 59° northern latitude (Perm).

7. Sleep disorders were revealed with a questionnaire that allowed estimating sleep quality as per a 5-score scale according to 5 criteria basing on subjective descriptions given by patients (Table 2). To interpret the results, we calculated a total score. A total score equal to 22 or higher meant a patient didn't have any sleep disorders; 19–21 scores meant borderline sleep disorders; less than 19 scores, apparent sleep disorders [17].

8. We determined whether patients suffered from concomitant diseases of the gastrointestinal tract and liver such as gastroesophageal disease, non-alcoholic hepatosis, and cholelithiasis; to do that, clinical and instrumental data were applied (complains, a medical examination, and US of the abdominal cavity organs).

All the obtained data were statistically analyzed in «Biostatistics» Center (Tomsk). Selected parameters that are given in the text and tables below have the following denominations: n means a number of people in an analyzed sub-group; Me, median; 25 % and 75 %, interquartile range; M, simple mean; S, standard deviation; m, error of the mean; p, achieved significance. Critical significance was taken to be equal to 5 %. We applied the following statistical analysis procedures: testing whether quantitative attributes distribution was normal with Kolmogorov-Smirnov test; contingency tables analysis; risk ratio with calculating Pearson's χ^2-square; two-tailed Fischer's test, %. Relative risk (*RR*) was calculated with the use of fourfold contingency tables. At $RR > 1$ it was concluded that a factor caused an increase in a number of outcomes (a direct correlation).

Results and discussion. Correlation analysis of impacts exerted by age on weight didn't reveal any direct dependence in all groups. But still, picking out specific age category «younger than 35» and «35 and older» within the groups allowed revealing certain contingency between weight and age as well as BMI and age within «35 and older» subgroup (Table 3). Literature data indicate that metabolic reactions physiologically tend to slow down as a person grows older; certain hormonal shifts also occur in older people and they can result in fat accumulating in a female body [18, 19].

Table 2

A questionnaire for obtaining a score estimate of subjective sleep descriptions (Vein A.M., 2016)

Sleep description	Scores				
	5	4	3	2	1
Time necessary to fall asleep	Instantly	Not long	Average	Long	Very long
Sleep duration	Very long	Long	Average	Short	Very short
Awakenings at night	Never	Rarely	Sometimes	Often	Very often
Dreams	Never	Sometimes	Average	Multiple	Multiple and troubled
Sleep quality	Excellent	Good	Average	Poor	Very poor
Awakening quality	Excellent	Good	Average	Poor	Very poor

Table 3

Contingency with BMI higher than 25 kg/m^2

Parameter	Acheived «p»	Cramer's V
Age being 35 and older	0. 0412	0. 3030
Obesity type: android/gynoid	0.0001	0. 6694
Unsatisfactory nutrition	0. 0231	0. 3437
Season (cold: October 01 – April 30)	0. 1880	0. 2775
Low PA	0. 008	0. 3969
Chronic diseases of the gastrointestinal tract and liver	0. 8620	0. 1305
Sleep disorders	0. 2361	0. 2899

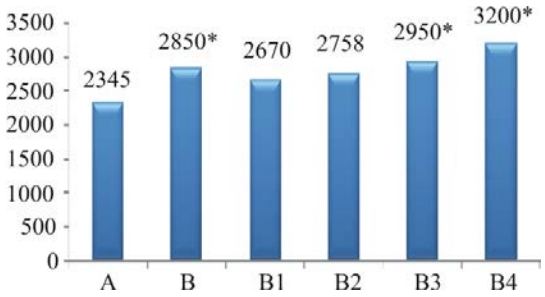

Figure 2. Daily calorie consumption (Kcal) by women from different subgroups
* means $p < 0.005$ (against the group A)

We analyzed questionnaires on adherence to specific nutrition stereotypes and revealed significant nutritional disorders in the group B. We detected that women in the basic group B and in all subgroups daily consumed calories in a quantity than was more than 2,600 kilocalories (Figure 2). And it is especially alerting as a woman in reproductive age employed at a workplace with mental labor and low physical loads is recommended to consume 2,400–2,600 kcal per day [15]. We revealed a direct dependence between weight and consumed calories quantity.

We detected that 85 % patients from the basic group consumed fats in excess quantities; there were only 34 % ($p < 0.01$) women in the control group who consumed them in such quantities. Women from both groups mostly consumed animal fats (butter, milk fats, and animal fats with meat). As opposed to vegetable fats, these fats have higher concentrations of saturated fatty acids such as palmitic acid, stearic acid, etc. A need in saturated fatty acids accounts for only 5 % of the total daily ration or 30 % of the total quantity of fats consumed a day. Total quantity of all consumed fats should not exceed 1 gr/kg of body weight. Only 30 % of saturated fats break down in a body; the rest doesn't participate in metabolism and produces negative effects on functioning of all organs and systems in a body (atherogenicity index grows, fats accumulate in deposits).

Respondents from both groups consumed vegetable oil and fish oil in quantities not more than 10 grams a day thus depriving their bodies of Omega-3,6,9 fat acids and fat-soluble vitamins; they didn't consume those health-giving nutrients in sufficient quantities. And it should be noted that these substances produce hypocholesteremic, hypotriglyceridemic, antithrombotic, anti-inflammatory, cardioprotective, and oncoprotective effects [20].

Excess energy intake in the test group was due to consumed food being high-caloric with fats prevalence in a daily ration and daily nutrition rhythms being impaired.

Practically all women with fat metabolism imbalance had disrupted daily nutrition rhythms (91 %); the same was detected for each fifth woman with normal body weight (23 %, $p < 0.001$). Abundant meals at night (after 10 p.m.) were the most frequent (33 % and 7 % accordingly, $p < 0.01$). Fast-food meals were detected in 42 % cases in the test group and 15 % cases in the control one ($p = 0.02$); sweet fizzy waters consumption was detected in 52 % and 23 % cases accordingly ($p = 0.02$). It is rather alerting that practically all patients from the test group (91 %) and 2/3 patients in the control one (62 %) consumed mostly preserved and refined food products. It is well-known that manufacturers add taste enhancer and stabilizers in semi-cooked and preserved food products. Such substances induce overeating and block any feeling of being sated with food. Semi-finished products are often fried in a great quantity of oil and it is an additional source of «excess» calories in a daily ration.

Besides, we detected nutritional behavior disorders in the test group. Hyperphagic reaction was revealed in 68 % cases in the test group and in 39 % cases in the control one as per questioning results. Such a state occurs under psychoemotional strain, anxiety, or stress. Appetite grows drastically, and a person has an overwhelming wish to eat; food is not differentiated, and a person eats anything he or she can get still giving preference to fat and sweet products. Another nutrition behavior disorder, compulsive hyperphagia, was detected in each third patient in the test group (33 %) and in less than 5 % patients in the control group. This eating disorder is characterized with sudden uncontrollable food consumption that has nothing to do with physiological satiation. Compulsive overeating is believed to occur due to depres-

sion, melancholy, and low self-esteem that are often caused by disharmony in family relations [21]. Night hyperphagia was detected in 24 % women from the test group.

Nutrition behavior disorders get only worse due to social significance attributed to meals. A lot of families go to fast-food cafes («McDonald's», «KFC», «Chicken», etc.) to celebrate a family event or to give a «reward» to children or adults in a family; such cafes provide their clients with food that contains a lot of carbohydrates and fats.

Therefore, unsatisfactory nutrition as a significant factor was detected in 75 % cases in the test group and in 46 % cases in the control one. This predictor turned out to be statistically significant ($\chi^2 = 31.8$, $p < 0.001$) and one of three most significant factors in calculation of relative risks ($RR = 3.33$ at CI 1.95–5.16) that could cause fat metabolism disorders (Table 4).

Individual energy consumption by a person depends on three factors. The first one is basic metabolism that corresponds to energy expenses spent on maintaining basic physiological functions under normal conditions. The second is dynamic effects produced by food (thermogenic effects) that account for approximately 5–10 % of the overall energy expenses and are associated with additional energy spent on digestion. The third one is physical activity that requires the most energy [15]. Over the last decades normal physical activity of women in Russia during their leisure time is replaced with hypodynamia, for example watching TV or spending time in the Internet instead of doing sports [22].

We examined such a predictor as «physical activity» in our research and obtained the following results. Each second woman (52.1 %) with normal body weight was sufficiently physically active; the same was true only for each fifth woman with fat metabolism disorders (22.6 %; $\chi^2 = 20.858$, $p < 0.001$). When giving comments in questionnaires, women explained their low physical activity by changes in external living conditions (sedentary activities both at home and at work) and changes in ways to travel from place to place (elevators and cars). Such factors as growing urbanization, physical labor being replaced with machines, and computerization of many spheres lead to low physical activity of people. Besides, internal factors were also significant, namely, no motivation to be physically active and mobile (on-line shopping and food delivery) and do sports; existing habits in a family, unwillingness to pursue healthy lifestyle. 3.5 % women from the test group noted they loved themselves with any body weight as they belonged to so called «body positive» movement advertised by mass media and social networks. Unfortunately, this movement only aggravates a problem related to such a disease as «obesity». Low PA or even absence of it and excess food consumption are not disapproved of by such patients and they consider it an insult when somebody mentions diets or fitness centers in talks with them.

Table 4

Calculating relative risks развития of fat metabolism disorders in women of reproductive age

Risk factor	*RR*	Low limit of 95 % *CI*	Upper limit of 95 % *CI*	*p*	Correlation strength
Nutrition	3. 333	1. 959	5. 669	<0.001	Average*
Physical activity	2. 617	1. 583	4. 327	<0.001	Average*
Age 35+	2.036	1. 594	2. 601	<0.001	Average*
Smoking	1.790	1. 376	2. 330	<0.001	Average*
Cold season	1.174	0. 870	1.585	0. 286	Insignificant***
Gastrointestinal tract and liver diseases	1.499	0. 937	1. 536	0. 002	Average*
Sleep disorders	1. 456	1. 060	2. 001	0. 016	Weak**

Note: * means average correlation at $RR > 1.450$; ** means weak correlation at $RR = 1.449$–1.2; *** means insignificant correlation at $RR < 1.2$.

Recommended physical loads often result in patients being disappointed as they don't allow achieving fast and significant weight loss; it is due to redistribution of fat mass that goes down whereas muscle mass grows. And in spite of a low decline in overall body weight there is a decrease in visceral fat; it results in insulin becoming more sensitive to tissue receptors. Single short-term physical loads (less than 45 minutes) provide only liver glycogen expense while long-term ones (more than 45 minutes) lead to fat deposits losses [22].

Genetically people are prone to fat accumulating before a cold season starts [23]. It was very important for our predecessors. Fat tissue had several functions; it protected from cold and provided necessary energy in late winter and early spring when food reserves were scarce. Another probable reason for this seasonal increase in weight is influence exerted on a human body by hormones. Changes in their levels result in changing appetite, in this case, in its growing, and we subconsciously start to eat more fatty food. Besides, shorter daylight hours in winter can lead to a seasonal depression, and an efficient way to elevate one's mood is to increase consumption of products that contain carbohydrates in high quantities (chocolate, sweets, buns, cakes, etc.). Most people tend to have significantly low PA in winter. Another reason is a decrease in vitamin D quantity that results in slower fat break-up and induces its accumulation [20]. According to our data, there were no revealed correlations between a seasonal factor (winter-summer) as overweight predictor and obesity (Table 4).

Low melatonin concentration caused by sleep disorders produces negative effects on metabolism. As per data given by E. Van Cauter, repeated nights with not enough sleep reduce sensitivity to insulin without its compensatory secretion [24]. In our research we detected a weak correlation between sleep disorders as a risk factor and obesity (*RR* 1.456 at *CI* 1.060–2.001 $p = 0.016$). It can probably be due to examined women being young as the factor becomes truly significant during menopause [19].

There was an average correlation between smoke and fat metabolism disorders; smoking women ran 1.8 times higher risk of obesity than non-smoking ones. Android obesity occurrence turned out to be statistically significant for smoking women against non-smoking ones with excess fat tissues in their bodies ($p < 0.05$) (Figure 3). There is a positive correlation between a number of smoked cigarettes and abdominal fat accumulation [25]. Nicotine makes for developing resistance to insulin and type-II diabetes occurrence; it also contributes into lipid profile shifting towards atherogenicity. Even if smoking people probably weighed less than in case they didn't smoke, they still had high contents of visceral and subcutaneous fat tissues thus running elevated risks of cardiovascular diseases [26].

Effects produced by nicotine make people strongly addicted to it and it is a basic reason for smokers constantly craving for cigarettes. Giving up smoking often results in growing body weight and it is the main obstacle that prevents smokers, especially female ones, from abandoning this bad habit or makes them return to it shortly after giving it up [25]. Therefore, an issue related to determining what is a cause and what is an effect in «smoking – obesity» correlation requires further investigation.

Chronic gastric and liver diseases (gastroesophageal disease, non-alcoholic hepatosis, and cholelithiasis in a compensation period) as a risk factor had average correlation with obesity with relative risk being equal to 1.499. When body weight grows, certain changes occur in it and they can become a pathogenetic basis for occurrence of many diseases in the digestive organs [27]. Pathophysiological processes occurring in

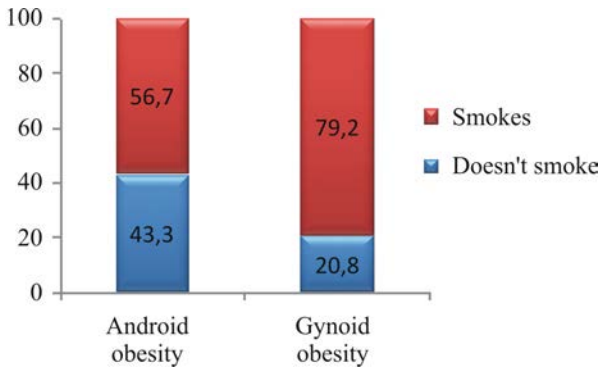

Figure 3. Number of smoking women (%) in the test group Depending on obesity type

a person with obesity, such as elevated abdominal pressure, excess synthesis of adipokins and cholesterol, elevated secretion of free fatty acids, result from excess fat tissue accumulation and redistribution in a body. Therefore, these diseases can be considered an outcome caused by obesity and not a cause of it. A certain vicious circle occurs when obesity causes diseases and they, in their turn, induce further weight increase.

Conclusions. Therefore, our research allowed revealing a significant correlation between elevated risk of overweight and obesity and unsatisfactory nutrition stereotypes (*RR* = 3.3); low physical activity (*RR* = 2.6); age being 35 and older (*RR* = 2.1); smoking (*RR* = 1.8), gastric and liver diseases (*RR* = 1.5); sleep disorders (*RR* = 1.5). It is necessary to implement efficient activities in public healthcare aimed at motivating fertile Russian women to pursue healthy lifestyle and keep fit. Patients with overweight and obesity should be treated as running high risks associated with fat metabolism disorders not only in themselves but in their future children as well. Monitoring over weight should become a standard procedure during preparation to pregnancy and birth. It is primary healthcare clinics that can successfully implement programs aimed at control over weight. Doctors of all specialties should bear responsibility for preserving health of future parents and new generations. To changes one's lifestyle is simultaneously a very simple and very complicated task that can be solved only by combining efforts made by both patients and their doctors.

Funding. The research was not granted any sponsor support.

Conflict of interests. The authors declare there is no any conflict of interests.

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Received: 20.11.2019
Accepted: 02.06.2020
Published: 30.06.2020

UDC 613.955
DOI: 10.21668/health.risk/2020.2.05.eng

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HYGIENIC OPTIMIZATION OF EDUCATIONAL PROCESS AT SCHOOL INVOLVING MASSIVE USE OF ELECTRONIC LEARNING DEVICES

I.E. Aleksandrova

National Medical Research Center for Children's, 2 Bld., 1 Lomonosovskii Ave., Moscow, 119991, Russian Federation

Active use of electronic learning devices (ELD) in educational process increases its efficiency and makes knowledge more available to children; but at the same time it creates risks for schoolchildren's health. Intense visual and information loads can result in schoolchildren being over-exhausted.

Our research goal was to give scientific grounds for hygienic optimization of education process (a typical class and a schedule) that would allow preventing apparent exhaustion in schoolchildren studying in a digital environment.

To solve the fixed tasks, we applied hygienic, physiological and statistical research techniques. We analyzed factors occurring in school environment and components in education process structure; we examined parameters of body functional state (BFS) on a sampling made up of more than 600 schoolchildren attending 5–9th grades, namely, parameters that characterized their mental and visual working abilities.

Results were statistically processed with parametric and non-parametric analysis techniques. Relative risks of unfavorable outcomes in body functional state were calculated as per evidence-based medicine principles depending on how education process was organized (a structure of a class and classes schedules).

We developed methodical approaches to hygienically rational organization of a class and schedule provided that school environment was optimal (microclimate, luminance, electromagnetic fields, furniture in rooms, etc.) and electronic learning devices were applied according to age-related regulations.

Research results proved that implementation of suggested approaches would make for favorable dynamics of children's functional state as well as prevention of education-related diseases.

***Key words**: schoolchildren, digital environment, over-exhaustion, hygienic optimization, class, schedule, body functional state, prevention of education-related diseases.*

In a hyper-information society, one of the most important tasks is to preserve health of the younger generation. Digital environment has a serious impact on behavior, lifestyle and forms additional risk factors for the health of children and adolescents [1, 2]. There is an increase in information load and psycho-emotional overexertion, growth of information dependence in various forms [3–5], an increase in the prevalence of borderline mental and behavioral disorders in children and adolescents [6]. The extended use of the Internet by children is associated with a decrease in verbal intelligence and brain development disorders in the area responsible for speech, attention, emotions, etc. [7]. A significant number of publications' authors relating to digital media impact on health characterize their use by nowadays children and adolescents as excessive, which is seen as the main factor that can hinder the formation of a «healthy psycho-physiological tolerance» [8–12].

At the same time, the main and most noticeable trend in current education is primarily associated with the increasing use of digital tools in educating children and adolescents. Having huge opportunities that increase the education efficiency, studying within digital environment forms a complex of factors that have a potentially negative effect on schoolchildren health. These factors include an increased visual load, intensification of learning work, increased static tension and hypokinesia [13, 14].

In recent years, the impact of the most common ELDs (personal computer, laptop, interactive whiteboard, tablet) on schoolchildren's BFS has been studied [15–18]. The works showed that the unregulated use of ELDs in educational process causes deteriora-

Irina E. Aleksandrova – Doctor of Medical Sciences, Chief researcher at the Laboratory for complex problems of children and teenagers hygiene (e-mail: accialex@yandex.ru; tel.: +7 (495) 917-10-60; ORCID: https://orcid.org/0000-0002-8664-1866).

tion of general physical and mental condition, decrease in visual, mental working capacity of students, impossibility to keep optimum visual distance; makes for formation of a «forward» working posture in a student.

As a result of analyzing changes in functional state of students' bodies in a lesson dynamics, based on different time-periods of ELDs using, the tolerable duration for their use was determined, exceeding which the significant negative dynamics of BFS indicators was detected. In the course of this research, regulations were established for safe use of: computer, interactive board and laptop at lessons, escalatory influence of ELDs on educational activity and student's BFS is shown provided their rational, in terms of hygiene, application [17, 18]. Positive effect was expressed, first of all, in emotional activation of central nervous system, optimization of visual analyzer function, increasing level of mental working abilities of a student.

Using electronic devices changes the tedium of a lesson for students. Research was carried out to identify factors that determine exhaustion from a current lesson in school. It was established that the multi-component concept of a lesson' tedium includes: difficulty of an educational subject, student's abilities and inclinations, conditions of education. The difficulty scales of educational subjects were justified to organize educational schedules for 1–9 grade students and its hygienic assessment [19].

Teachers themselves, assessing positively the effect of current digital lessons on schoolchildren development, also noted the increase in informational load, intensification of learning activities [20, 21].

The emergence of new risk factors for the development and health of students who are almost permanently in a «digital school» environment necessitates their comprehensive study. Along with the inter-school environment conditions (including physical parameters of ELDs themselves, their placement, regulations for operation, etc.) and the duration of e-Learning tools using, it is necessary to assess, in terms of hygiene, the organization of a current learning process: architecture of a school lesson, a schedule. Only this approach will give an opportunity to take into account and minimize the eventual health risks for schoolchildren.

The goal of the present research was to give the scientific grounds for hygienic optimization of educational process to prevent an apparent exhaustion in schoolchildren studying in the conditions of digital environment.

To achieve this goal, the following tasks were solved:

– to study the relationship between BFS indicators of students and indicators characterizing the organization of a lesson;

– to study the effect of preventive actions at a lesson with ELDs on indicators of mental and visual working abilities;

– to justify hygienic assessment technique for a lesson;

– to study the correlation of students BFS indicators with the «hygienic rationality» of a lesson schedule.

Data and methods. We applied a complex of hygienic, physiological, and also statistical methods of research.

In conditions of using ELDs for lessons, we assessed factors of school environment and BFS parameters of 607 students in 5–9 grades. The research was based on the study of mental working abilities (MWA), which is an overall indicator of BFS in children[1]. MWA is of crucial importance for learning activities. MWA was assessed based on the results of the corrective test – a time-proportioned technique which allows for obtaining information about the major parameters that characterize mental performance: quantity of works performed and quantity of errors made. The ratio of these parameters determines the work productivity, and it is given a comprehensive assessment («excellent», «good», «satisfactory», «bad», «unsatisfactory»). Based on the sum ratio of «excellent» and «good» marks to the sum of «bad» and 'unsatisfactory' ones, an overall indicator of a class working ability is calculated.

[1] Unified Methodology for Hygienic Study of Organizing the Conditions and Regime of Computer-Assisted Educational Classes: Methodical Recommendations (in Russian). In: G.N. Serdyukovskaya ed. Moscow, 1987, 91 p. (in Russian).

Functional state of the central nervous system in dynamics was assessed taking into account the nature of individual changes in working abilities from the beginning to the end of a lesson. To analyze the effect of a teaching process' organization on schoolchildren's MWA, we chose the most «unfavorable» variations in changes reflecting the apparent and expressed exhaustion, when there was a decrease (preservation) in the number of characters viewed at the same (the increasing) number of errors, or a decrease in the number of viewed characters at increasing errors.

In a school day dynamics, the MWA indicators of 211 schoolchildren attending 5–9 grades with different lessons organization (varying density of a lesson, varying number of learning activities) and drawing-up an educational schedule (at different compliance with hygienic recommendations) were evaluated.

We assessed MWA indicators in 396 secondary school students (grades 5–9) depending on the presence (or absence) of a set of preventive measures (ophthalmic exercises and physical activity) during class. In addition, visual exhaustion indicators were studied in this group of children. We used methods to determine critical flicker fusion frequency (CFFF), accommodation amplitude and fatigue level of ciliary muscle. CFFF study technique is designed to determine the lability of visual analyzer cortical link, which, if decreasing, is evidenced by a decrease in the frequency of individual light flickers differentiation that allows talking of visual fatigue of a student. Accommodation amplitude characterizes the change in eye optical power during accommodation, and the fatigue level of the ciliary eye muscle is characterized by the fatigue factor – the percentage ratio of the difference between accommodation amplitudes at the beginning and at the end of observation to the initial accommodation amplitude. A negative value of the fatigue factor indicates an increase in accommodation amplitude, while a positive one speaks for its decrease.

In order to identify the nature and duration of various learning activities in a lesson, we used a stop-watch study. The stop-watch study in organization of 32 lessons was carried out. We estimated the lesson density (the lesson amount of time spent on learning activity to the total lesson time, in percentage), the number of changes of learning activity types.

The educational schedule was analyzed using the «Electronic methodical complex for hygienic assessment of school schedule»[2] created by the authors based on the new scales of difficulty for academic subjects, designed with reference to the current application of ELDs in lessons. Fifteen options for daily schedules and five options for weekly school timeschedules were assessed. The hygienic rationality in drawing up a schedule was determined, first of all, by correspondence of the dynamics of educational subjects' difficulty during a school day (week) to the physiological «curve» of schoolchildren's MWA [22–24].

The results were statistically processed using parametric and non-parametric analysis techniques. Following the principles of evidence-based medicine, we determined the values of relative risk – the probability of «unfavorable» BFS indicators in students depending on the educational environment (lesson construction, educational schedule), which, along with hygienically inefficient organization, become the «risk factors». The number of «unfavorable» BFSs occurred was correlated with the lessons of different density (70 % and below: over 70 %; 80 % and below: over 80 %; 90 % and below: over 90 %), and the varying number of changes in educational activities (5 and below: more than 5; 6 and below: more than 6; 7 and below: more than 7), as well as with studying against the school schedule drawn up with the different rationality (rational – irrational), from the point of hygiene. So, for example, the lesson density of over 90 % means «risk factor available», and the lesson density of 90 % and below – «risk factor absent», the number of schoolchildren with

[2] Aleksandrova I.E., Stepanova M.I., Kurganskiy A.M. Electronic Methodical Complex for Hygienic Assessment of School Schedule. Object of intellectual property, database: Certificate No. 2017621265 of 01.11.2017. Bulletin No. 11-2017 (in Russian).

an «unfavorable» type of BFS by the end of the lesson means «outcome present», schoolchildren with no «unfavorable» type of BFS by the end of the lesson means «no outcome», etc.

This way the 4-blocks table of conjugation was filled in (Table 1).

Table 1

Conjunction table

Indicator	Outcome present (1)	No outcome (0)	In-Total
Risk factor available (1)	A	B	A + B
Risk factor absent (0)	C	D	C + D
In-Total	A + C	B + D	A + B + C + D

The value of relative risk was determined by a formula:

$$RR = (A / (A + B)) / (C / (C + D)) = \\ = (A \cdot (C + D)) / (C \cdot (A + B)), \quad (1)$$

where A, B, C, D are the number of observations in the conjugation table fields. After determining the boundaries of the 95 % confidence interval (not including the unit) we compared the values of relative risk with the unit: we took values over 1, considering that the factor increases the frequency of outcomes. We calculated: sensitivity (A/A+C·100) and specificity of methods D/B+D·100. The etiologic factor (EF) for the lesson organization impact on schoolchildren's MWA, which causes an apparent and expressed exhaustion, was determined according to the «evaluation degree of causal connection of health disorders with activities»[3].

Results and discussion. The classroom conditions, where the research took place, were optimized to the maximum extent possible following the requirements of sanitary regulations. All ELDs used for the lessons had the necessary documentation allowing their use in children's educational institutions.

In the course of analysis, we selected students with «unfavorable» changes in MWA by the end of the lesson, reflecting the development of their apparent and expressed exhaustion.

We determined relative risk (*RR*) for occurrence of the indicated MWA changes depending on such indicators of the lesson organization as lesson density, educational activity changes frequency (Table 2).

The significant risk of increasing the apparent and expressed exhaustion events in schoolchildren was recorded at the lessons with educational density of over 90 % and with frequency changes in educational activity exceeding 7. In other options of lesson organization, no similar risk was revealed ($RR < 1$).

The etiologic factor of a lesson organization impact on MWA of schoolchildren, which causes an apparent and expressed exhaustion, was described as «high» degree (57.3 %) – for lesson educational density (above 90 %) and «average» degree (41.1 %) – for the frequency of changes in educational activities (above 7), because the duration and consistency of school factors impact on the growing body defines the need to assessing them in a similar way to professional ones.

Table 2

Relative risk of apparent and expressed exhaustion in schoolchildren as a function of lesson organization

BFS indicators of a student	Lesson organization indicators	*RR*	*CI**	*EF*, %	*Se*	*Sp*
Changes in MWA indicators, reflecting an apparent and expressed exhaustion in students	Lesson density over 90 %	3,34	2,47–4,49	57,3	0,46	0,94
	Over 7 changes of educational activity	2,5	1,4–3,2	41,1	0,96	0,37

N o t e: *$p < 0.05$; *RR* – Relative risk, *CI* – Confidence interval, *EF* – Etiologic factor, *Se* – Sensitivity of method, *Sp* – Specificity of method.

[3] Izmerov N.F., Denisov E.I. Occupational Health Risks to Workers: A Guidance. Moscow, 2003, 448 p. (in Russian).

Table 3

MWA dynamics of students in lessons with and without preventive measures (ophthalmic exercises and physical activity breaks)

Indicators		5–9 grades			
		Lessons with preventive actions		Lessons without preventive actions	
		Lesson start	Lesson end	Lesson start	Lesson end
Number of research studies		199	199	197	197
Number of characters viewed, $M \pm m$		296.7±2.3	304.7±2.1	301.7±2.5	282.6±3.1
Number of standardized errors per 500 ch., $M \pm m$		7.11±0.19	6.97±0.21	6.54±0.17	7.30±0.19
Overall performance indicator, conventional units		0.95	1.25	1.51	0.96
Share of MWA changes with apparent and expressed exhaustion, %			28.8		35.7
CFFF	Number of research studies	100	98	57	56
	$M \pm m$, Hz	26.8±0.21	26.4±0.22	31.5 ±0.31	27.6±0.29*
Accommodation	Number of research studies	56	56	55	51
	Accommodation amplitude, diopter	13.9±0.30	13.5±0.30	14.2±0.30	12.8±0.30**
	Ciliary muscle fatigue coefficient, %		+3.1		+9.7

Note: * – $p < 0.05$; ** – $p < 0.01$; MWA – Mental Working Ability, CFFF – Critical Flicker Fusion Frequency.

Also, our research confirmed the effectiveness of preventive activities (ophthalmic exercises and physical activity) in the lessons with using ELDs (Table 3).

After the lessons with the preventive actions taken, the indicators of students' mental and visual working abilities improved. Thus, the overall performance of a class (the sum ratio of «excellent» and «good» marks of MWA to the sum of «bad» and «unsatisfactory» ones) increased by the end of the lesson, which included ophthalmic exercises and physical activity breaks and, on the contrary, decreased in the «control» class. In addition, there was a significant decrease in flicker discrimination frequency in children at the lesson without preventive actions taken (from 31.55 ± 0.31 Hz to 27.6 ± 0.29 Hz, $p < 0.05$), a decrease in accommodation amplitude and, accordingly, the fatigue rate of ciliary eye muscle.

The data obtained on the dependence of students' BFS on a lesson educational density, frequency of changing the types of teaching activities, availability of preventive measures in a lesson (taking into account the earlier researches outcomes [12, 13] to prove regulations for using ELDs in lessons) made it possible to substantiate the hygienic assessment technique for a lesson under conditions of using ELDs.

The technique consists in scoring a lesson by the following parameters:

1. Lesson educational density (90 % max);
2. Number of changes in types of educational activity (max 7);
3. Duration of continuous using ELDs (following the age-related regulations);
4. Duration of ELDs using in total (per lesson) (following the age-related regulations);
5. Set of preventive measures available.

1 point is assigned for each parameter, if hygienic recommendations are met, for non-compliance – 0 points. According to the final (total) score of a lesson, the certain level of hygienic rationality was assigned in the following way: hygienically rational lesson: 5 points; insufficiently rational lesson: 3–4 points (herewith each parameter of a lesson no. 1, no. 3, no 4 must be evaluated as 1 point); and hygienically irrational lesson: 2 or less points.

This technique for lessons hygienic assessment is recommended to be used both by an educational organization (administration, teachers, medical professionals) for educational process «self-audit» in order to reduce its tedious effect on student body, as well as by specialists of Rospotrebnadzor agencies in the course of surveillance activities.

An important component of the educational process organization is the schedule of lessons.

We assessed the interrelation between an impact of the irrational, from the hygienic point of view, schedule, and the outcomes – the number of schoolchildren having changes in MWA reflecting the expressed exhaustion by the end of the school day: significant values of relative risk have been established (Table 4). The etiologic component of the factor – irrationality of the weekly schedule: 53.3 % which was estimated as high correlation between the factor and the outcome. The etiologic component of the factor that reflects the weekly schedule irrationality: 30.7 % was estimated as «average» correlation between the factor and the outcome.

The prevalence of indicators for expressed exhaustion in students increases, when they study against the irrational school schedule (without using an updated «scale of difficulty» for educational subjects created with respect to wide application of ELDs in lessons).

Conclusion. The electronic media widely introduced into current school education causes new health risks for students. The hygienic assessment of «digital» factor of a school environment along with characteristics of an electronic learning device itself, its placement conditions, etc. also entails the analysis of educational process organization: of lesson, of schedules.

The work substantiates optimal, in physiologically-hygienic context, structure of a lesson with using ELDs. We proved the significant risks of increasing the apparent and expressed exhaustion indicators of schoolchildren at the lesson density exceeding 90 % ($RR = 3.34$); at frequency of changes in educational activity of more than 7 ($RR = 2.5$), and the efficiency of preventive actions at a lesson is confirmed. The proposed technique of a lesson hygienic assessment will allow for timely correction of its organization.

Significant risks of unfavorable changes in mental working ability in the dynamics of education against irrational (without taking

Table 4

Relative risk of expressed exhaustion among students depending on hygienic rationality of school schedule

Student's indicator of BFS (Outcome)	Educational process factor	*RR*	*CI*	*EF*	*Se*	*Sp*
Changes of MWA indicators reflecting expressed exhaustion of students	1. Non-compliance of the academic subjects «difficulty curve» with the weekly dynamics of mental working ability	2.13*	1.04–3.22	30.7	0.84	0.42
	2. Non-compliance of the academic subjects «difficulty curve» with the daily dynamics of mental working ability	2.64*	2.13–3.27	53.3	0.29	0.96

Note: – $p < 0.05$; *RR* – Relative risk; *CI* – Confidence interval; *EF* – Etiologic factor; *Se* – Sensitivity of method, *Sp* – Specificity of method.

into account the academic subjects difficulty using the updated scales) weekly and daily school schedules (respectively $RR = 2.13$ and $RR = 2.64$) were established.

Hygienic optimization of a lesson and a school schedule in the conditions of digital environment, including also the methodical tools proposed for use, will contribute to maintain favorable dynamics of a students' body functional state and reduce risks of developing an over-exhaustion in process of learning.

Funding. The research was not granted any sponsor support.

Conflict of interests. The authors declare there is no any conflict of interests.

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Received: 13.02.2020
Accepted: 09.06.2020
Published: 30.06.2020

UDC 331.461.2:616-089.168.86(470.57)
DOI: 10.21668/health.risk/2020.2.06.eng

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RISK OF A SUDDEN DEATH AT A WORKPLACE CAUSED BY NON-OCCUPATIONAL DISEASES IN BASHKORTOSTAN

L.K. Karimova[1], N.A. Muldasheva[1], A.B. Bakirov[1], Z.F. Gimaeva[1,2], L.N. Mavrina[1]

[1]Ufa Research Institute of Occupational Health and Human Ecology, 94 Stepana Kuvykina Str., Ufa, 450106, Russian Federation
[2]Bashkir State Medical University, 3 Lenina Str., Ufa, 450008, Russian Federation

The article deals with a pressing issue in occupational medicine, namely, examining sudden deaths at workplaces caused by non-occupational diseases. It contains statistical data on sudden deaths of workers at their workplaces caused by non-occupational diseases in different economic entities operating in Bashkortostan; there are data on basic death causes revealed via forensic medical examinations; economic branches are ranked as per levels of risks related to sudden deaths at workplaces.

We detected that 268 people died due to non-occupational diseases at enterprises located in Bashkortostan. Number of people who died due to non-occupational diseases at their workplaces increased from 36 to 42 % out of the whole number of people who died at their workplaces. Most frequently sudden deaths occurred among people aged 56–60, with long work experience and blue-collar occupations. Given that, we can assume that there were adverse factors related to working environment and labor process at their workplaces; those factors could produce certain effects on a body during the whole period of working and could aggravate risks of sudden death.

Hidden cardiovascular pathology or a cardiovascular disease that has not been diagnosed while a worker was still alive is a major etiologic factor of a sudden cardiac death.

Most common diseases that cause sudden deaths and risks groups have been determined, and it calls for the necessity to improve periodical medical examinations involving medical experts with necessary specializations and applying a wider range of diagnostic procedures. We have developed a program aimed at reducing risks of sudden deaths at a workplace caused by non-occupational diseases; the program includes a basic set of preventive activities aimed at preventing or reducing probability of a sudden death at a workplace.

Key words: *sudden death, mortality, production, non-occupational diseases, workplace, preventive activities, cardiovascular system, circulatory system diseases, working conditions.*

Sudden deaths at a workplace remain a pressing issue all over the world. According to estimates made by the International labor Organization (ILO), approximately 2.3 million men and women annually die due to accidents that happened at their workplace or due to work-related diseases; on average, it amounts to 6,000 thousand people every day [1, 2].

As Hans-Horst Konkolevsky, General Secretary of the International Social Security Association (ISSA) stated during the 4th All-Russian Week of Labor Protection (2016), annually 2.8 million people die at their workplaces. And only 15 % of all these deaths are caused by industrial accidents whereas most of them result from health disorders [3, 4]. Circulatory system diseases cause the greatest share of sudden deaths at a workplace and it often happens they have not been diagnosed while a worker was still alive [5–9].

First sudden deaths at workplaces were fixed in 1969 in Japan; they were called «karoshi» that meant sudden death at a workplace due to cardiac infarction or a stroke

Liliya K. Karimova – Doctor of Medical Sciences, Professor, Chief researcher at the Occupational Medicine Department (e-mail: iao_karimova@rambler.ru; tel.: +7 (347) 255-57-21; ORCID: https://orcid.org/0000-0002-9859-8260).

Nadezhda A. Muldasheva – Researcher at the Occupational Medicine Department (e-mail: muldasheva51@gmail.com; tel.: +7 (917) 416-44-42; ORCID: https://orcid.org/0000-0002-3518-3519).

Akhat B. Bakirov – Doctor of Medical Sciences, Professor, Bashkortostan Academy of Sciences Academician, Director (e-mail: fbun@uniimtech.ru; tel.: +7 (347) 255-19-57; ORCID: https://orcid.org/0000-0001-6593-2704).

Zul'fiya F. Gimaeva – Candidate of Medical Sciences, Senior researcher, Associate Professor at the Department for Therapy and Occupational Diseases (e-mail: gzf-33@mail.ru; tel.: +7 (927) 312-11-97; ORCID: https://orcid.org/0000-0001-6668-2196).

Liana N. Mavrina – Candidate of Biological Sciences, Senior researcher at the Occupational Medicine Department (e-mail: Liana-1981@mail.ru; tel.: +7 (903) 35-39-307; ORCID: https://orcid.org/0000-0002-0250-2683).

caused by exhaustion, overwork, and stress [10–15]. It was established that deceased people worked 80 hours more per month that they had to in 90 % cases; in 50 % cases they worked 100 hours more than it was actually required by their working schedule. In relation to that, in 2016 a law was passed in Japan that imposed a limitation on excess working hours (45 hours per month, 360 hours per year) for workers employed by large companies [16].

A correlation between long working hours and cardiovascular diseases was confirmed in multiple research works performed in Europe, Asia, and the USA [17–20].

According to some predictions, in the nearest future a risk of sudden death caused by cardiovascular diseases is going to grow among employable population due to rowing prevalence of such risk factors as labor intensity and intense life tempo [9, 21].

Russian research works devoted to determining frequency and clinical and morphological signs of sudden death mostly focus on workers with hazardous occupations such as motor transport drivers, engine drivers, pilots, sailors, coal miners, etc. [22–27].

The most complete data were obtained from the Russian Independent Trade Union of Coal Miners; according to those data, over a period from 2000 to 2013 approximately 2,000 acute cardiovascular deaths occurred among coal miners and overall number of workers who died at their workplaces was considerable higher than a number of those who perished in methane explosions in a mine; the trend was observed in different years. Cardiac infarction was established to be the most frequent cause of sudden death [28].

Given all that, it seems vital to epidemiologically assess prevalence of sudden death at a workplace due to natural reasons and to determine risk groups with the subsequent development of relevant prevention programs. As the issue is truly urgent, it requires full-scale research on frequency and peculiarities of sudden deaths at workplaces occurring at enterprises operating in various branches [29].

Our research goal was to examine reasons of sudden death at a workplace due to non-communicable diseases that were not work-related (common ones) and to develop a scientifically grounded program aimed at preventing and reducing them; enterprises and organizations operating in Bashkortostan were taken as our examples.

Data and methods. In order to achieve the fixed goals, we examined a database provided by the State Labor Inspection, Bashkortostan Regional Office, collected in 2014–2018.

In order to perform comprehensive analysis of sudden deaths at workplaces, we analyzed each case when a worker died at a workplace due to a common disease and we paid great attention to specific circumstances and causes of deaths obtaining all the necessary data from reports on investigations of accidents.

Sudden deaths at workplaces at specific enterprises were summed up as per economic activities and it allowed us to obtain absolute data on a number of deceased, make up a list of organizations with the greatest number of sudden deaths at workplaces due to common diseases and to generalize data as per the following parameters: economic activity types in absolute figures; legal forms of enterprises; positions held by deceased workers; workers' sex and age; data and time at which an accident occurred (month, day of week, time); working conditions categories according to the specific assessment of working conditions; work and leisure regimes; medical examinations; causes of death (disease).

To determine frequency of worker's sudden death at a workplace at different enterprises, we calculated relative mortality at a workplace due to common diseases as per different types of economic activities performed in Bashkortostan. Deaths were calculated per 1,000 workers taking into account average number of workers employed by one company according to data provided by the Federal state Statistic Service, Regional Office in Bashkortostan.

Mortality at a workplace due to common diseases was calculated as per economic activities according to the Russian Classifier of Economic Activities (RCEA). We applied

the older version, RCEA029-201, to analyze data collected in 2014–2016, and a new one, RCEA-2 (RCEA0.29-2014), to analyze data collected in 2017–2018. Then all the data were systematized according to the comparison table that allowed comparing old and new codes.

Death causes due to common diseases were classified as per the International Classification of Diseases (ICD-10).

Results and discussion. We established that totally 268 workers died at their workplaces due to common diseases in Bashkortostan over the analyzed period. It is rather alerting that in the analyzed period a share of workers who died at their workplaces due to common diseases grew from 36 to 42 % of the total number of those who died at workplaces.

We analyzed sudden deaths at workplaces due to common diseases as per legal form of enterprises or organizations where such deaths occurred. The analysis revealed that 40 % sudden deaths occurred in limited liability companies (LLC); 29 %, state and municipal organizations; 11 %, joint-stock companies; 8 %, closed corporations; and 6 %, public companies.

We calculated mortality due to common diseases per 1,000 workers as per economic activity types and revealed that the first rank place in 2014–2016 belonged to production and distribution of electricity, gas and water (0.11‰), and in 2017–2018, to information and telecommunication (0.21‰).

Over the analyzed period 32 vehicle drivers died when they were performing their work tasks. It is well known that working conditions for drivers involve great psychoemotional strain together with hypodynamia as well as exposure to such occupational factors as vibrations, noise, and contamination of working area air with hazardous substances.

Over the analyzed period 13 tractor, bulldozer, and engine drivers died at their workplaces. These occupations involve exposure to specific occupational factors that are mostly physical in their essence (noise and vibration), as well as forced body postures, hypodynamia, and necessity to work in shifts.

All these data indicate that workers with these occupations run higher risks of sudden death at a workplace.

Having analyzed sudden deaths as per gender, we revealed that men died more frequently than women. Gender-related ratio of sudden deaths at a workplace is shown in Figure 1.

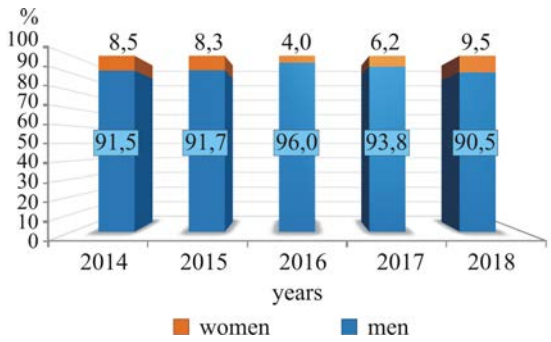

Figure 1. Gender-related ratio of sudden deaths at a workplace due to natural reasons (%)

We detected a decrease in frequency of sudden deaths due to common diseases depending on age. Both men and women aged 56–60 died most frequently (Figure 2).

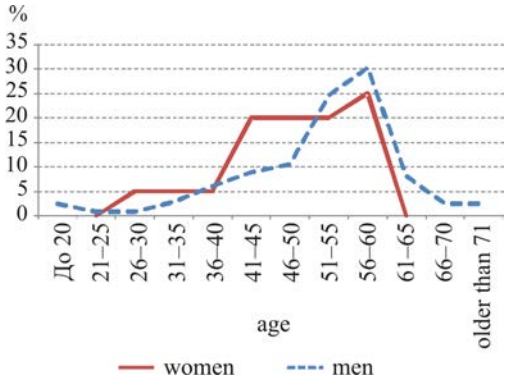

Figure 2. Frequency of sudden deaths due to common diseases among men and women in different age groups (%)

We didn't reveal any authentic discrepancies in number of sudden deaths taken as per months or days of week. As for sudden deaths being distributed as per time of a day, we revealed that the greatest number of sudden deaths occurred in the morning (from 7 a.m. to noon) and in the afternoon (from 1 to 6 p.m.), 44.4 % and 35.8 % accordingly. There were a bit fewer sudden deaths in the evening and at night (10.8 %).

We revealed that most deceased workers (61.6 %) performed their work tasks at workplaces with working conditions category being acceptable as per data obtained via specific assessment of working conditions (SAWC). 22.3 % deceased worked under hazardous conditions; 15.3 %, under working conditions belonging to 3.1 hazard category; 6.3 %, 3.2 hazard category; 0.7 %, 3.3 hazard category; there were no data on working conditions category for 16 % deceased workers (Figure 3).

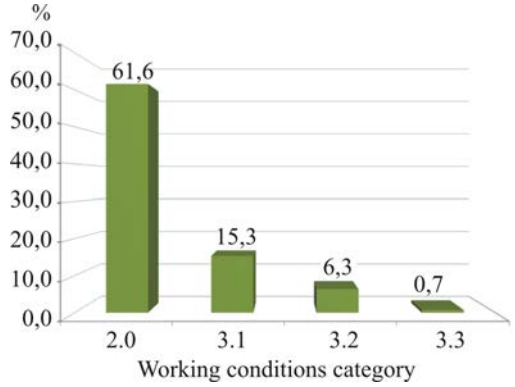

Figure 3. Working condiitons category as per sepcial assessment of working conditions for workers who died at their workplaces due to common diseases (%)

We should note that workers with long work experience died most frequently, overwhelming majority of them being blue-collar workers (88 %). Having analyzed forensic reports, we revealed that sudden deaths at workplaces were due to circulatory system diseases (91.4 %); respiratory organs diseases (1.9 %); urogenital system diseases (0.4 %); anaphylactic shock and hypothermia (0.8 and 0.45 % accordingly). We can assume that deceased workers had been exposed to adverse occupational factors at their workplaces and the said exposure might have been producing adverse effects on their health and might have become an aggravating risk factor that caused sudden death. Results obtained via investigations of lethal accidents due to common diseases allowed establishing that only 19 % deceased workers had undergone an obligatory medical examination prior to being employed, and only 42.2 % had had periodical medical examinations.

According to the Order by the RF Public Healthcare Ministry issued on April 12, 2011 No. 302n, groups of workers that are to have obligatory medical examinations are determined basing on the results of SAWC depending on adverse and/or hazardous occupational factors occurring at workplaces[1].

But still, it is not likely that data on working class category that existed at workplaces where deceased workers performed their functions are truly authentic. They were obtained via SAWC and it is practically impossible to adequately assess working conditions with this procedure due to certain parameters being groundlessly excluded from it; first of all it comes to parameters that make working conditions more hazardous. Special assessment of working conditions at a given workplace is to be accomplished every five years, except some specific cases. Results obtained via industrial control procedures that are accomplished annually could provide more comprehensive data on variety and levels of exposure to adverse occupational factors; unfortunately, these results are absent in the research data.

Consequently, should working conditions be assigned not so hazardous category as they should be, it results in absence of obligatory medical examinations for workers aimed at determining whether their health corresponds to working tasks they have to perform; absence of timely diagnostics of diseases that can turn out to be medical contraindications for further work that involves exposure to hazardous factors; occupational diseases not being detected at their initial stage.

[1] On Approval of the list of adverse and(or) hazardous occupational factors and work tasks that require obligatory preliminary and periodical medical examinations, and of the procedure for accomplishing obligatory preliminary and periodical medical examinations of workers who are employed at workplaces involving hard labor or workplaces with adverse and (or) hazardous working conditions: The Order by the RF Public Healthcare Ministry issued on April 12, 2011 No. 302n (last edited on May 18, 2020). *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_120902/ (19.01.2020) (in Russian).

To obtain authentic data on working class category, it is necessary to harmonize legislation on SAWC and sanitary-hygienic requirements regarding lists of occupational factors and factors related to labor process that are to be examined and measured. Should there be any doubts in quality of performed special assessment of working conditions when an investigation of accident is taking place, we believe it is necessary to submit SAWC results for a state inspection. These data are to be inspected and working conditions are to be reassessed by state experts.

It is also difficult to interpret data due to different approaches to putting up diagnoses used by clinical experts, pathologists, and forensic scientists; sometimes diagnoses from pathologists' reports do not coincide with the International Classification of Diseases (ICD-10).

As we can see form the data given above, circulatory system diseases (CSD) caused sudden death at a workplace in more than 90 % cases. Having looked into it in greater detail, we revealed certain gender-related differences. Thus, men mostly died due to «Other ischemic acute heart diseases» (53.8 %); «Acute myocardial infarction» (11.5 %); «Other forms of chronic ischemic heart diseases» (10.3 %). Women mostly died due to «Other ischemic acute heart diseases» (47.4 %); «Intracerebral hemorrhage» (26.3 %); «Cerebral infarction» (10.4 %).

Consequently, a basic etiologic factor that causes sudden cardiac death is a hidden pathology in the heart and vessels that wasn't diagnosed while a worker was still alive or a cardiovascular system disease that was compensated by the moment of death.

We can assume that people who suffered from cardiovascular system diseases didn't have any medical examinations and therefore were allowed to perform their work tasks under hazardous working conditions.

Determinations of risk groups and most common diseases that cause sudden death calls for improvements in periodical medical examinations with wider participation of medical experts with various specialties and wider range of applied diagnostic procedures.

There are no data in the research on a deceased worker having to work longer hours; whether he or she took annual paid vacations or additional ones during the whole period of work; whether he or she had to perform working tasks under hazardous conditions. It prevented us from establishing any correlations between sudden death at a workplace and exhaustion.

The research gave grounds for creating «The program for reducing risks of death at a workplace due to common diseases»; its main components are sanitary-hygienic, and medical and preventive activities, creating motivation to pursue a healthy lifestyle, and making social and psychological atmosphere within a work team more comfortable for workers.

This program can be an integral part of a consolidated action plan aimed at providing safe working conditions and preserving workers' health, first of all, at enterprises that are considered to be hazardous industrial objects as well as in organizations where sudden deaths at workplaces have been registered.

Special attention should be paid to making medical aid more available for workers via creating and developing services for rendering primary medical aid by aid posts located at industrial objects and settlements for shift workers. These posts should be equipped with all necessary medical devices (electrocardiograph, screening U-sound devices for examining vessels, and defibrillators) and have an ambulance car.

When implemented, the program will allow reducing economic losses and prevent labor losses caused by untimely deaths at workplaces due to common diseases.

Conclusions.

1. We established that annually in Bashkortostan workers suddenly died at their workplaces due to common diseases (268 registered cases over 2014–2018).

2. Most deceased workers who suddenly died at their workplaces due to common dis-

eases had been employed by companies operating in such spheres as manufacturing, 23 %; transport and logistics, 11.6 %; electricity, gas, and steam supply, 10.8 %; construction, 10.4 %. Overall, more than 60 % sudden deaths occurred in companies operating in these branches of economy.

3. The highest mortality at workplaces due to common diseases per 1,000 workers was registered for the following economic activities: production and distribution of electricity, gas, and water, 0.1 ‰; mining, 0.11 ‰; construction, 0.084 ‰; information and telecommunications, 0.21 ‰, water supply and sewage, 0.17 ‰; administrative activities, 0.14 ‰; electricity, gas, and steam supply, 0.13 ‰.

4. Men run greater risks of sudden death at a workplace due to common diseases. A share of men among deceased workers varied from 90.5 % to 96 % in different years. Sudden death most frequently occurred among people aged 56–60, both men and women.

5. Circulatory system diseases were the most common reason for sudden death as they accounted for 91.4 % cases. Average age of workers who died due to circulatory system diseases amounted to 51.7 ± 9.3. Mortality due to CSD accounted for 91.1 % among men and 95 % among women.

6. Analysis of all the obtained data doesn't allow establishing or disproving any cause-and-effect relations between sudden death at a workplace due to a common diseases and violated requirements to labor safety, exposure to hazardous occupational factors, or improper work and leisure regimes that could influence a deceased worker's health.

7. We scientifically substantiated a set of activities aimed at preventing or reducing risks of sudden death at a workplace due to common diseases; the set includes sanitary-hygienic and medical and preventive measures.

8. In future it is advisable to perform monitoring over parameters of sudden death at a workplace due to a common disease and related economic burden as it will allow assessing its dynamics, economic losses, as well as efficiency of investments into prevention of sudden deaths at workplaces.

Funding. The research was not granted any sponsor support.

Conflict of interests. The authors declare there is no any conflict of interests.

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Received: 19.02.2020
Accepted: 02.06.2020
Published: 30.06.2020

UDC 616.1
DOI: 10.21668/health.risk/2020.2.07.eng

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STRUCTURAL PECULIARITIES OF METABOLIC SYNDROME IN WORKERS EMPLOYED AT OIL EXTRACTING ENTERPRISE

A.E. Nosov, E.M. Vlasova, A.S. Baidina, O.Yu. Ustinova

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

Our research goal was to establish prevalence and structure of metabolic syndrome in workers employed at an oil-extracting enterprise and peculiarities of a relation between working experience and metabolic syndrome components as well as medical behavior of workers given that there were cardiovascular risk factors.

Data and methods. We examined 292 oil and gas extraction operators (test group) who were exposed to adverse industrial factors (chemical factor, noise, labor hardness, and unfavorable microclimate) and 65 office workers employed at the same enterprise (reference group). We determined whether workers had metabolic syndrome components and if yes, which ones (arterial hypertension, abdominal obesity, dyslipidemia, improper glycemia on an empty stomach); we also examined a relation between working experience and probability of these components being detected in a worker.

Results. Arterial hypertension syndrome was registered in 44.9 % oil and gas extraction operators and in 36.9 % office workers (RR=1.22 (95 % CI 0.86–1.71)); abdominal obesity was detected in 53.8% workers in the test group and 50.8 % office workers from the reference group (RR=1.06 (95 % CI 0.82–1.38)); dyslipidemia was registered in 59.6 % and in 58.5 % workers accordingly (RR=1.02 (95 % CI 0.81–1.27)). Carbohydrate metabolism disorders were registered in 18.2% oil and gas extraction operators and in 12.3% office workers (RR=1.45 (95% CI 0.72–2.89)).We detected dependence between probable AH occurrence and working experience in oil and gas extraction operators (b_0=–2.5; b_1=0.09; F=1,224.3; R^2=0.83; p=0.0001) with a significant relation between the disease and working experience under exposure to adverse industrial factors; whereas there was no such dependence detected for office workers from the reference group. Dependency of abdominal obesity, dyslipidemia, and hyperglycemia on working experience was also more significant among oil and gas extraction operators (R^2=0.43–0.56; p=0.0001) than among office workers (R^2=0.11–0.52; p=0.02–0.0001). There was a greater % of smokers among oil and gas extraction operators, they tended to have higher systolic, diastolic, and pulse arterial pressure. Workers didn't receive hypotensive and hypolipidemic medications in sufficient number of cases but office workers managed to achieve normal blood pressure 2.5 times more frequently.

Key words: *oil-extracting enterprise, adverse industrial factors, metabolic syndrome, obesity, arterial hypertension, working experience, work-related pathology.*

At the end of the 20th century there was a significant growth in morbidity and mortality caused by cardiovascular pathologies all over the world. Predictive value of certain factors that could cause chronic non-communicable pathologies (including cardiovascular ones) was scientifically substantiated at the turn of the century and it allowed overcoming this negative ascending trend in mortality and morbidity [1, 2]. Over the last 15 years total mortality in Russia clearly tends to decline (from 16.1 ‰ in 2005 to 12.4 ‰ in 2018); mortality among employable population follows the same trend going down from 8.3 ‰ in 2005 to 4.8 ‰ in 2018. Over 2000–2018 mortality caused by cardiovascular pathologies went down from 8.46 ‰ to 5.83 ‰[1]. But still, in spite of overall positive trends, cardiovascular diseases still play the leading role in the structure of mortality in Russia, and achieved decrease in mortality among employable population is not enough. Diseases that contribute most into overall mortality are poly-etiologic in their essence and in some cases are also

Aleksandr E. Nosov – Candidate of Medical Sciences, Head of In-patient Clinic (Therapeutic Work-related Pathology Department) (e-mail: nosov@fcrisk.ru; tel.: +7 (342) 236-87-80; ORCID: https://orcid.org/0000-0003-0539-569X).

Elena M. Vlasova – Candidate of Medical Sciences, Head of the Work-related Pathology Center (e-mail: vlasovaem@fcrisk.ru; tel.: +7 (342) 236-85-06; ORCID: http://orcid.org/ 0000-0003-3344-3361).

Anastasiya S. Baidina – Candidate of Medical Sciences, cardiologist (Therapeutic Work-related Pathology Department) (e-mail:anastasia_baidina@mail.ru; tel.: +7 (342) 236-87-60; ORCID: https://orcid.org/0000-0003-3131-5868).

Ol'ga Yu. Ustinova – Doctor of Medical Sciences, Deputy Director responsible for Clinical Work (e-mail: ustinova@fcrisk.ru; tel.: +7 (342) 236-32-64; ORCID: https://orcid.org/0000-0002-9916-5491).

[1] Russian annual statistical report. 2019: Statistic data collection. *Rosstat*. Moscow, 2019, 708 p. (in Russian).

work-related [3]. Risk factors that cause their development are both traditional lifestyle ones and adverse occupational factors that at present are not being given sufficient attention [4]. Metabolic syndrome (MS) is a supra-nosologic structure that combines several most significant risk factors such as arterial hypertension (AH), abdominal obesity (AO), improper tolerance to dextrose, increased concentration of lower density lipoproteins and triglycerides [1, 3, 5]. According to clinical recommendations, MS can be diagnosed should there be any three out of the above listed signs. An increase in number of MS components diagnosed in one patient leads to a considerable growth in risks of cardiovascular complications [1, 6]. Workers employed at an oil-extracting enterprise are exposed to some adverse occupational factors during their work (chemical factors, noise, vibration, physical overloads, and unfavorable meteorological conditions) that can be also considered risk factors of MS and cardiovascular pathology [7–9]. At the same time, an extent to which MS components in workers employed at oil-extracting enterprises are occupationally induced has not been examined properly so far.

Our research goal was to determine prevalence and structure of metabolic syndrome in workers employed at an oil-extracting enterprise, peculiarities related to a relation between working experience and metabolic syndrome components, as well as medical behavior of workers when factors causing cardiovascular risks were present.

Data and methods. 292 oil and gas extraction operators took part in the research; their average age was 39.43 ± 10.6 and average duration of their working experience was 13.15 ± 9.86 years (test group). Our reference group (workers not exposed to adverse occupational factors) was made up of 65 supervisors and administrative workers employed at the same enterprise; their average age was 40.28 ± 9.83, average duration of working experience was 18.5 ± 9.58 years. Both groups were comparable in terms of age, working experience, lifestyle, and gender (all the examined workers were men). To perform our research, we divided workers from both groups into sub-groups according to duration of their working experience (shorter than 10 years; 10 years and longer).

Working conditions for workers who directly deal with collecting well production and preliminary oil treatment involve combined exposure to in-plant noise, adverse chemicals, and such unfavorable factors as labor hardness and adverse microclimate. Adverse chemicals occurring at a workplace predominantly belong to 2–4 hazard categories (oil and its components and hydrogen sulfide).

When technological operations are being performed, certain chemicals are emitted into working area air; prevailing ones are aliphatic saturated hydrocarbons C_{1-10} (recalculated as per C) but their levels do not exceed hygienic standards. Besides, dihydrosulfide also occurs in working are air with its concentrations being by 0.5–1.9 mg/m^3 higher than it is acceptable (working conditions category as per its hazard is 3.1–3.2). Noise reaches 87–88 dBA at workplaces of oil and gas extraction operators and it is by 7–8 dBA higher that the maximum permissible level (hazard category is 3.1). Labor hardness occurs due to necessity to maintain a fixed pose during 60 % out of the total working time and to cover long distances (more than 8 km, hazard category is 3.1–3.2). Overall assessment of labor process allows assigning it into 3.2–3.3 hazard category.

Overall, as per results of special assessment of working conditions (SAWC) that took place the at examined enterprise in 2015 it was established that oil and gas extraction operators had to work under hazardous conditions according to the Guide[2] and it applied to 100.0 % working places of workers from our test group.

Workers were examined by a cardiologist according to conventional procedures. Blood pressure (BP) was taken with Little doctor tonometer and auscultatory method with measuring precision being up to 2 mm Hg, twice, with a 5-minute interval between measuring; a patient was sitting during the procedure. Average of two measurements was taken for

[2] G 2.2.2006–05. Guide on hygienic assessment of occupational and labor process factors. Criteria and classification of working conditions / approved by G.G. Onitshcenko, the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Well-being and the RF Chief Sanitary Inspector on July 29, 2005, 142 p. (in Russian).

analysis. Systolic blood pressure equal to 140 mm Hg and higher and diastolic blood pressure equal to 90 mm Hg and higher was considered increased blood pressure. Waist circumference was measured at navel high at the middle point between the upper edge of the flank bone and the lower edge of the costal margin. Waist circumference exceeding 94 cm was considered increased. We determined dextrose concentration on an empty stomach (concentration equal to 6.1 mmol/L and higher was considered increased), cholesterol of low density lipoproteins (concentration equal to 3.0 mmol/L and higher was considered increased), cholesterol of high density lipoproteins (concentration equal to 1.0 mmol/L and lower was considered decreased), and triglycerides (concentration equal to 1.7 mmol/L and higher was considered increased) according to conventional biochemical procedures. Should any parameter in this lipidogram deviate from its physiological standard, we diagnosed dyslipidemia in a worker.

We applied the following diagnostic criteria to determine whether a worker had MS.

The basic criterion was:

– central (abdominal) obesity that became apparent via waist circumference (WC) exceeding 80 cm in women and 94 cm in men;

Additional criteria were:

– BP (blood pressure ≥ 140/90 mm Hg);

– increased triglycerides concentration ≥ 1,7 mmol/L;

– a decrease in cholesterol of high density lipoproteins (≤1.0 mmol/L in men; <1.2 mmol/L in women);

– an increase in cholesterol of low density lipoproteins ≥ 3.0 mmol/L;

– hyperglycemia on an empty stomach (dextrose in blood plasma on an empty stomach is ≥ 6.1 mmol/L);

– improper tolerance to dextrose (dextrose in blood plasma is within >7.8 and <11.1 mmol/l 2 hours after tolerance to it was tested).

In case a patient had central obesity and two other criteria or three any criteria out of the above mentioned ones, MS diagnosis was well substantiated [3, 10].

We statistically processed all the data with specialized software developed by the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies. Qualitative binary signs were assessed with exact Fischer's test, relative risk calculation, and confidence interval (the results were given as (95 % CI). Quantitative signs were compared as per Student's t-test ($t > 0.2$) with statistical significance being equal to 0.05 ($p < 0.05$).

To substantiate response markers, we built up models for dependence between a probability of deviation in a parameter and working experience. Models were built separately for each response parameter via non-linear logistic regression analysis that allowed assessing parameters of a model given with the following formula (1):

$$p = \frac{1}{1+e^{-(b_0+b_1x)}}, \quad (1)$$

where p is a probability that a laboratory parameter of a response deviates from its physiological standard; x is working experience duration; b_0, b_1 are mathematical model parameters determined according to the least square method with applied software for statistical data analysis.

We performed our research in full conformity with the ICHGCP rules, ethical principles stated in Helsinki Declaration (last edited in 2008), RF National Standard GOST-R 52379-2005 «Good Clinical Practice» (ICH E6 GCP)[3]. The research program was approved by the Ethical Committee of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies (Meeting report No. 55 dated December 20, 2018). All the workers were provided with exact information on the research goals and they all gave their voluntary informed consent to take part in it.

Results and discussion. Table 1 contains data on MS components prevalence among workers from the test and reference groups. Our research revealed that there were no statistically significant differences as per relative

[3] GOST-R 52379-2005. Good Clinical Practice (ICH E6 GCP): RF National Standard. *KODEKS: an electronic fund for legal and reference information*. Available at: http://docs.cntd.ru/document/1200041147 (13.02.2020) (in Russian).

Table 1

MS components prevalence

Disease	Test group $n = 292$	Reference group $n = 65$	RR (CI 95 %)
Morbidity in both groups			
Arterial hypertension, *n* (%)	131 (44.9)	24 (36.9)	1.22 (0.86–1.71)
Carbohydrate metabolism disorders (R73.9), %	53 (18.2)	8 (12.3)	1.45 (0.72–2.89)
Abdominal obesity (E66), %	157 (53.8)	33 (50.8)	1.06 (0.82–1.38)
Dyslipidemia (E78), %	174 (59.6)	38 (58.5)	1.02 (0.81–1.27)
Morbidity among workers with working experience shorter than 10 years			
Arterial hypertension, *n* (%)	43 (31.2)	8 (28.6)	1.09 (0.57–2.06)
Carbohydrate metabolism disorders (R73.9), %	13 (9.4)	1 (3.6)	2.64 (0.35–19.35)
Abdominal obesity (E66), %	58 (42.0)	8 (28.6)	1.47 (0.79–2.73)
Dyslipidemia (E78), %	71 (51.4)	11 (39.3)	1.31 (0.80–2.13)
Morbidity among workers with working experience longer than 10 years			
Arterial hypertension, *n* (%)	88 (57.1)	16 (43.2)	1.32 (0.89–1.96)
Carbohydrate metabolism disorders (R73.9), %	40 (25.9)	7 (18.9)	1.37 (0.67–2.82)
Abdominal obesity (E66), %	99 (64.3)	25 (67.6)	0.95 (0.74–1.23)
Dyslipidemia (E78), %	103 (66.9)	27 (72.9)	0.91 (0.73–1.15)

risks of MS components detection among oil and gas extraction operators and administrative staff. However, we should note there were still certain peculiarities in detected morbidity. AH was registered in 44.9 % workers from the test group and only in 36.9 % workers from the reference group (RR = 1.22 (95 % CI 0.86–1.71)). As working experience became longer, a share of people with AH increased from 31.2 % to 57.1 % in the test group, and from 28.6 % to 43.2 % in the reference group. Relative risk of AH occurrence among oil and gas extraction operators grew from RR = 1.09 (95 % CI 0.57–2.06) with working experience shorter than 10 years to RR = 1.32 (95 % CI 0.89–1.96) with working experience longer than 10 years.

Abdominal obesity as a determining MS component was detected in 53.8 % workers from the test group and in 50.8 % workers from the reference group (RR = 1.06 (95 % CI 0.82–1.38)). As working experience became longer, a share of people with AO grew from 42.0 % to 64.3 % in the test group, and from 28.6 % to 67.6 % in the reference group. Relative risk of AO amounted to 1.47 (95 % CI 0.79–2.73) for oil and gas extraction operators with their working experience being shorter than 10 years, and to 0.95 (95 % CI 0.74–1.23) for those with working experience being longer than 10 years.

Dyslipidemia was detected in 59.6 % workers from the test group and 58.5 % workers from the reference group (RR = 1.02 (95 % CI 0.81–1.27)). As working experience became longer, a share of people with dyslipidemia increased from 51.4 % to 66.9 % in the test group, and from 39.3 % to 72.9 % in the reference group. Relative risk of dyslipidemia amounted to 1.31 (95 % CI 0.80–2.13) for oil and gas extraction operators with their working experience being shorter than 10 years, and to 0.91 (95 % CI 0.73–1.15) for those with working experience being longer than 10 years.

Carbohydrate metabolism disorders (hyperglycemia on an empty stomach) were detected in 18.2 % workers from the test group and 12.3 % workers from the reference group (RR = 1.45 (95 % CI 0.72–2.89)). As working experience became longer, a share of people with hyperglycemia on an empty stomach increased from 9.4 % to 25.9 % in the test group, and from 3.6 % to 18.9 % in the reference group. Relative risk of hyperglycemia on an empty stomach amounted to 2.64 (95 % CI 0.35–19.35) for oil and gas extraction operators with their working experience being shorter than 10 years, and to 1.37 (95 % CI 0.67–2.82) for those with working experience being longer than 10 years.

The next stage in our work involved assessing MS structure as per a number of MS

components (comorbidity) detected in each examined worker employed at the enterprise (Table 2). There was a bit lower share of workers without any MS components or having only 1 among oil and gas extraction operators (RR = 0.76 (95 % CI 0.46–1.26) and RR = 0.89 (95 % CI 0.58–1.36) accordingly). However, relative risk of 2 or 3 components occurring in a worker tended to grow in the test group and amounted to RR = 1.46 (95 % CI 0.82–2.59) and RR = 1.11 (95 % CI 0.67–1.85) accordingly. Relative risk of detecting all 4 MS components was a bit lower for workers from the test group (RR = 0.85 (95 % CI 0.36–2.01)). Complete MS (3 or more components) was diagnosed in 31.8 % oil and gas extraction operators and in 30.8 % administrative workers (RR = 1.04 (95 % CI 0.69–1.55)).

We analyzed and compared comorbidity with MS components in groups with different working experience and revealed that workers from the test group with their working experience being shorter than 10 years ran lower relative risk of MS components absence (RR = 0.63 (95 % CI 0.38–1.04). However, a relative risk that 1 MS component occurred amounted to RR = 1.17 (95 % CI 0.62–2.19) in the test group; relative risk of 2 components occurring amounted to RR = 1.96 (95 % CI 0.64–5.99). The greatest number of MS components among workers with short working experience was revealed in the test group only, 2.9 % cases against 0 % in the reference group. Relative risk of MS components absence or only 1 component occurring amounted to RR = 1.12 (95 % CI 0.34–3.70) and RR = 0.66 (95 % CI 0.36–1.18) accordingly among workers from the test group with their working experience exceeding 10 years. At the same time, relative risk of comorbidity (2 or 3 components occurring) amounted to RR = 1.29 (95 % CI 0.67–2.51) and RR = 1.28 (95 % CI 0.69–2.38) accordingly for the same workers. Comorbidity with 4 MS components was detected in 12.3 % workers from the test group, and 16.2 % workers from the reference group (RR = 0.76 (95 % CI 0.33–1.77).

Table 2

Comorbidity with metabolic syndrome components

Number of components	Test group *n* = 292	Reference group *n* = 65	RR (CI 95 %)
Comorbidity with MS components in the whole groups			
Absent, %	51 (17.3)	15 (23.1)	0.76 (0.46–1.26)
1 component, %	76 (26.0)	19 (29.2)	0.89 (0.58–1.36)
2 components, %	72 (24.7)	11 (16.9)	1.46 (0.82–2.59)
3 components, %	70 (23.9)	14 (21.5)	1.11 (0.67–1.85)
4 components, %	23 (7.9)	6 (9.2)	0.85 (0.36–2.01)
Complete MS	93 (31.8)	20 (30.8)	1.04 (0.69–1.55)
Comorbidity with MS components in groups with working experience shorter than 10 years			
Absent, %	37 (26.8)	12 (42.8)	0.63 (0.38–1.04)
1 component, %	46 (33.3)	8 (28.6)	1.17 (0.62–2.19)
2 components, %	29 (21.0)	3 (10.7)	1.96 (0.64–5.99)
3 components, %	22 (15.9)	5 (17.8)	0.89 (0.37–2.16)
4 components, %	4 (2.9)	0	–
Complete MS	26 (18.8)	5 (17.9)	1.06 (0.44–2.51)
Comorbidity with MS components in groups with working experience longer than 10 years			
Absent, %	14 (9.1)	3 (8.1)	1.12 (0.34–3.70)
1 component, %	30 (19.5)	11 (29.7)	0.66 (0.36–1.18)
2 components, %	43 (27.9)	8 (21.6)	1.29 (0.67–2.51)
3 components, %	48 (31.2)	9 (24.3)	1.28 (0.69–2.38)
4 components, %	19 (12.3)	6 (16.2)	0.76 (0.33–1.77)
Complete MS	67 (43.5)	15 (40.5)	1.07 (0.69–1.65)

Table 3

Parameters of logistic regression
«exposure marker (working experience) – response indicator (the disease)»

Exposure marker	Effect marker	A trend in parameter change	b_0	b_1	F	R^2	p
Test group							
Working experience	Arterial hypertension	Ascending	–2.5	0.09	1224.3	0.83	0.0001
Working experience	Abdominal obesity	Ascending	–1.85	0.05	211.2	0.43	0.0001
Working experience	Carbohydrate metabolism disorders	Ascending	–2.59	0.07	324.7	0.53	0.0001
Working experience	Dyslipidemia	Ascending	–0.21	0.05	371.0	0.56	0.0001
Reference group							
Working experience	Arterial hypertension	Ascending	–	–	–	–	–
Working experience	Abdominal obesity	Ascending	–1.66	0.06	6.41	0.11	0.02
Working experience	Carbohydrate metabolism disorders	Ascending	–2.48	0.07	32.9	0.49	0.0001
Working experience	Dyslipidemia	Ascending	–1.02	0.13	58.86	0.52	0.0001

We performed logistic regression analysis to examine dependence between MS components occurrence and duration of working experience in the test and reference groups: the results are given in Table 3. We revealed statistically significant dependence between duration of working experience and AH probability among oil and gas extraction operators ($b_0 = –2.5$; $b_1 = 0.09$; $F = 1224.3$; $R^2 = 0.83$; $p = 0.0001$) and the correlation between the diseases and duration of the working experience was strong. There was no similar correlation revealed in the reference group.

Dependence between AH and duration of working experience was greater in the test group ($b_0 = –1.85$; $b_1 = 0.05$; $F = 211.2$; $R^2 = 0.43$; $p = 0.0001$) than in the reference one ($b_0 = –1.66$; $b_1 = 0.06$; $F = 6.41$; $R^2 = 0.11$; $p = 0.02$).

Carbohydrates metabolism disorders increased statistically significantly in both groups but dependence between this diseases and duration of working experience was higher among oil and gas extraction operators ($b_0 = –2.59$; $b_1 = 0.07$; $F = 324.7$; $R^2 = 0.53$; $p = 0{,}0001$) than in the reference group ($b_0 = –2.48$; $b_1 = 0.07$; $F = 32.9$; $R^2 = 0.49$; $p = 0.0001$).

There was also more apparent dependence between longer working experience and dyslipidemia among oil and gas extraction operators ($b_0 = –0.21$; $b_1 = 0.05$; $F = 371.0$; $R^2 = 0.56$; $p = 0.0001$) than among administrative workers ($b_0 = –1.02$; $b_1 = 0.13$; $F = 58.8$; $R^2 = 0.52$; $p = 0.0001$).

Case histories of workers from the examined groups had their peculiarities; for example, 42 % workers from the test group smoked whereas there were only 19 % smokers in the reference group ($p = 0.0001$). By the moment the research took place 25 % workers from the test group had given up smoking; 24.1 %, in the reference group ($p = 0{,}83$). On average, a worker from the test group had been smoking (or had smoked before giving it up) for 14.8 years against 12.5 years for workers from the reference group ($p = 0.15$). Workers from the test group tended to have a lot of physical activity every day (96 % in the test group against 74 % in the reference group, $p = 0.0003$).

Clinical examinations revealed that workers from the test group tended to have statistically significantly higher systolic blood pressure (131.6 ± 15.6 mm Hg against 125.2 ± 11.8 mm Hg, $p = 0.0001$) and diastolic one (84.0 ± 11.4 mm Hg against 80.3 ± 9.8 mm Hg, $p = 0.007$). Pulse pressure was also statistically significantly higher in the test group than in the reference one (47.82 ± 1.19 mm Hg against 45.48 ± 1.86 mm Hg, $p = 0.04$). Pulse arterial pressure being higher than 60 mm Hg as a parameter indicating that arterial stiffness was increased was also more frequently detected in the test group, 16.8 % against 7.6 % ($p = 0.01$). 19.1 % workers from the test group took hypotensive medications against 16.9 % workers from the reference one ($p = 0.66$). And workers from

the reference group achieved normal blood pressure in 66.7 % cases due to treatment whereas there were only 27.9 % such workers in the test group (p = 0.014). 3.5 % workers from the test group permanently took statins against 2.6 % workers from the reference group doing the same (p = 0.65).

Metabolic syndrome (MS) is a set of clinical and metabolic disorders that occur against resistance to insulin and are a most significant risk factor that causes cardiovascular complications [11].

G.A. Chumakova et al. give data on MS prevalence in the overall population in the world being 14–40 % [12]. As per data provided in various papers, MS occurs in 23–25 % population in the USA, and in Russia MS is diagnosed in 18.6 % men who are younger than 40 and in 44.4 % men aged from 40 to 55 [2, 12].

According to data provided by O.P. Rotar' et al., MS prevalence in four cities in Russia (Saint Petersburg, Orenburg, Kaliningrad, and Kursk) varied from 48.1 % to 53.1 %. According to this research work, different MS components were registered in these cities as follows: AO, from 63.0 % to 73.4 %; AH, from 58.1 % to 67.3 %; carbohydrates metabolic disorders, from 23.0 % to 49.2 %; dyslipidemia, from 23.6 % to 58.7 %. A share of examined people who had at last 1 MS component reached 86.4–93.7 % [13]. Hwee-Soo Jeong et al. analyzed MS prevalence among workers exposed to lubricants, metals, dusts, and noise at their workplaces. The authors diagnosed MS in 19.8 % workers. There were statistically significant discrepancies as per morbidity with MS obtained for workers who contacted lubricants during their work (OR = 1.79; 95 % CI 1.06–3.01). The authors state that elevated MS prevalence among this occupational group occurs due to potential subclinical systemic inflammation caused by inhalation exposure to chemicals [14, 15]. Ramin Mehrdad et al. assessed MS prevalence among workers employed at a car-making plant in Iran. MS was diagnosed in relatively small share of workers: 7.3 % among administrative staff; 7.9 %, among those dealing with hard physical labor; and 7.8 % among those exposed to chemical factors; there were no statistically significant discrepancies between groups. But still, the authors revealed decreased high density lipoprotein contents in blood of workers who contacted chemicals during their work and increased diastolic blood pressure among those who dealt with hard physical labor [16]. The authors note that MS prevalence in Iran varies from 10 % to 60 % depending on age, sex, and a region where a person lives [17]. The discrepancies, in the authors' opinion, are due to «a healthy worker» effect, young age of workers, and periodical medical examinations being quite efficient.

M. Strauß et al. compared firefighters (exposed to physical loads and work stress) and office workers in Germany. MS prevalence amounted to 14 % among firefighters whereas it was 33 % among office workers [18]. At the same time, in the USA MS prevalence among office workers reaches 45 % [19].

In 2012–2013 A.S. Baidina et al. examined MS prevalence among workers employed at an oil and gas extracting enterprise and revealed that it amounted to 44 %; AH was registered in 44.2 %; dyslipidemia, in 55.2 %; hyperglycemia on an empty stomach, in 20.0 %; hyperuricemy, in 42.0 %. Cardiovascular risk assessed as per SCORE scale amounted to 2.4 ± 0.7 % for oil and gas extraction operators, and to 0.85 ± 0.30 % for engineers ($p < 0.001$). The authors conclude that MS is a work-related disease for workers with this occupation (EF = 36.75 %, average dependence between health disorder and occupation) [20].

I.I. Logvinenko et al. examined 125 men with their average age being 35.3 and revealed various MS components in 73.6 % of them; AO was detected in 32.8 %; AH, 23.2 %; hypercholesterolemia, 59.2 %. Combinations of these clinical signs were detected in 52.17 % cases [21, 22].

G.G. Gimranova et al. showed that AH prevalence grew among workers employed at an oil extracting enterprise from 11.1 % among those aged 20–29 to 62.7 % among those older than 50 (an average value being equal to approximately 41 %). A share of people with AH reached 50 % among workers with their working experience exceeding 10 years and 57 % among those who had been working for more than 15 years. The authors showed that AH was to a great extent work-related among drivers (RR = 2.8; EF = 64.3 %)

and to an average extent among drilling operators (RR = 1.6; EF = 37.5 %) [8, 9].

We established MS (3 or more components) in 31.8 % oil and gas extraction operators and in 30.8 % administrative workers in our research. But still, at least 1 MS component was detected in 82.5 % workers from the test group and in 76.9 % workers from the reference one. MS prevalence differs significantly in all the above mentioned research works; it is probably due to different age, ethnic, and occupational groups being examined in them. Besides, different diagnostic MS criteria were likely to be applied in analysis. Overall, our data are well in line with other research works performed in Russia with their focus being MS prevalence among workers employed in oil extraction.

Conclusions.

1. There tend to be high prevalence of metabolic syndrome components among workers employed at an oil extracting enterprise (arterial hypertension, abdominal obesity, dyslipidemia, and carbohydrates metabolism disorders); this prevalence grows among workers with longer working experience under adverse working conditions. Approximately 80 % oil and gas extraction operators and administrative staff had 1 or more metabolic syndrome components that led to elevated cardiovascular risks. Metabolic syndrome was registered in 1/3 workers from both groups.

2. There was a more apparent cause-and-effect relation between working experience and metabolic syndrome components among oil and gas extraction operators; when it comes to arterial hypertension, such a relation was detected only in this group.

3. There were more smokers among oil and gas extraction operators than among administrative staff; they tended to have higher systolic, diastolic, and pulse arterial pressure. Hypotensive and hypolipidemic medications were not taken by all the workers who needed them in both groups but administrative workers achieved acceptable blood pressure 2.5 times more frequently than oil and gas extraction operators.

4. The obtained data indicate it is necessary to improve medical and prevention activities involving workers employed at an oil extracting enterprise; these activities should be aimed at eliminating risk factors that cause metabolic syndrome as it allows perverting cardiovascular diseases among workers who are in their pre-retirement age.

Funding. The research was performed within the Main Activities Plan adopted by the Federal scientific Center for Medical and Preventive Health Risk management Technologies for 2019.

Conflict of interests. The authors declare there is no any conflict of interests.

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Received: 18.05.2020
Accepted: 04.06.2020
Published: 30.06.2020

UDC 616-02: 613.63: 669]-084
DOI: 10.21668/health.risk/2020.2.08.eng

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CORPORATE PROGRAMS FOR PREVENTING HEALTH DISORDERS AMONG WORKERS EMPLOYED AT ADVERSE PRODUCTIONS AS A TOOL FOR OCCUPATIONAL RISK MANAGEMENT

O.Yu. Ustinova[1,2], N.V. Zaitseva[1], E.M. Vlasova[1], V.G. Kostarev[3]

[1]Federal Scientific Center for Medical and Preventive Health Risk Management Technologies, 82 Monastyrskaya Str., Perm, 614045, Russian Federation
[2]Perm State University, 15 Bukireva Str., Perm, 614990, Russian Federation
[3]Federal Service for Surveillance over Consumer Rights protection and Human Well-being, Perm regional office, 50 Kuibysheva Str., Perm, 614016, Russian Federation

Given the existing social and economic conditions, a true priority in activities performed by specialists in occupational medicine and labor protection is to preserve workers health and to prolong periods of their working capability. Experience in cooperating with employers who were interested in preserving their highly qualified personnel revealed that implementation of corporate prevention programs at an enterprise allowed reducing work-related and occupational health risks for workers.

Our research goal was to assess efficiency of a corporate prevention program bearing in mind managing occupational and work-related risks.

Data and methods. Our test group included 221 male workers employed at chemical productions in Perm (aged 55–40, average working experience amounted to 19.2 ± 7.8 years): our reference group was made up of 79 office workers employed at the same enterprises (aged 55–39, average working experience amounted to 21.2 ± 7.6). The research involved analyzing result of specific assessment of working conditions; medical documentation analysis; clinical, laboratory, and instrumental research; mathematical processing of all obtained data with creating predictive evolution models of occupational risks.

Results. A priori occupational risks for workers from the test group were high (intolerable) and average (significant); risks for workers from the reference group were small and negligible. An assessment of a cause-and-affect relation between work and health disorders revealed that AH (EF=66 %) and respiratory organs diseases (EF=51 %) were to a great extent work-related. Basic pathogenetic mechanisms of circulatory system diseases and respiratory organs diseases were determined as per research results; they were syndromes of endothelial dysfunction, sub-clinic inflammation, and oxidative stress; given that, we developed a corporate prevention program aimed at preventing health disorders among workers.

Results of the program implementation revealed that there was an authentic decrease in number of workers who had high blood pressure at the moment of a periodical medical examination (38 % prior to the program implementation and 11 % after it had been implemented, $p < 0.05$); there was 1.8 times decrease in number of workers who were not admitted to perform specific work tasks due to detected circulatory system diseases (14 workers prior the program implementation and 8 workers after it had been implemented, $p < 0.05$) and practically 3 times decrease in number of workers who were not admitted due to respiratory organs diseases (32 workers prior the program implementation and 11 workers after it had been implemented, $p < 0.05$); there was also a decrease in number of workers who applied for medical aid.

Key words: *occupational risk, risk management, corporate prevention programs, prevention of health disorders, assessment of working conditions, circulatory system diseases, respiratory organs diseases.*

Given contemporary socioeconomic conditions, a top priority in activities performed by experts in labor protection and occupational medicine is to preserve employable population's health and prolong employment as much as it's only possible. A decrease in probability of untimely deaths caused by non-communicable diseases leads to labor potential preservation [1]. Health protection and safe working conditions are guaranteed by law[1]; they may as well be

Olga Yu. Ustinova – Doctor of Medical Sciences, Associate Professor, Head of Human Ecology and Life Safety Department (e-mail: ustinova@fcrisk.ru; tel.: +7 (342) 236-32-64; ORCID: http://orcid.org/0000-0002-9916-5491).

Nina V. Zaitseva – Academician of the Russian Academy of Sciences, Doctor of Medical Sciences, Professor, Scientific Director (e-mail: znv@fcrisk.ru; tel.: +7 (342) 237-25-34; ORCID: https://orcid.org/0000-0003-2356-1145).

Elena M. Vlasova – Candidate of Medical Sciences, Head of Prevention Center (e-mail: vlasovaem@fcrisk.ru; tel.: +7 (342) 236-87-60; ORCID: http://orcid.org/0000-0003-3344-3361).

Vitalii G. Kostarev – Candidate of Medical Sciences, Chief State Sanitary inspector in Perm region, Head of Rospotrebnadzor office in Perm region (e-mail: urpn@59.rospotrebnadzor.ru; tel.: +7 (342) 239-35-63).

[1] The RF Constitution adopted on December 12, 1993 by the nation-wide voting (with amendments made by the RF Laws on Amendments to the RF Constitution issued on December 30, 2008 No. 6-FKZ, December 30, 2008 No. 7-FKZ, February 05, 2014 No. 2-FKZ, July 21, 2014 No. 11-FKZ). *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_28399/ (20.05.2020) (in Russian).

fixed by a collective labor contract[2]. Any labor potentially causes damage to health [2–4]. Chemical production usually involves complex negative effects produced by occupational factors on workers; these factors include in-plant noise, vibration, microclimate, chemicals in working area air (WAA) that are typical for a specific production and industrial dusts in concentration higher than maximum permissible ones (MPC). There are also adverse working conditions such as labor hardness and intensity and occupational stress. Exposure to chemicals used in technological processes is intermittent in its essence during a work shift [5]. Long-term permanent combined exposure to adverse chemical and physical factors together with adverse working conditions leads to a decrease in body functional reserves and disorders in biochemical processes (intensified gluconeogenesis, atherogenesis, and free radical damage to cell membranes) consequently resulting in pathological changes in organs and systems (most frequently, cardiovascular disorders) [5, 6]. Clear stages in development of pathological changes in a body is registered depending on target organs or systems, mechanism of action, and intensity of effects produced by an occupational factor [3]. Exposure to chemical factors most frequently leads to primary non-specific changes in circulatory and respiratory systems (arterial hypertension (AH), atherosclerosis with damage to peripheral and extracranial arteries, as well as multi-focal atherosclerosis and airway conductance disorders) [6, 7]. Occupational risks could be ranked from negligible to high depending on working conditions. Exposure to industrial aerosols authentically increases risks of somatic pathology in the respiratory organs. Diagnosing subclinical disorders during a periodical medical examination (PME), including those performed on workers with long working experience, will allow a delay in diseases occurrence and will ensure working ability preservation [7, 8].

Occupational and work-related risks assessment and management is an integral component in labor protection that includes preserving workers' life and health during their occupational activities (determining correlations between health disorders and work; developing procedures that allow estimating occupational risks) [9–11].

In practice, PMEs are the basic preventive activity that should be performed by an employer; they are regulated by the Order No. 302n[3] and aimed at detecting clinical forms of diseases that are medical contraindications to any further work. This conventional approach doesn't have either medical-preventive components or any elements of occupational risk management.

Our experience in interacting with employers who take genuine interest in preserving their highly qualified personnel revealed that when corporate prevention programs were implemented at an enterprise taking into account risks of occupational diseases, it allowed minimizing health risks for workers and preserving their working abilities [7].

Our research goal was to assess efficiency of a corporate prevention program in view of occupational risk management.

Data and methods. To achieve the fixed goals, we made up a test group that included 221 male workers employed at chemical productions operating in Perm region (aged 55–40, average working experience was 19.2 ± 7.8 years), and a reference group that included 79 administrative workers from the same enterprises (aged 55–39, average working experience was 21.2 ± 7.6). Workers from the test group mostly had the following occupations: a chlorination operator, an operator dealing with melted salts electrolysis, a founder, a non-ferrous metals and alloys caster, and a baking worker. The reference group included specialists in labor protection and industrial safety, and engineers who were not exposed to adverse occupational factors at their workplaces. Both groups were comparable in terms of sex, social position, working experience duration, and age. To analyze contributions made by occupational factors into health disorders as working experience grew longer, we divided workers from both groups into sub-groups accor-

[2] The RF Labor Code issued on December 30, 2001 No. 197-FZ (last edited on August 02, 2019). *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_34683/ (20.05.2020) (in Russian).

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ding to their working experience: 0–5 years; 5.1–10 years; 10.1–15 years; 15.1 years and longer.

Our research involved analyzing results obtained via special assessment of working conditions (SAWC) performed at examined workers' workplaces; analyzing medical documentation and ultimate PME reports; clinical examinations by medical experts with assessing functional state of the circulatory and respiratory systems; laboratory and instrumental examinations; mathematical processing of the obtained data together with building up prognostic evolution models for occupational risks [12].

We also performed sociologic research on prevalence of non-occupational risk factors that exerted their influence on circulatory system diseases (CSD) and respiratory organs diseases (ROD); it was done via handing out questionnaires to respondents who were selected via targeted sampling [13].

To assess functional activity of vessel endothelium, we tested flow-dependent (endothelium-dependent) vasodilatation of the brachial artery with «Vivid q» (GE Vingmed Ultrasound AS, Norway) u-sound scanner with the linear device 4–13 MHz (D.S. Celermajer).

Morphological structure of extracranial sections in the brachiocephalic arteries (BCA) was assessed with «Vivid q» (GE Vingmed Ultrasound AS, Norway) u-sound scanner with the linear device 4–13 MHz. We assessed Intima-media Thickness (IMT).

Heart rhythm and balance between sections in the vegetative nervous system (VNS) were assessed as per the conventional procedure (R.M. Baevskiy, 1979; D. Zhemaytite, 1989) with «Poly-Spectr-8/EX» software package (Neirosoft, Russia).

External breath was analyzed via spirography performed with SP-20 device (Schiller AG, Switzerland).

Laboratory examinations included tests performed with unified hematologic, biochemical, and ELISA techniques that allowed assessing functional state of target organs. Laboratory diagnostics was performed with automatic analyzers (hematologic AcT5diff AL device, the USA, and Backman, France; biochemical Konelab 20 device, ThermoFisher, Finland; and «Infinite F50 Teca» device for ELISA test, Austria).

Risks were assessed in conformity with Guide R 2.2.1766-03[4]. A relation between a health disorder and working conditions was established basing on relative risk (RR), confidence interval (CI), and etiological fraction of responses caused by exposure to occupational risk factors (EF); to do that, we used an electronic calculating device [9].

We processed all the data statistically with variation statistics techniques. Statistic hypotheses were tested against model parameters with Student's t-test and chi-square (χ^2). Should distribution be normal and Student's t-test applied, the data were given as simple mean (S) and standard deviation (SD); in case distribution was not normal, the data were given as median (Me) and interquartile range (the 25th and 75th percentiles). Significance was taken as $p = 0.05$ ($p < 0.05$). All the obtained data were processed with SPSS 16.0, Stata/SE 12.1 software packages for Windows, and a program module made as MS Excel macro. We also performed situation modeling [14–16].

The research was performed within the Scientific Research Program adopted by the Federal scientific Center for Medical and Preventive Health Risk Management Technologies for 2018 in conformity with the standards fixed in Helsinki Declaration (last edited in 2008) and ICHGCP rules as well as in conformity with the RF National Standard GOST R 52379-2005 «Good Clinical Practice» (ICH E6 GCP). The research program was approved on the local ethical Committee meeting (meeting report No. 33 dated February 12, 2018).

Results and discussion. Working conditions at workplaces of workers with basic occupations existing at chemical productions involved combined exposure to chemical factors (chlorine and its compounds; sulfur and its compounds), physical factors (noise, vibration, and microclimate), and labor hardness. According to SAWC, working conditions were assessed as «hazardous» at 100 % workplaces of workers from the test group; they were «acceptable» for workers from the reference group (Table 1).

[4] Guide on assessing health risks for workers. Organizational and methodical grounds, principles, and assessment criteria. 2.2. Occupational hygiene. *KODEKS: the electronic fund for legal and reference documentation.* Available at: http://docs.cntd.ru/document/901902053 (20.05.2020) (in Russian).

Table 1

Workplaces of workers form the test and reference groups ranked as per working conditions according to special assessment of working conditions, %

Group	Specific weight of workplaces with different working conditions categories				
	1 and 2	3.1.	3.2.	3.3.	3.4.
Test group	0	30	55	15	0
Reference group	100	0	0	0	0

Table 2

Occupational risks for workers with most common occupations existing at chemical productions (G 2.2.1766-03)

Test group		Reference group	
Workplace	Occupational risk	Workplace	Occupational risk
Chlorination operator	high (intolerable)	Foreman	small (moderate)
Melted salts electrolysis operator	average (substantial)	Senior foreman	small (moderate)
Non-ferrous metals and alloys caster	average (substantial)	Team supervisor	negligible
Founder	average (substantial)	Assistant to workshop head	negligible
Baking worker	average (substantial)	Workshop head	negligible

Workers from the test group ran a priori high (intolerable) and average (substantial) occupational risks; workers from the reference group ran small and negligible occupational risks (Table 2).

Having analyzed prevalence of behavioral risk factors, we revealed that there were no statistically authentic differences between two groups ($p > 0.05$). In particular, a share of smokers amounted to 31 % and 27 % in the test and the reference group accordingly ($p > 0.05$). Workers from the test group had been smoking on average for 20 years (15 cigarettes a day on average), and workers from the reference group, for 18 years (13 cigarettes a day, $p > 0.05$). We analyzed attitudes towards drinking alcohol and also didn't reveal any authentic differences. We established that most examined workers drank alcohol 2 times per month (86 % workers from the test group, 77 % workers from the reference group, $p > 0.05$). Choice on spirits was influenced by education. Workers with high education preferred low alcohol spirits (wine) in 62.2 % cases, V Cramers = 0.464, $p < 0.05$. People with primary and secondary education chose fortified wines or strong spirits, V Cramers = 0.469, $p < 0.05$. We revealed a weak relation ($r = 0.2$, $p < 0.05$) between a worker's age and beer consumption; workers younger than 30 drank beer once a week or more often in a quantity exceeding 1 liter (43.7 % in the test group and 38.2 % in the reference group; V Cramers = 0.469, $p < 0.05$).

Questioning performed among workers from the test group revealed either absence of complaints due to «a healthy worker syndrome» or them being non-specific; it made early diagnostics and prediction of working ability in the future more complicated. Clinical examinations allowed establishing that the leading place belonged to astheno-vegetative syndrome (increased fatigue, a decrease in working ability, often changes in moods, and sleep disorders); it was revealed practically in all examined workers form the test group.

Arterial hypertension (AH) determined as per office arterial blood pressure (BP) was detected in 33 % workers from the test group and in 18 % workers from the reference one ($\chi^2 = 6.7$, p = 0.01, RR = 1.7; 95 % CI = 1.1–3.1; EF = 66 %). There was a growth in number of workers with the verified diagnosis depending on their working experience. Workers from the test group with their working experience exceeding 10 years tended to have AH 3.5 times more frequently ($\chi^2 = 4.3$, $p = 0.03$), and 2.7 times more frequently in case working experience exceeded 15 years ($\chi^2 = 6.7$, $p = 0.01$). The results are given in Table 3.

Table 3

Prevalence of arterial hypertension depending on working experience duration in the test and reference groups, %

Group	Prevalence of arterial hypertension depending on working experience duration			
	0–5 years	5.1–10 years	10.1–15 years	More than 15 years
Test	12.7	17.6	30.6	59.6
Reference	4.0	5.0	9.0	22.3
*p**	$p > 0.05$	$p > 0.05$	$p < \mathbf{0.05}$	$p < \mathbf{0.05}$

Note: *p means validity of discrepancies between the test and reference groups.

Respiratory organs diseases (ROD) with obstructive disorders in the lower respiratory tracts more frequently occurred in workers from the test group as the parameter was 3 times higher than in the reference group (χ^2 = 17.6, $p < 0.001$, RR = 3.2, 95 % CI = 1.7–5.8, EF = 51 %). 19.1 % workers with their working experience being 15 years or longer had chronic obstructive lungs disease; there were only 5 % workers with the same disease in the reference group ($p < 0.05$). Pathology in the respiratory organs occurs in workers employed at chemical productions with certain peculiarities in the process; one of them is a long latent period in the disease development and external breath remaining within its conditional physiological standards due to functional reserves.

According to data taken from literature, occupational factors can act as triggers and induce pathogenetic mechanisms of non-communicable diseases occurrence and development. Adverse occupational factors (physical, chemical, and psychophysiological ones) cause imbalance between oxidant and anti-oxidant systems [17–20].

We assessed functional activity of the brachial artery endothelium with endothelium-dependent vasodilatation test; the assessment revealed that there was a pathologic reaction in 85.5 % workers from the test group whereas a similar one was detected only in 3.7 % workers from the reference group (χ^2 = 168.6, $p < 0.001$, RR = 22.5; 95 % CI = 7.4–68.4; EF = 85 %). A growth in the brachial artery diameter after reocclusion amounted to 5.22 ± 1.34 in workers from the test group and to 13.53 ± 1.08 in their counterparts from the reference group ($p < 0.001$); average value of sensitivity coefficient was 5 times lower in workers from the test group than in those from the reference one (0.053 ± 0.024 and 0.265 ± 0.058, $p < 0.001$). These results confirm the assumptions on a relation between disorders in endothelium functional activity and exposure to adverse occupational factors [21].

Mathematic modeling revealed that AH probability was predominantly related to in-plan noise (F = 1,621; R^2 = 0.95; p = 0.001, r = 0.3); ROD, to elevated concentrations of chlorine and its compounds in WAA (F = 296; R^2 = 0.79; p = 0.003, r = 0.3); endothelial dysfunction, both to in-plant noise (F = 3,387; R^2 = 0.96; $p < 0.001$; r = 0.6) and concentrations of chlorine and its compounds (F = 54; R^2 = 0.29; $p < 0.001$).

Atherosclerosis signs, namely local increase in IMT, were registered practically in each third worker from the test group (29 % workers from the test group and 15 % workers from the reference group, p = 0.05, OR = 2.3, 95 % CI = 1.2–4.4; RR = 1.9, 95 % CI = 1.1–3.3). Ultrasound scanning performed on BCA revealed authentic discrepancies in IMT on extracranial level, 0.99 ± 0.02 mm in workers from the test group against 0.77 ± 0.05 mm in workers from the reference one ($p < 0.001$). And IMT growth rate amounted to 0.16 mm per year in workers from the test group with their working experience exceeding 10 years whereas the physiological standard for the parameter is not more than 0.0138 mm per year.

We analyzed results obtained via heart rhythm assessment and revealed grave disorders in compensatory mechanisms in 35 % workers from the test group and only in 12 % workers from the reference one. Those disorders were accompanied with pathologic stabilization of heart rhythm modulation with transition to neurohumoral regulation (χ^2 = 15.6, $p < 0.01$, RR = 3.9, 95 % CI = 1.5–2.3; EF = 46 %). Our research revealed that HF strength (respiratory waves that reflect how active parasympathetic cardioinhibitory center in the medulla is) that characterizes activity of parasympathetic section in the regulation goes down greater than LF strength (that reflects how active sympathetic centers in the medulla are including cardioacceleratory and vasoconstrictive ones) in older workers from the test group. We observed a close relation between HF strength and RMSSD time parameters (a square root out of an average sum of squared differences between neighboring NN intervals) and pNN50 (a number of neighboring NN intervals pairs) and it mostly indicated that the parasympathetic system was quite active. Normally, weaker activity of parasympathetic influences and greater activity of sympathetic ones results in a decrease in the heart rhythm variability (HRV) structure only in people older than 50. Average HF waves value in quiescence (HF1, %) in workers from the test group was within its physiological standards but it was authentically lower than the same parameters in workers from the reference group (33.2 ± 3.4 % in the test group, 27.9 ± 3.1 % in the reference one, p = 0.026) and it indicated that central ergotropic and humoral-metabolic mechanisms

were substantially active. Vagosympathetic interaction index (LF/HF1) was practically 2 times higher in workers from the test group than in those from the reference one (1.9 ± 0.5 and 1.0 ± 0.3 accordingly, p = 0.008). Having analyzed HRV time parameters, we revealed a decrease in SDNN1 in the test group (50.5 ± 5.9 μs in the test group, 64.5 ± 11.9 μs in the reference group, p = 0.042); RMSSD1 (43.0 ± 7.7 μs, 66.1 ± 16.7 μs accordingly, p = 0.013) and it confirmed a decrease in HRV and greater tonus of the sympathetic nervous system against lower tonus of the parasympathetic nervous system in workers from the test group as compared with their counterparts from the reference one (Table 4).

Having analyzed all the obtained results, we established that there was dependence between a probable increase in vagosympathetic interaction index (LF/HF1) and a growth in inplant noise (F = 1,257; R^2 = 0.9; $p < 0.001$, r = 0.6) as well as elevated concentrations of chlorine (F = 61; R^2 = 0.3; $p < 0.001$, r = 0.3) and hydrochloride (F = 136; R^2 = 0.5; $p < 0.001$, r = 0.3) in working area air.

We analyzed spirography results and didn't reveal any deviations from physiological standards either in workers from the test group or those from the reference one. However, having analyzed spirography parameters in dynamics, we established that there was an annual decrease in fixed tidal volume per 1 sec in 29 % workers from the test group; it went down by 39.2 ± 5.8 ml per year while permissible decrease should not exceed 30 ml per year. Annual decrease in fixed tidal volume per 1 sec in workers from the reference group on average amounted to 31.5 ± 3.1 ml a year ($p < 0.05$) and it indicated that ROD developed subclinically in them.

We analyzed results obtained via laboratory examinations and revealed that there were certain deviations in parameters obtained for workers from the test group; those deviations reflected subclinical disorders in the circulatory and respiratory systems, namely already existing risks of cardiovascular disorders (RR = 1.8, 95 % CI = 1.2–2.8; EF = 45 %) as well as secondary immunodeficiency signs and apparent adaptation reactions [21–23]. Workers from the test group had elevated concentrations of uric acid, up to 378 [313; 420] μmol/dm^3 (the parameter was 302 [251; 358] μmol/dm ^{3} in the reference group, $p < 0.05$). The said changes were revealed in workers with longer working experience, starting from 5.1–10 years (389 (362; 421] μmol/dm^3, 296 [239; 364] μmol/dm^3 in the reference group, $p < 0.05$). There was a statistically significant increase in atherogenic fraction, or low density lipoproteins, in workers from the test group: 4.2 [3.7; 5.5] mmol/dm^3, (3.2 [2.8; 3.6] mmol/dm^3 in the reference group, $p < 0.05$). Concentration of supersensitive C-reactive protein was authentically higher in workers from the test group (6.7 [6.2; 7.2] mg/dm^3) than the same parameter in the reference one, 5.0 [4.5; 5.5] mg/dm^3 ($p < 0.05$), and VEGF concentrations in workers from the test group reached 345 [242; 510] pg/dm^3 (179 [90; 299] pg/dm^3 in the reference group,

Table 4

Time and spectral analysis of heart rhythm variability in quiescence in workers employed at chemical productions

Parameter	Physiological standard	Test group	Reference group	*P**
SDNN1, μs	54.5–65.1	50.5 ± 5.8	64.6 ± 11.9	**<0.05**
RMSSD1, μs	36.3–48.5	42.9 ± 7.6	66.2 ± 16.6	**<0.05**
TP1, μs^2	1561–4754	3021 ± 673	5223 ± 2212	>0.05
VLF1, μs^2	355.8–1175.1	1138 ± 222	1574 ± 507	>0.05
LF1, ms^2	513.1–1425.5	1040 ± 280	1438 ± 697	>0.05
HF1, μs^2	461.1–1618.0	853 ± 292	2213 ± 1190	**<0.05**
LF/HF1	0.5–2.3	1.9 ± 0.5	1.1 ± 0.3	**<0.05**
VLF1, %	17.51–39.79	41.4 ± 4.2	37.2 ± 4.3	>0.05
LF1, %	24.63–42.72	33.2 ± 3.4	27.9 ± 3.1	**<0.05**
HF1, %	21.05–50.53	25.6 ± 4.1	34.9 ± 5.1	**<0.05**
LF1 norm, n.u.	41.2–60.0	57.5 ± 4.9	46.3 ± 5.4	**<0.05**
HF1 norm, n.u.	40.0–58.8	42.4 ± 4.7	53.7 ± 5.5	**<0.05**

Note: *p means validity of discrepancies between the test and reference groups.

$p < 0.001$). Comparative analysis of the parameter in sub-groups with different working experience duration revealed its maximum concentration in workers with their working experience being 15.1 years or longer (471 [332; 695] pg/dm^3 in the test group and 106 [81; 259] pg/dm^3 in the reference group, $p < 0.001$). Homocysteine concentration amounted to 12.5 [10.0; 14.4] μmol/dm^3 in the test group and to 7.8 [4.6; 12.2] μmol/dm^3 in the reference one ($p < 0.001$); statistically significant discrepancies were revealed in workers with their working experience being 15.1 years and longer, 13.7 [10.8; 14.9] μmol/dm^3 in workers from the test group and 8.5 [4.6; 13.6] μmol/dm^3 in workers from the reference one ($p < 0.05$). It should be noted that hydrocortisone concentration in blood was higher in workers from the test group (287 [191; 487] nmol/cm^3) than the same parameter in workers from the reference one (204 [178; 352] nmol/cm^3 ($p < 0.05$).

Having analyzed immunologic status and reactivity, we revealed that leucocytes concentration in blood was authentically higher in workers from the test group than in their counterparts from the reference one (6.6 [5.7; 8.5]·10^9/dm^3 and 5.9 [5.1; 7.2]·10^9/dm^3 accordingly, $p < 0.001$). The most apparent inter-group discrepancy was detected for workers with their working experience being 15.1 years and longer (6.7 [5.6; 8.7]·10^9/dm^3 in workers from the test group, 5.5 [4.7; 7.2]·10^9/dm^3 in workers from the reference group, $p < 0.05$). Phagocytic section disorders were also predominantly detected in workers from the test group (absolute phagocytosis in the test group was 2.11 [1.54; 2.83]·10^9/dm^3; in the reference group, 1.77 [1.40; 2.23]·10^9/dm^3, $p < 0.05$); the same was true for humoral section in the immunity (IgA level amounted to 2.4 [1.93; 2.83] g/dm^3 in workers from the test group, and to 1.79 [1.40; 2.16] g/dm^3 in workers from the reference one ($p < 0.001$) as well as for activation of cellular section in the immunity (CD16 + 56 + lymphocytes concentration amounted to 0.32 [0.27; 0.60]·10^9/l in workers from the test group, and to 0.22 [0.21; 0.25]·10^9/l in workers from the reference one, $p < 0.05$; CD3 + CD25 + concentration amounted to 0.35 [0.24; 0.52]·10^9/l in the test group, and to 0.14 [0.10; 0.16]·10^9/l in the reference one, $p < 0.001$).

Research results allowed us to determine basic pathogenetic components in CSD and ROD development; they were endothelial dysfunction, subclinical inflammation, and antioxidant stress. Taking them into account, we developed a corporate program aimed at preventing health disorders among workers [7].

Our experience in interacting with enterprises revealed that such programs would be implemented more efficiently in case there was interaction with experts in labor protection. Hygienic activities allow reducing risks for workers' health.

Having built mathematical models for «exposure – working experience – response» dependence, we established a probability of work-related ROD depending on level and duration of exposure to adverse occupational factors. Risk of ROD occurrence in workers employed at chemical productions, given the existing working conditions, will create 6 additional cases by the end of the 1st working year; by the end of the 5th year there will be 14 additional cases. As for work-related AH, by the end of the 1st year there will be 8 additional cases; by the end of the 10th year, 25 additional cases per year.

Situation modeling revealed that a decrease in chlorine concentration in working area air to its MPC can make for 42 % lower individual ROD risks for workers with long working experience (5 years and longer) (from 14 to 6 cases per year).

Taking all the obtained results into account, we developed a corporate health preservation program with workers being distributed into several risk groups:

– the 1st group included workers who didn't have any complaints, any clinical signs of ROD and/or CSD (satisfactory adaptation or resistance);

– the 2nd group included workers who didn't have any complaints but still had certain functional disorders without any clinical symptoms (unsatisfactory adaptation);

– the 3rd group included workers who had complaints and laboratory or functional signs of CSD and/or ROD (strain in adaptation);

– the 4th group included workers with first diagnosed CSD or ROD who didn't have any contraindications to continuing their work (adaptation failure).

The risk groups were created as per PME results.

Corporate programs should involve interaction between labor protection and industrial safety services existing at an enterprise and medical organizations and centers for occupational pathologies treatment.

Following PME results, an employer makes a decision whether it is advisable to develop and implement a corporate prevention program, then signs a contract with a scientific organization and entitles it to assess health risks for workers and to develop and implement relevant prevention programs.

Activities aimed at labor resources preservation that are employer's responsibility are: production modernization including creation of new workplaces with working conditions at them being «acceptable» for workers in pre-retirement age who have contraindications to working under hazardous conditions; providing workers with information on occupational risks; reducing influences exerted on workers by adverse factors (protection via time, lower doses, or distance); application of up-to-date individual protection means (active noise-absorbing earphones, semi-masks with replaceable filters, etc.); providing more qualitative PMEs.

According to workers' distribution into risks groups as per results obtained via a previous PME, workers from this contingent underwent more profound annual medical examination that included a greater range of procedures than it was stipulated by the Order No. 302n; after the examination workers were again distributed into risk groups in order to perform medical-preventive or medical-rehabilitating activities for those who needed them.

Primary prevention of circulatory system and respiratory organs diseases included the following: a worker was informed that CSD or ROD could probably occur and was provided with a short preventive consultation; motivation to preserve health was created; a worker was advised to control BP, body mass index, waist and thighs circumference, to give up smoking and to avoid passive smoking, to give up alcohol intake, to take regular and moderate physical exercises, to do sports and take annual walks outdoors, to keep healthy daily regime (to sleep for not less than 8 hours), to have balanced and rational nutrition, and to avoid stressful situations.

Medical activities included more profound medical examinations than it was regulated for a typical PME for workers who ran average and high occupational risks; such workers were also examined annually at a canter for occupational pathology.

Medical and rehabilitation activities recommended for workers from the 1st risk groups included informing workers about occupational health risks; short preventive consultations; non-specific seasonal immune prophylaxis and motivation to preserve health.

Workers form the 2nd risk group were provided with more profound preventive consultations; non-specific seasonal immune prophylaxis and anti-influenza vaccination; physical prevention including physiotherapy (aeroionization), acupuncture, head and neck massage, 10 sessions of therapeutic exercises, 14-day prevention treatment in a sanatorium.

Prevention programs for workers form the 3rd risk group were added with vaccination with «Pnevmo 23» vaccine for workers who had often recurrent ROD; such workers were also provided with preventive medications including antioxidants, poly-vitamin and poly-mineral complexes taken for 14 days 2 times a year. In case of necessity they were provided with therapy to treat ROD and/or CSD. Physical prevention included medicinal phonophoresis and magnetotherapy, 10 sessions each, chest massage, and respiratory gymnastics, also 10 sessions each; antioxidant therapy, energy-saving mediations, and beta-carotene with minerals, all taken for 30 days.

Workers from the 4th group were informed about occupational risks and forecasts for their future occupational activities; motivation to preserve health was created; they were provided with physical and medicinal prevention as well as treatment for their main disease (permanent hypotensive therapy and/or bronchodilators and mucolytic medications etc.); they also spent 21 days in a sanatorium and were provided with rehabilitation treatment there.

Medical-preventive and medical-rehabilitation activities include 4 stages. *The first stage* involves activities aimed at preventing ROD and CSD in workers from the 1st group and they take place at an aid post belonging to an enterprise. *The second stage* involves activities aimed at preventing ROD and CSD in workers from the 2nd risk group and those who often fall sick with long colds; it is implemented via organizing outpatient observations at an aid post of an enterprise together with a specialist in occupational pathology from a medical organization. *The third stage* is regular health improvement provided for workers with initial non-communicable ROD and with detected CSD predictors (the 3rd risk group); such workers have medical examinations at a center

for occupational pathology treatment where their occupational abilities are estimated. *The fourth stage* involves medical and rehabilitation activities provided for workers form the 4th risk group annually at a center for occupational pathology treatment where their occupational abilities are estimated and a relation between a disease and occupational activities is determined.

Medical-preventive and medical-rehabilitation activities are aimed at life quality improvement, better tolerance to physical loads, working ability preservation, elimination or reduction in CSD and ROD symptoms, reduction in number of recurrent ROD or CSD gravity, and reduction in mortality.

One year after the corporate prevention program was implemented there was another medical examination. Its results revealed that a share of work-related circulatory system diseases went down (EF = 66 % prior to the program implementation; EF = 47 % after it was implemented); the same was true for respiratory organs diseases (EF = 51 % prior to the program implementation; EF = 39 % after it was implemented). A number of workers in the test group who had high BP at the moment the examination took places decreased authentically (33 % prior to the program implementation; 11 % after it was implemented, $p < 0.05$, RR = 1.1; 95 % CI = 1.0–3.3; EF = 39 %); there was a 1.8 time decrease in number of workers who had contraindications to fulfilling certain work tasks as per PME results due to CSD (14 workers prior to the program implementation, and 8 workers after it was implemented, $p < 0.05$); and number of workers with such contraindications due to ROD went down by 3 times (32 workers prior to the program implementation, and 11 workers after it was implemented, $p < 0.05$); a number of workers who applied for medical aid due to CSD and ROD including acute respiratory infections when down by 2.5 times; there was a decrease in number of workers who needed additional examinations (from 35 % to 20 %) and whose occupational abilities were to be estimated (from 30 % to 14 %); there was practically a 3-time decrease in number of workers who couldn't continue their work due to contraindications (from 33 % to 11 % due to AH, and from 14.5 % to 5 % due to respiratory organs diseases). There was a positive dynamics revealed via comparative analysis of the examination results (Table 5).

We analyzed functional activity of the brachial artery endothelium and revealed that prior to the program implementation minimal growth in diameter amounted to 5 %, and maximum one, to 32 %, variation range R = 27; after the program was implemented, the parameters became equal to 10.42 % and 28.57 % accordingly, R = 18.15 % (Table 6).

Table 5

Comparative analysis of laboratory parameters prior to the program implementation and after it

Parameters	Prior to the program implementation	After the program was implemented	*p**
Low density lipoproteins, mmol/dm^3	5.5 ± 0.5	4.9 ± 0.2	**<0.05**
C-reactive protein, supersensitive, mg/dm^3	6.7 ± 2.2	4.7 ± 0.5	**<0.05**
Uric acid, μmol/dm^3	390 ± 82.7	267 ± 37.3	**<0.05**
Homocysteine, mg/dm^3	15.1 ± 3.2	8.9 ± 2.4	**<0.05**

Note: **p* means validity of discrepancies between groups.

Table 6

Functional activity of the brachial artery endothelium: comparative analysis prior to and after the program implementation

Parameter	Prior to the program implementation	After the program was implemented	*p**
Minimal growth in the brachial artery diameter, %	5	10.42	**<0.05**
Maximum growth in the brachial artery diameter, %	32	28.57	**<0.05**
Variation range (a difference between minimal and maximum growth in diameter, %)	27	18.15	**<0.05**

Note: **p* means validity of discrepancies between the test and the reference groups.

Table 7

Ultrasound scanning performed on brachiocephalic arteries: comparative analysis of the results prior to and after the program implementation

Parameter	Prior to the program implementation	After the program was implemented	*p**
Intima-media thickness	1.2 ± 0.09	0.9 ± 0.07	**<0.05**

Note: **p* means validity of discrepancies between the test and the reference groups.

Ultrasound scanning performed on BCA prior to the program implementation and after it revealed a decrease in IMT and it also indicated that there was an improvement in vessel endothelium structure (Table 7).

We assessed efficiency of prevention program implementation and revealed that a relation between atherogenic cholesterol fractions (LDLP) and working conditions ceased to be authentic (RR = 1.2, 95 % CI = 0.9–1.6); and there was a decrease in etiological fraction and relative risks for such parameters as contents of uric acid in blood (RR = 1.3, 95 % CI = 1.3–9.6; EF = 32.5 %) and functional activity of the brachial artery endothelium (RR = 2.1, 95 % CI = 1.1–6.3; EF = 33 %); that is, there was a reduction in risks of circulatory system diseases and respiratory organs diseases

Conclusions.

1. When the corporate prevention program was implemented, it resulted in lower occupational causality of certain diseases for workers employed at chemical production; it was true for circulatory system diseases (EF = 66 % prior to the program implementation; EF = 47 % after it was implemented) and respiratory organs diseases (EF = 51 % prior to the program implementation; EF = 39 % after it was implemented).

2. The prevention program implementation led to practically a 3-time decrease in number of workers who couldn't continue their work due to contraindications (from 33 % to 11 % due to AH, and from 14.5 % to 5 % due to respiratory organs diseases).

3. Implementation of corporate prevention programs at enterprises allows reducing risks of circulatory system diseases and respiratory origins diseases, gives a worker an opportunity to preserve his or her working ability, and helps an employer preserve labor potential of an enterprise.

Funding. The research was not granted any sponsor support.

Conflict of interests. The authors declare there is no any conflict of interests.

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Received: 23.04.2020
Accepted: 03.06.2020
Published: 30.06.2020

HEALTH RISK ANALYSIS IN EPIDEMIOLOGY

UDC 57.032; 614.446.3
DOI: 10.21668/health.risk/2020.2.09.eng

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DYNAMICS OF LOCAL EPIDEMIC COVID-19 OUTBREAK THROUGH THE PRISM OF COMPARTMENT MODELING

V.F. Obesnyuk

The Southern Urals Biophysics Institute of the RF Federal Medical and Biological Agency, 19 Ozerskoe drive, Ozersk, 456780, Russian Federation

Our research goal was to tentatively assess necessary volumes and quality of statistic description necessary for describing coronavirus epidemic outbreak. We took COVID-19 epidemics development in Hubei (China) as an example and showed that an existing system of descriptive epidemiologic concepts based on lethality, mortality and the basic reproduction number can turn out to be insufficient for full-fledged description of an epidemic and prediction of its outcomes. The said province was chosen as an object for analysis at a period when the outbreak was just starting; during that period activities aimed at epidemiologic investigations and coercive limitations of contacts between people didn't yet yield expected results.

Data and methods. We revealed that more qualitative statistic description given for infectious processes in a population could be gained with a relatively simple and well-known compartment-model; deviations of actual epidemiologic observations from its parameters can be interpreted as being purely stochastic ones.

Results. To improve prediction abilities, it is necessary to abandon a conventional epidemiologic approach as it is based on a mixture of effects produced by two completely different biological factors in one or two combined parameters. It is advisable to separately describe a process of epidemic spread and a retrospect relation between risks of death and risk factors spread among an infected part of a population over a period of epidemic.

Unsatisfactory insight into a mechanism of infection development in a population and absence of control over its dynamics can impede efforts aimed at suppressing it. A model of an epidemic process can be applied when individual medical insurance schemes are developed and utilized capacities of infectious hospitals and observators are predicted.

Key words: *model, SIR, SEIR, parameter, lethality, mortality, reproduction number, hidden variables, confidence interval.*

Introduction and overview. This work is devoted to finding the correct statistical description of infectious outbreaks in the interests of health insurance development [1]; however, this would not have been possible without taking into account certain specific details of any epidemic process, which we will consider in terms of recent events in Wuhan (China).

Despite clear and explicit warnings [2, 3], the massive COVID-19 epidemic caused by the 2019-nCoV coronavirus (type SARS-CoV-2) took local health authorities by surprise. The first reports of sick and dead in Wuhan in December 2019 did not cause much concern, as all reported cases were perceived in the context of seasonal increases in endemic acute respiratory infections. Only by mid-January 2020, it became clear that more than 40 identified cases of severe pneumonia did not respond to traditional treatment, because the patients had recently been carriers of a new form of coronavirus. In January, it was found that the pathogen was a coronavirus with its genome being only about 70 % similar to SARS. This allowed assuming there would be completely new peculiarities in epidemics development and they did not slow down to manifest themselves.

The very first case-control pilot studies [4] made it possible to state that the new virus was significantly transmissible and was predominantly spread via droplet contacts. The onset of the infection proceeds with mild symptoms and a very variable incubation pe-

Valerii F. Obesnyuk – Candidate of Physical-Mathematical Sciences, Associate Professor, Senior researcher (e-mail: v-f-o@subi.su; tel.: +7 (35130) 7-52-36; ORCID: https://orcid.org/0000-0002-2446-4390).

riod from 2 to 20 days. The presence of the virus in biological fluids can be determined by the results of the reverse real-time transcriptase-polymerase chain reaction (PCR test) carried out, as a rule, after typical symptoms of the disease have become apparent. Samples are usually taken from the nasopharynx; however, the test does not guarantee error-free operation. The report [5] indicated that when testing the characteristics of the test on a group of SARS-CoV-2 carriers, false-negative results were observed in 28–37 % cases. A smaller proportion of false-negative cases (<7 %) was demonstrated by the analysis of samples of bronchoalveolar fluid. During the asymptomatic period, it was usually impossible to detect carriers of the virus; however, four confirmed cases of COVID-19 transmission in Germany were recorded as a result of contacts during a business negotiation with a Chinese business representative who did not have symptoms of the disease [6]. Reports by Chinese doctors also confirm such contagion is quite possible [7].

It was stated that immunocompromised people or people with chronic diseases san the highest risks of contagion, despite the fact that everyone, regardless of age, had a chance of contracting a new virus. Most people with clinical signs were aged from 28 to 89. Children and young people below 20 were almost absent among people with confirmed infection. According to data as of January 28, the World Health Organization noted that approximately 80 % of the infected people had COVID-19 in a mild form; 14 % – in severe (pneumonia with bilateral diffuse damage to the alveoli, with formation of hyaline membranes, pulmonary edema, and leukopenia); 5 % – in critical one (respiratory tract failure, organ failure, septic shock). Confirmed risk factors included age (older than 65, *RR* = 2.15: 95 % *CI*: 1.11–4.14; $p = 0.023$); severity of the disease (*RR* = 11.12; 95 % *CI*: 4.63–26.68; $p < 0.01$); a jump in the level of neutrophils at the beginning of the disease and diffuse darkening on the chest radiograph upon admission (*RR* = 3.30; 95 % *CI*: 1.42–7.6; p = 0.005) [4]. In fact, the same set of risk factors for death was confirmed later in a cohort study [8]. And high fever (≥39 °C) was associated with more probable occurrence of acute respiratory syndrome (*RR* = 1.77; 95 % *CI*: 1.11–2.84) and lower probability of lethal outcome (*RR* = 0.41; 95 % *CI*: 0.21–0.82). As Zhang Dingyu, the head of Wuhan Jinyintan Hospital, reported to Xinhua News Agency [9], people in Wuhan who had already overcome the disease had antibodies in their blood that inhibited development of the infection, prevented complications and even cured seriously ill patients who were given plasma transfusions from recovered people. Other antiviral medications that were given to patients in grave cases included kaletra (a combination of two medications applied to treat HIV infection, lopinavir and ritonavir) and remdesivir. The first blocks effects produced by enzymes-proteases that are necessary for viruses to infect cells; the second one inhibits functions of a genome corrector that corrects SARS-CoV-2 virus mistakes. Oseltamivir-124 as well as anti-bacterial treatments were also widely used. Patients with acute respiratory syndrome were treated with methyl prednisolone as it reduced risks of lethal outcome (*RR* = 0.38; 95 % *CI*: 0.20–0.72) [8]. The above-mentioned treatment procedure didn't guarantee complete recovery. However, in spite of all PCR tests errors [10], authenticity of an observed epidemic is undoubted. More than 1,000 medical personnel got infected and several dozens of them died.

In connection with the emergence of a new disease, the natural task arises – assessing the scale of the epidemic or of the possible consequences when it occurs again basing on available descriptive epidemiological data. Understanding a mechanism of infection is important. It may be useful for forecasting, taking into account social and non-pharmaceutical prevention.

The research goal was an attempt to assess the necessary volume and quality of statistical description given to coronavirus epidemic outbreak. The current methodology based on using a system of two or three statistical indicators seems very primitive in this area of knowledge due to the direct borrowing of description tools from non-infectious epidemiology. First of all, it is related to such

concepts as cumulative death rate and case fatality rate. Even experts working at sanitary-epidemiologic establishments tended to confuse these two terms. Both values are used in one of two dichotomous schemes: either «sick – dead» or «infected – dead». It seems none of them can be used to perform a comprehensive analysis of an epidemic process as a whole; however, their limited capabilities are mentioned only in case there is another outbreak, let alone complete absence of specific parameters that could be used by epidemiologists and infectiologists to predict an unfavorable outcome given a combination of certain conditions. Moreover, experience accumulated via observations, both over an epidemic outbreak in Hubei province, and over a pandemic which is now spreading all over the world indicated that death rate and case fatality rate can't be considered constant characteristics assigned to a specific communicable disease; they are a changeable process influenced by multiple factors.

In order to achieve our goal, **the task was set to study** a different technology for assessing the epidemic process development on the basis of compartment modeling which would include the visibility of the traditional epidemiological post factum description along with some predictive capabilities. The SIR (susceptible – infected – removed) [9] and SEIR (susceptible exposed – infected – removed) [10] models were taken as the basis in question; these models have been known for almost a hundred years, but their application in practices by epidemiologists is still under question, or ends with separate sporadic attempts[1]. Basically, this area of research today is more likely to be described as "mathematical epidemiology" [11] and most practicing epidemiologists perceive it as an oxymoron. Meanwhile, the epidemic outbreak of coronavirus in Hubei Province seems unique in terms of the practical verification of epidemiological models due to the unprecedented measures taken by the Chinese authorities and people to limit the infection spread both in the epicenter of infection - the city of Wuhan and throughout China. This circumstance significantly localized the outbreak and made it possible to operate with the concept of "compartment". Direct public monitoring of the epidemic turned out to be directly related to compartment modeling [12, 13].

Data and methods. A statistical forecast of dynamics is possible only basing on generalization of known analogues, observations over the epidemic outbreak itself and an assessment of its quantitative values. First of all, it regards death rate and case fatality rate. The Epidemiological Dictionary by J. Last[2] defines the first value as «… the proportion of representatives of the group who died during a certain period …» (CDR). The second is defined as the ratio of the increase in the number of «… cases of a certain disease ending in a fatal outcome for a certain period … to the number of diagnosed cases of the disease [*for the same period*]» (CFR). It is clear from the definitions that in the first case we deal with n probabilistic cohort value for narrow-specific subgroups of the population (subcohorts); in the second, with the ratio of two speeds, i.e. population value not related to the probabilistic nature of a disease. The values simultaneously characterize not only the properties of viral activity, but also the quality of treatment, which makes it difficult to predict the dynamics when procedures for treating a new disease have not yet been developed. Moreover, both death rate and fatality rate themselves are the processes subject to the influence of a lot of factors. It became quite obvious in case of Chinese coronavirus infections. At that, none of the values claims to be a comprehensive tool for reliable prediction what outcomes an epidemic outbreak can possibly have.

The specificity and limitations of the description with CDR and CFR values has been realized long ago. However, observations demonstrate that the transition to more detailed

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schemes with more than two states, for example, based on the well-known nonlinear probabilistic SIR model [11] is also not infallible, as this concept often results in higher expectations of damage to the population. The reason lies in a compartment of «susceptible» to infection not being determined clearly at the stage of initial almost exponential growth in the number of infected. If the latter significantly exceeds single cases, then the dynamics should be well described by the basic nonlinear differential equation of the SIR model:

$$\frac{dI}{dt} = \alpha \cdot S \cdot I - \eta \cdot I \qquad (1)$$

where $S, I -$ are numbers of susceptible and infected; $t -$ is calendar time; $\alpha, \eta -$ are probabilistic parameters of the process. It is easy to see that at the beginning of an epidemic outbreak, when $S(t) \approx N,$ where $N -$ is a potential number of all participants in the epidemic process, the equation (1) does lead to an almost exponential increase for I according to the law $I(t) \sim \exp\left[(\alpha \cdot N - \eta)\, t\right]$ along with a typical doubling time period $DT \approx \ln(2)/(\alpha \cdot N - \eta),$ that could be observed empirically. The existence of this growth phase is similar to a hypothesis on an increase in a number of infected according to the geometric progression law. However, it is impossible to determine hidden parameters α and N simultaneously and independently and directly from the observations of a single exponent as well as to predict the value N in advance, since the latter is associated not so much with the properties of a viral infection as with social and non-pharmaceutical measures aimed at creating barriers to its spread. For this reason separate monitoring over a rate at which new infected cases occur and new cases in which participants in the epidemic process exit out of it due to death or recovery is usually used in order to assess the initial phase. The ratio of such rates $R0 = \alpha \cdot S/\eta \approx \alpha \cdot N/\eta$ in the framework of this approach is an almost constant value. It is called the base reproductive infection number. According to the reference, [14, 15] it can be considered as an expected number of infections directly caused by one infection carrier in a population where all individuals are susceptible (provided there is no deliberate intervention in the transmission of the disease) during the exponential growth phase. By definition, $R0$ cannot be changed using vaccination campaigns, it is not a biological constant for a pathogen, it is influenced by various environmental factors, and the value of the indicator may depend on the mathematical model used [14, 15].

A couple of estimates $R0$ or DT already allows us to make some predictions, however, practical review of such modeling [16] demonstrates that the predicted results of a coronavirus outbreak in Hubei should have been significantly more destructive than they actually are [12, 13]. Indeed, the SIR model at values $R0 \approx 3-5$ leads to the expectation of only $\approx \exp(-R0) < 2\,\%$ of those not affected by the infection at the epicenter, and blocking an epidemic outbreak would require prevention of infection for $(1-1/R0) > 75\,\%$ of the population. With 12 million people living in Wuhan, the limit of the epidemic growth should have been observed at the level of several million infected people, while in reality by mid-March 2020 their number in the whole China did not exceed 200 thousand people. It is important to note that the available observational statistics [12, 13] make it possible to extend the SIR compartment model not only to the initial phase of the epidemic growth, but also to its middle, when the number of susceptible people is already significantly different from N. However, it turned out that the deviation of real observations from model predictions from a statistical point of view cannot be interpreted as random. This circumstance directly indicates the inadequacy of the three-compartment SIR model along with a system of death rate and fatality rate values.

The research method used in this article was based on a modified version of another well-known model – SEIR [10]. It allowed integrating the concepts of death rate, fatality rate and an analogue of the basic reproductive number, and besides, provided a statistically

significant agreement between observations and predictions. Practically observed deviations [12, 13] in the dynamics of the number of infected and removed from strictly exponential laws also made it possible to obtain reasonable estimates of the total number of participants in the infection process.

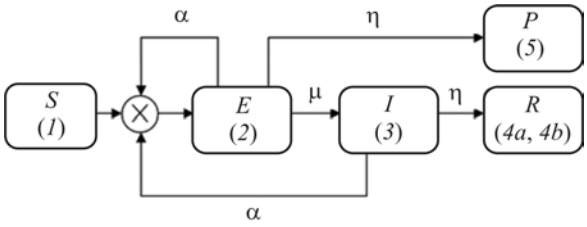

Figure 1. Markov diagram showing states of epidemic process participants. Indications: *1* – susceptible; *2* – exposed; *3* – confirmed infection; *4a* – recovered; *4b* – dead; *5* – resistant

In our opinion, the statistical discrepancy between the known epidemiological models and reality is due to the unaccounted increased transmissibility of COVID-19 and to the uncertain interpretation of the incubation period concept. The fact [6], the source of which is a country with a fairly high level of medical care, indicates that virus carriers are able to infect other people in an asymptomatic period. At the same time, in the same group there is a substantial proportion of persons overcoming the disease asymptomatically and not falling into official statistics. Our modified version of the Markov structural diagram of the model is presented in Figure 1. Its main difference from the original SEIR model was in the fact that the modified model allowed the possibility of infection from both persons with proved infection and from asymptomatic carriers. We neglected mortality from other causes and migration due to the short duration of the epidemic outbreak and severe restrictions for transportation within the province (one focus of infection – one epidemic process). We also neglected the chance of re-infection during the outbreak. It is clear from the diagram that for a complete description of the dynamics, at least 5 values are necessary (3 parameters of the intensity of transitions from state to state and 2 initial conditions for states «E» and «S»). However, it should be noted that the statistics of the states «S», «E» and «P», unfortunately, are practically unavailable with modern capabilities for monitoring over epidemiological processes. However, we shouldn't view the given modeling as a tool to predict future situation as SEIR model lacks a priori and direct allowing for structure of social relations between persons as well as an overall number of participants in an epidemic process. The value was also estimated as per empirical data as an actual parameter in the model.

In order to obtain a quantitative description, a system of three basic differential equations was solved numerically

$$\frac{dS}{dt} = -\alpha \cdot (S + E) \cdot I, \qquad (2)$$

$$\frac{dE}{dt} = \alpha \cdot (S + E) \cdot I - \mu \cdot E - \eta \cdot E, \qquad (3)$$

$$\frac{dI}{dt} = \mu \cdot E - \eta \cdot I, \qquad (4)$$

and was supplemented by three more equations, allowing to find cumulative values for newly infected $C(t)$, resistant $P(t)$ and removed $R(t)$ by calculated continuous process speeds. Using two discrete-valued cumulative processes C_k and R_k observed in practice, the model was adjusted in accordance with the five-parameter functional

$$\Omega(\alpha, \mu, \eta, S_0, E_0) = \sum_{k=1}^{k\max-1} \left[\frac{\left(\ln(C_k) - \ln(C(t_k))\right)^2}{\sigma_C^2} + \frac{\left(\ln(R_k) - \ln(R(t_k))\right)^2}{\sigma_R^2} \right] \qquad (5)$$

where σ_C and σ_R – are observational log-normal variation parameters C_k and R_k, defined empirically by their stochastic bias from the time trend in semi-logarithmic coordinates. Minimization of functional (5) allows finding the transition intensity parameters α, μ, η alongside with the initial conditions S_0, E_0. The parameter η was responsible for the in-

tensity of individuals being removed from the compartments «E» and «I». It is accepted the same in both cases, since there was no reason to assume otherwise. The same applies to the parameter α, which is a contribution to the intensity of each new infection from individual representatives of either compartment «E» or compartment «I». The initial conditions for the instantaneous values of the variables I, R, P, C were borrowed from empirical observations as of January 15, 2020.

The use of the functional (5) can be approximately interpreted as a Bayesian method for estimating model parameters under the assumption of a lognormal distribution of cumulative values C_k and R_k subject to the choice of a uniform prior in the most practically significant part in the space of logarithmic parameter values. Logarithm operations were used because it was necessary to work with fundamentally non-negative quantities, as well as for approximation purposes. Such an interpretation allows not only to find the best values of the model parameters, but also to estimate confidence intervals, despite the obvious incompleteness of the description of observations. It also allows you to evaluate the quality of the approximation achieved by recording the inevitable minimum deviation of the functional Ω from the ideal zero value due to independent random fluctuations of a real discrete-valued process (analog of the chi-square test) during daily observation.

Results and discussion. It turned out that within the framework of the proposed scheme, it is possible to give a satisfactory description (Fig. 2) of the available data [12, 13] based on the cumulative dynamics of those infected and those who left without even appealing to additional information on the impact exerted by the identified risk factors and age structure of the population in Hubei Province.

The analysis was based on data for 45 days of the outbreak from January 15 to February 28. The results obtained via comparing the model and actual data are presented in Fig. 2, and a full forecast of the epidemic outbreak for Hubei is shown in Fig. 3, which demonstrates the dynamics of the current

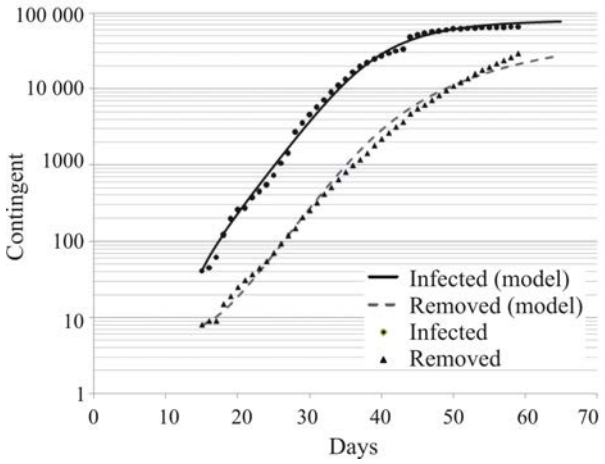

Figure 2. Comparison of cumulative dynamics of infected and removed due to death or recovery with SEIR model calculations. The beginning of 2020 is taken as zero abscissa

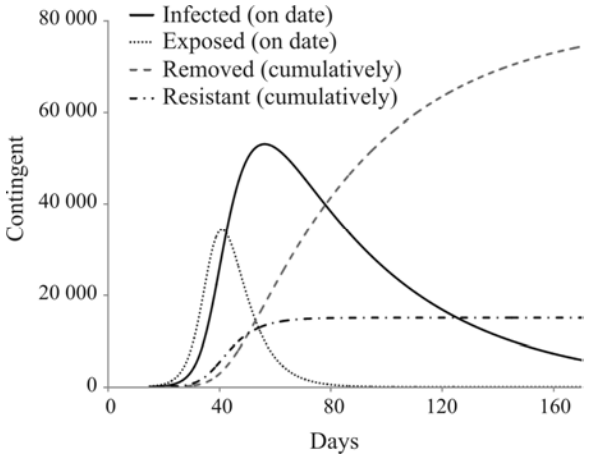

Figure 3. The result of modeling the population dynamics of various compartments. The beginning of 2020 is taken as zero abscissa

numbers of exposed and infected as of the date of observation. According to the forecast, provided that the unprecedented measures aimed at isolating the population living in the province are maintained, the current number of infected peaks at 53 thousand people on February 26, 2020, but this value should decrease quite slowly throughout the first half of the year. The total number of people infected in Hubei Province for a year will not exceed 100 thousand people. It is interesting to note that this estimation doesn't contradict an expert opinion expressed by M.O. Favorov, Doctor of Medical sciences and a famous Russian and American field epidemiologist. Using his own experience, he predicted that Chinese epidemiologists would take extreme measures as well as expected outcomes in his interview to «Echo of

Moscow» radio station on February 03, 2020. He said that «…my colleagues and I… professors from Soviet times held a conference over Skype and concluded that [there will be] 100 thousand immunized, very roughly… some having a mild form of the disease, some a severe one…» [18].

As a result of the calculations, an estimate of the total number of participants in the infection process that has not yet ended in Hubei was obtained: $N =$ 95 thousand people (95 % *CI*: 64.4–140.3), as well as process intensity parameters – $\alpha = 3.2$ per day per million carriers of the virus (95 % *CI*: 2.21–4.65); $\eta = 0.021$ per day (95 % *CI*: 0.019–0.022); $\mu = 0.113$ per day (95 % *CI*: 0.041–0.316). It should be noted that the reciprocal value for μ can be interpreted as the characteristic transition time between the «E–I» states, which will be part of the incubation period, i.e. 8.9 days (95 % *CI*: 3.2–24). The central values in our case are close to the median estimates.

The achieved extreme value of the evaluation functional (5) was 88.03 units, which did not go beyond the 95 % confidence area with 83 degrees of freedom of the functional (5) and $\chi^2_{crit} = 105.3$. For comparison, this is significantly better than the result of applying a competing three-parameter SIR model with a minimum value of the evaluation functional $\Omega_{\min} \approx 161.81$, which allows us to assert the existence of a statistically significant difference in the quality of the description by the likelihood ratio test ($P < 0.001$). Obviously, the parameters η and μ characterize both the disease itself and the physiological properties of the infected population; on the contrary, the parameter α carries not only information about the transmissibility of the SARS-Cov-2 virus, but also reflects the inherent intensity of social relations in the Chinese province. This knowledge may be useful for future predictions when, due to the transition of the epidemic to its pandemic stage, it would be possible that the diseases returned to China again. It is also important to note that the latent number of people exposed at the beginning of the period of systematic observation (January 15) was estimated to be 165 people (95 % *CI*: 87–312), that is more than the officially confirmed total number of infected people at this date. According to sources in the Chinese press opening stepwise, this estimate starts to be proved, although it is not (will not be) included in official statistics. There is no doubt that in other foci of infection – in the cities of Bergamo (Italy), Daegu (South Korea), Qom (Iran) – a sharp outbreak of the infection process was due to the same circumstance.

It also seems important to point out a number of unexpected features in the compartment models, the existence of which was difficult to assume based on the type of structural diagram in Figure 1. Many epidemiologists closely monitoring the behavior of the fatality rate in different periods of epidemic outbreaks and in different countries had noted that the fatality rate for the one and same virus varies markedly in different regions, and over time behaves extremely non-monotonously. Fatality rate as the ratio between two cumulatively determined process rates over a period has a statistically significant decline at the beginning of the epidemic and a statistically significant increase towards its end. The usual explanations given in this case associate the initial decline with the adaptation of the virus to virus carriers directly during the epidemic, and the subsequent increase with a delay in the processes of death and recovery in relation to the infection processes, which should lead to an agreement between fatality and death rates after the end of the epidemic if their cumulative values are equally expressed in percentage form [18]. As it turned out in our case, the adaptation/maladaptation hypothesis is redundant here, because the system of equations (2–4) essentially describes the transition process of switching a population from one almost stationary state to another. The nonmonotonic dynamics of a certain combination of system state variables in this case may be its intrinsic feature. The degree of non-monotony intensity depends on the ratio between the initial variables, and the presence of single superspreaders at the start of the epidemic can play a certain role in this. Judging by model calculations and their agreement with empirical data, this concerns not only the fatality rate, but also the effective reproductive number (Figs. 4 and 5). The trend of the removing rate is the closest analogue to the trend of cumulative fatality

rate, but unlike the latter, it has not only the number of deaths in the numerator, but also the number of recovered. By analogy with the «case fatality rate/ratio», it could be called the «case removing ratio» (CRR). Obviously, it does not reflect the quality of treatment provided for patients or the conditional risk of their death, but the dynamics of competition between the flows of events in the infection process. If a death rate is known, which depends to a large extent on the distribution of risk factors among infected people, on the strength of the «factor – effect» relationships and on the quality of treatment, then one can switch from CRR to fatality rate by simple multiplication. A report [17] could be an example of such prototype if its authors did not rely on the poorly chosen CFR and the inappropriate concept of person-days at risk, used by analogy with person-years in non-infectious epidemiology. Assessment of methylprednisolone usage can also serve as an example of an analysis of the impact of treatment quality on traditional indicators of the infectious process [8]. In this case, it is important to take into account the statistically significant difference in the intensity of death rate processes, with a slight difference in the probabilities of survival, indicating low treatment efficiency.

For example, it is known that death rate from coronavirus in Hubei Province at the beginning of the epidemic varied around 30–50 %, then from Fig. 4 it follows that the nominal fatality rate at the end of January 2020 reached 2–3 %, which is in good agreement with the recorded statistics.

Conclusion. Thus, it was stated that in context of a rapidly developing infectious and epidemic process its traditional statistical description using death rates and fatality rates is not quite consistent with the purposes of descriptive epidemiology as it does not allow assessing or predicting the expected consequences and to take response measures that are adequate to the situation. Attracting an additional concept of the epidemic's basic reproductive number also does not save the situation. Moreover, the observed values of $R0$ can diverge significantly from those that are theoretically assumed. The main dynamics of the epidemic process within one infectious focus

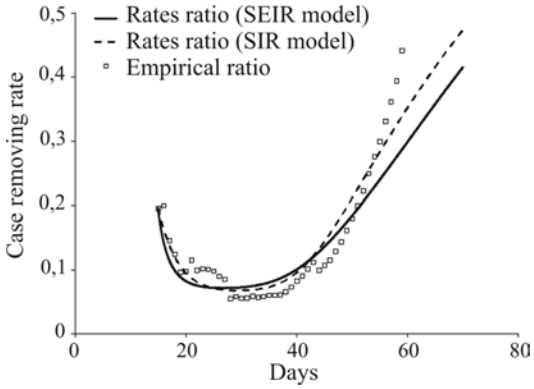

Figure 4. Comparison of the model and empirical dynamics of the cumulative removal rate, introduced by analogy with the fatality rate, taking into account both reasons for leaving the epidemic process. The beginning of 2020 is taken as zero abscissa

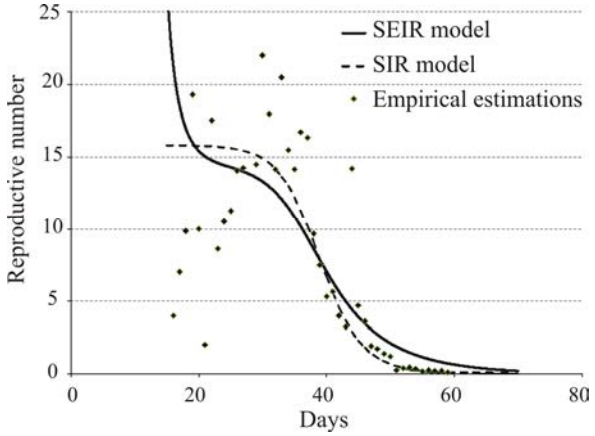

Figure 5. Evaluation of effective reproductive numbers in an epidemic process using three approaches. The beginning of 2020 is taken as zero abscissa.

can and should be described at least in the framework of the simplest compartment models, not narrowed down to 1–2 values. In addition to the dynamics, the traditional retrospective cohort study «factors – risk» taking into account the severity of the course of the infectious disease and the quality of treatment should be an additional the object of the epidemiological study. The description of the transition from the epidemic stage to the pandemic stage will require even more significant complication of the descriptive language due to considering the age, social and geographical stratification of the population of countries, which will inevitably lead to the convergence of traditional and mathematical epidemiology in the future.

Funding. The research was not granted any sponsor support.

Conflict of interest. The authors declare there is no any conflict of interests.

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Received: 04.05.2020
Accepted: 04.06.2020
Published: 30.06.2020

UDC 613.2+614.31+613.636
DOI: 10.21668/health.risk/2020.2.10.eng

Read online

BACTERIAL PROFILES AND PHENOTYPIC BIOMARKERS OF MICROBIOTA ISOLATES IN HABITAT: HAZARD IDENTIFICATION FACTORS

N.V. Dudchik[1], S.I. Sychik[1], O.E. Nezhvinskaya[1], N.D. Kolomiets[2], E.V. Fedorenko[1], E.V. Drozdova[1], O.V. Tonko[2], O.A. Emel'yanova[1]

[1]Scientific Practical Centre of Hygiene, 8 Akademicheskaya Str., Minsk, 220012, Belarus
[2]Belarus Medical Academy for Post-graduate Studies, 3/3 P. Brovki Str., Minsk, 220013, Belarus

The present work focuses on assessing bacterial profiles of microbiota existing on technological equipment applied in food products manufacturing, objects located inside medical and preventive facilities, and water objects in recreation zones; another goal was to examine phenotypic properties of opportunistic pathogenic bacteria isolates as hazard identification factors within the framework of risk assessment concept.

Our research objects were strains of Escherichia, Klebsiella, Enterobacter, Staphylococcus, Pseudomonas, Citrobacter and Serratia families that were detected and extracted due to hygienic monitoring activities performed in 2013–2017.

Samples were taken via washing, direct inoculation, membrane filtration, and instrumental aspiration technique. Microbial status was analyzed with cultural and biochemical techniques on nutrient and differential-diagnostic media with subsequent confirmation with polymerase chain reaction (PCR). Phenotypic peculiarities were examined in vitro with conventional biochemical and microbiological techniques in conformity with the requirement fixed in Good Laboratory Practice.

We revealed peculiarities of microbial profiles belonging to opportunistic pathogenic microbiota on different objects in habitats. The greatest groups included staphylococci detected in the air inside medical organizations with 1–4 cleanness degree (44 %); Enterobacteriaceae family bacteria, in washes off objects located in manufacturing and medical and prevention facilities (64 % and 69 % accordingly); Pseudomonas family bacteria, in water objects (46 %). 60 (36 %) isolates out of 167 examined ones had modified morphological and tinctorial signs regarding those typical for a family. Most isolates had a set of modified or atypical metabolomic signs such as hemolytic and lecithinase activities, apparent persistent factors, and ability to create biofilms. Opportunistic pathogenic bacteria strains extracted from washes off objects located inside food products manufacturing and medical and preventive facilities were the most potentially aggressive. Isolates from the same families extracted from water objects in recreation zones and air inside medical and preventive facilities had less apparent phenotypic properties that characterized their pathogenic potential. Our experimental data provide useful materials for examining a phenomenon related to changes in phenotypic properties; they can be applied during revealing and drawing up a hazard profile and for minimizing uncertainty within the concept of microbiological risk analysis.

Key words: *microorganisms, microbiota, microbial status, contamination, biomarkers, biofilms creation, recovery techniques, microbiologic risk analysis.*

Natal'ya V. Dudchik – Doctor of Biological Sciences, Associate Professor, Head of Microbiology Laboratory (e-mail: n_dudchik@mail.ru, n_dudchik@tut.by; tel.: +375 (17) 284-13-85; ORCID: https://orcid.org/0000-0002-5877-9307).

Sergei I. Sychik – Candidate of Medical Sciences, Associate Professor, Director (e-mail: rspch@rspch.by; tel.: +375 (17) 284-13-70; ORCID: http://orcid.org/0000-0002-5493-9799).

Ol'ga E. Nezhvinskaya – Junior researcher at the Laboratory of Microbiology (e-mail: rscph@rscph.by; tel.:+375 (17) 284-13-85; ORCID: https://orcid.org/0000-0002-4456-5922).

Natal'ya D. Kolomiets – Doctor of Medical Sciences, Professor, Head of the Department for Epidemiology and Microbiology (e-mail: ndkolomiets@mail.ru; tel.:+375 (17) 265-33-41; ORCID: http://orcid.org/0000-0002-4837-5181).

Ekaterina V. Fedorenko – Candidate of Medical Sciences, Associate Professor, doctoral candidate, Deputy Director responsible for support of practical sanitary-epidemiologic surveillance and work with the Eurasian Economic Commission (e-mail: rscph@rscph.by; tel.: +375 (17) 284-13-70; +375 (17) 284-03-45; ORCID: http://orcid.org/0000-0003-1240-1234).

Elena V. Drozdova – Candidate of Medical Sciences, Associate Professor, doctoral candidate, Deputy Director responsible for research (e-mail: rscph@rscph.by; tel.: +375 (17) 284-13-70, +375 (17) 284-03-45; ORCID: http://orcid.org/0000-0002-3032-0895).

Oksana V. Tonko – Candidate of Medical Sciences, Associate Professor at the Department for Epidemiology and Microbiology (e-mail: oxana_tonko@tut.by; tel.: +375 (17) 265-33-41; ORCID: https://orcid.org/0000-0002-5877-9307).

Ol'ga A. Emel'yanova – Candidate of Biological Sciences, Senior researcher at the Laboratory of Microbiology (e-mail: rscph@rscph.by; tel.: +375 (17) 284-13-70, +375 (17) 284-03-45; ORCID: https://orcid.org/0000-0001-6853-3431).

Contemporary medical and biological technologies and laboratory practices provide wide opportunities to examine microorganisms' properties both at phenotypic and genotypic levels; they give an insight into ecologic, physiological, and population aspects of microbiota and it helps providing hygienic safety of the environment people live in. Use of predictive biomarkers as significant instruments in the process enables understanding and studying mechanisms for strains' pathogenic potential occurrence taking into account anthropogenic loads on microbiota created by environmental objects. Such an approach is substantiated with provisions of effective biomedical technology «omics». Over the last years scientists have been making attempts to create a basis for constructive discussions, understanding, integration and use of omics data within the concept of microbiological risk existing in food and water matrices. Integration is aimed at solving certain tasks arising in microbiological risk assessment: study on phenotypic and genotypic variability and changeability of microorganisms; multidirectional interactions with biotic and abiotic environmental factors including changes in sets of biomarkers that create pathogenic and virulent potential. It provides the most complete identification of microbiological hazards and creation of objective risk profiles; it also minimizes uncertainties in risk analysis procedures [1, 2].

There is a phenomenon related to opportunistic and emergent infections; it has become a separate medical and biological problem. The phenomenon can be explained via phenotypic and genotypic signs being modified, including etiologic and pathogenetic properties of opportunistic pathogenic microorganisms under exposure to quantitatively and qualitatively changing anthropogenic factors [3, 4]. Food products, technological processes applied in food manufacturing, water objects, and environment inside medical and preventive organizations are viewed as completely new ecological niches that have occurred due to industrial development and considerable anthropogenic loads. All the above mentioned makes it necessary to perform more profound research on properties of microbiota existing in certain environmental objects, especially given wide and systematic use of modifying factors (disinfectants, preservatives, and physical factors) in order to develop efficient measures aimed at microbiological risks management.

Our research goal was to experimentally determine bacterial profiles typical for isolates of opportunistic pathogenic microbiota existing on and in certain anthropogenic environmental objects; another goal was to examine physiological, biochemical, tinctorial, and morphological biomarkers of pathogenic potential and then apply them in creating a microbiological risk profile.

Data and methods. *A procedure for detecting microorganisms on surfaces of technological equipment installed at food production facilities and on objects located inside medical and preventive organizations.* We applied wash-offs as the most conventional and most widely used method in field observations. Wash-offs were obtained with sterile wetted cotton tampons. A sample taken off a surface with its square being 10x10 cm (100 cm^2) was considered to be representative.

A procedure for detecting microorganisms from surface water objects located in recreational zones. We applied direct inoculation and membrane filtration of water samples.

A procedure for detecting microorganisms in air inside medical and preventive facilities. Air samples with their volume being 100–500 dm^3 were taken via instrumental aspiration on contact Petri dishes with nutritional or differential-diagnostic media.

Microbe status of all taken samples was analyzed with cultural procedures in nutritional and differential-diagnostic media; incubation was performed under conditions optimal for a detected microorganism. We took into account all colonies that emerged on the surface and within agar layers.

Identification up to pure culture species was performed with VITEK (*Biomerieux*) microbiological analyzer after samples had been dyed as per Gram; verification was per-

formed with polymerase chain reaction (PCR) according to GLP principles.

Hemolytic and lecitinase activity and ability to persist were assessed with the use of a pure daily culture after it had been cultivated on nutritional agar for 18–24 hours under optimal temperature according to the procedure described in [5, 6]. Ability to create films was examined with an optical technique and cultivating on plates; detection was accomplished at ƛ=540 nm and results were interpreted as per *Stepanovic* criterion [6].

All the measuring and test devices applied in the research were properly verified and calibrated.

Results and discussion. We examined bacterial profiles of objects located at food productions and inside medical and preventive facilities, air inside medical and preventive facilities, and water object located in recreational zones.

We should note that it is critically important to select well-grounded procedures for detecting bacterial strains in environmental objects and examining their phenotypic properties in order to perform truly representative microbiological monitoring. Acceptability of such procedures is based on assessing a type, essence, and microbial contamination of monitoring objects [7].

Microbiota plays an important role both in maintaining ecological balance and in providing hygienic safety of environmental objects; therefore, determining profiles of bacterial community can give us some additional information about potential risks [8, 9].

In this research we determined bacteriological profiles and examined phenotypic properties of microbiota existing in recreational zones near three water basins located in Minsk region in spring and summer. During that period we detected and examined more than 100 bacterial isolates, most of them having properties typical for psychrophylic or mesophilic saprophyte bacteria (69%); microbial community structure to a great extent depended on temperature regime. Our data are well in line with conclusions made in several works focusing on examining microbiome in fresh water sources [10, 11]. S.L. Chang et al. [10] note that bacteria from *Enterococcus, Staphylococcus, Streptococcus, Bacteroides, Clostridium, Finegoldia, Burkholderia, Clostridia, Bacilli and Klebsiella* stems occur in water objects, and T. Gorham et al. [11] also mention rather significant contamination with *Escherichiacoli* indicating there is fecal contamination.

Microbial status of air and objects inside medical and preventive facilities in Minsk was examined during hygienic monitoring performed inside rooms with 1–4th cleanness category in 2016–2018. More than 70% out of 250 isolated strains were psychrotrophic saprophytes; mesophilic opportunistic pathogenic bacteria accounted for a smaller share as it was confirmed by several research works [12–14]. S. Lax et al. and F. Bolookat et al. [12, 13] give data on bacteria from *Corynebacterium, Staphylococcus u Streptococcus* stems being frequently detected in air inside medical and preventive facilities and a smaller share of detected bacteria belonging to *Acinetobacter and Pseudomonas, Micrococcus and Prevotella,* stems that were associated with normal microbiota existing on human skin and mucosa. S. Fujiyoshi et al. [14] also give data obtained via meta-analysis of microbiota inside medical facilities. Such stems as *Corynebacterium, Streptococcus, Enterobacteriaceae, Staphylococcus, Propionibacterium, Lactococcus* are also associated with normal human microbiota; *Streptophyta, Pseudomonas, Acinetobacter and Sphingomonas,* with air.

Microbiota existing at food production was examined at three food manufacturing facilities during hygienic monitoring performed in 2013–2015. It was reported in several works that bacterial microbiota could not only survive but also increase its population on a wide range of surfaces such as plastic, stainless steel, glass, ceramics, and wood. It can lead to cross-contamination between finished food products, food raw materials, and personnel. In some authors' opinion, dynamic control over microbial contamination is a significant tool for hygienic control over conditions existing at food production faculties and for contamination reduction [15–18].

Bacteria from *Escherichia, Klebsiella, Enterobacter, Staphylococcus, Pseudomonas, Citrobacter and Serratia* stems are widely spread microbial contaminants. They are components in microbiota existing at food productions, inside medical and preventive facilities, in water object located in recreational zones and represent a habitat of emergent and opportunistic infections that are transferred with food, water, and air. In this research we isolated, identified, and examined 167 opportunistic pathogenic microorganisms' strains. 59 isolates were isolated from surfaces of technological equipment installed at food productions; 35 isolates, from objects located inside medical and preventive faculties; 34 isolates, from air inside medical and preventive facilities; 39 isolates, from surface water objects located in recreational zones.

Apart from bacterial isolates, we detected more than 90 cases when objects were contaminated with yeast fungi from *Candida* stem, mold fungi from *Penicillium* and *Aspergillu,* stems; pathogenic bacteria from *Legionella* stem were detected in one water sample; pathogenic bacteria from *Salmonella* and *Listeria* stems were not detected in wash-offs from equipment installed at food productions (these data are not given here).

Experimental data are given in Table 1.

Table 1

Phenotypic properties of bacterial isolates isolated from wash-offs taken from objects located at food productions, objects and air inside medical and preventive facilities, and water object located in recreational zones

Stem	Phenotypic properties					
	Hemolysis	Anti-lisozyme activity	Anti-interferon activity	Lecitinase activity	Film creation	Morphologic and tinctorial signs
Wash-offs from food productions						
Escherichia (18 isolates)	γ	+/-	+/-	-	+/-	variable
Klebsiella (6 isolates)	γ	+/-	+/-	+/-	max	variable
Serratia (6 isolates)	γ	+/-	+/-	-	+/-	variable
Enterobacter (5 isolates)	γ	+/-	+/-	-	+/-	variable
Citrobacter (3 isolates)	γ	+/-	+/-	+/-	+/-	variable
Staphylococcus (11 isolates)	α/β	+/-	+/-	+-	min	variable /stable
Pseudomonas (10 isolates)	α/β	+/-	+/-	+/-	+	variable /stable
Wash-offs taken from objects located inside medical and preventive facilities						
Escherichia (9 isolates)	γ	+/-	+/-	+/-	+/-	variable /stable
Klebsiella (4 isolates)	γ	+/-	+/-	+/-	+/-	variable /stable
Serratia (3 isolates)	γ	+/-	+/-	+/-	+/-	variable /stable
Enterobacter (4 isolates)	γ	+/-	+/-	+/-	+/-	variable /stable
Citrobacter (4 isolates)	γ	+/-	+/-	+/-	+/-	variable /stable

Staphylococcus (6 isolates)	α/β	+/-	+/-	+/-	+/-	variable /stable
Pseudomonas (5 isolates)	α	+/-	+/-	+/-	+/-	variable /stable
Air samples taken inside medical and preventive facilities						
Escherichia (3 isolates)	γ	+/-	+/-	-	+/-	stable
Klebsiella (1 isolates)	γ	+/-	+/-	-	+/-	stable
Serratia (1 isolates)	γ	+/-	+/-	-	+/-	variable /stable
Enterobacter (1 isolates)	γ	+/-	+/-	-	+/-	variable /stable
Citrobacter (2 isolates)	γ	+/-	+/-	-	+/-	stable
Staphylococcus (15 isolates)	α/β	+/-	+/-	+/-	+/-	variable /stable
Pseudomonas (12 isolates)	α	+/-	+/-	+/-	+/-	stable
Water samples taken from water object in recreational zones						
Escherichia (6 isolates)	γ	+/-	+/-	-	+/-	variable /stable
Klebsiella (2 isolates)	γ	+/-	+/-	-	+/-	variable /stable
Serratia (1 isolate)	γ	+/-	+/-	-	+/-	variable /stable
Enterobacter (2 isolates)	γ	+/-	+/-	-	+/-	variable /stable
Citrobacter (2 isolates)	γ	+/-	+/-	-	+/-	variable /stable
Staphylococcus (8 isolates)	α/β	+/-	+/-	+/-	+/-	variable /stable
Pseudomonas (18 isolates)	α	+/-	+/-	+/-	max	variable /stable

Bacteria from *Enterobacteriaceae* family most frequently occurred in wash-offs from objects located at food productions and inside medical and preventive facilities, accounting for 64% and 69% of the total opportunistic pathogenic bacteria accordingly. Their share was 24% in air inside medical and treatment facilities and 33% in water objects. Staphylococci prevailed among opportunistic pathogenic microorganisms occurring in air inside medical and preventive facilities (44%). Bacteria from *Pseudomonas* stem took the leading place among pathogens in water objects (46%).

In our research 60 opportunistic pathogenic isolates out of 167 examined ones (36%) had obvious morphologic and tinctorial signs that were modified in comparison to those typical for a specific stem; these modifications included tint variability as per Gram, intrapopulation cells polymorphism that became apparent through sizes, shapes of cells and colonies, etc.

It was noted in several research works that virulence and pathogenicity of microbial contaminants were enhanced by exogenous secretion of certain enzymes and toxins produced by bacteria [19–21]. We revealed in our work that opportunistic pathogenic bacteria isolates detected on objects located at food productions and inside medical and preventive facilities and in water objects located in recreational zones had atypical or modified prop-

erties such as hemolytic and lecitinase activity, greater ability to persist, and ability to create biofilms.

β-hemolytic activity was revealed in all the examined *S. aureus* isolates; several *Staphylococcus spp* isolates with incomplete hemolytic activity was detected in air; α-hemolytic activity was revealed in *P. aeruginosa* isolates detected in water objects and wash-off from technological equipment; certain *Pseudomonas* stem isolates turned out to be able to accomplish complete hemolysis, even under increased temperature, and it can indicate that they were able to produce two types of hemolysins, thermolabile phospholipase C and thermostable glycolipid. Isolates from *Enterobacteriaceae* family had γ-hemolytic activity.

100% examined *Staphylococcus aureus* strains had lecitinase activity. Anti-interferon and anti-lysozyme activities as persistence factors are aimed at inactivating protection mechanisms a host might have. These phenotypic properties were the most apparent in isolates from *Staphylococcus* stem, and a type of object those isolates were detected in didn't make any significant difference regarding persistence properties intensity. 15 out of 39 *Staphylococcus* isolates had anti-lysozyme activity under lysozyme concentration being 4 mg/ml or lower; 23 strains had anti-interferon activity under interferon concentration being 2 IU/ml, and other strains, under concentration being 1 IU/ml. This phenomenon correlates well with *Staphylococci* strains growing quite intensely in nutritional agar with fucidin under fucidin concentration being equal to 0.00015–0.0003 mg/ml.

Bacteria from *Pseudomonas* stem produced pigments from pyocyanin and pyoverdine groups while pigments from pyomelanin group were produced by a few isolates only, and pigment formation occurred with significantly different intensity. We isolated five strains that produced two pigments simultaneously; most isolates produced pigments from one group; and we also detected an isolate without any pigments. At present mutations that result in weaker ability to produce pigments are viewed by researchers as mechanisms that enhance pathogenic potential this bacterium has, in particular in case of polymicrobe infection.

However, it is films creation that is the most perfect and complicated strategy adopted by bacteria as a response to impacts exerted by environmental factors. Examined strains had different abilities to create biofilms in a monoculture. All *Klebsiella pneumonia* strains were greatly able to create films according to *Stepanovic* criterion. Coagulase-negative staphylococci (*S. haemoliticus, S. sciuri, S.epidermidis*) had minimal activity regarding films creation. Coagulase-positive staphylococci were more active as regards biofilms creation in a model experiment and it is also confirmed by recent research data on hemolysin participation in creating *S. aureus* biofilm [21]. An ability by bacteria to create biofilms is interesting due to the fact that many microorganisms can change their properties, and their consortium – in a form of a biofilms – can acquire new properties that are not characteristic for strains that are included into it. According to some authors, inter-species communications among bacteria can make for synchronization of specialized functions performed by different species in a group. Phenotypic properties of strains in a biofilms differ considerably from properties that are typical for a microorganism stem and species. It has to do with metabolic activity parameters; ability to produce exogenous enzymes; persistence or sensitivity to antibiotics, sulfonamides, disinfectants; resistance to impacts exerted by adverse physical environmental factors (temperature, pH, osmotic concentration, and irradiation); existing epidemically significant markers etc.

Use of «omics» principles is an up-to-date and quite efficient approach to further methodological development of microbiological risks assessment; these principles, among other things, should be aimed at examining phenotypic variability in order to minimize uncertainties in risk analysis procedures. Authors that describe this approach are sure that «omics» technologies provide correct use of biomarkers as tools for understanding signifi-

cance of dynamic changes in microorganisms' phenotypic parameters for strain pathogenesis. Certain pathogens exist as quasi-stems that are fluctuating populations made of genetically heterogeneous variants existing within one object [1, 2].

A population, a community, and an ecosystem are dynamic levels that characterize microbiota existing in different environmental objects. Microbial pathogens perform a lot of interactions with representatives from their species, other species, and abiotic environment. Thus, microbiota representatives compete for resources and it results in pathogenic factors and virulence becoming more intense in opportunistic pathogenic microorganisms thus making ecologic dynamics of their prevalence and distribution much more complicated.

Isolates of opportunistic pathogenic microorganisms with modified phenotypic properties that are isolated from environmental objects can be efficient test-models for revealing and quantitative assessment of anti-microbial impacts and hygienic regulation of chemical, physical, or biological environmental factors. It happens so due to them being highly specific and sensitive in a model experiment. We detected certain dependence between microorganisms' sensitivity to adverse chemical exposure and their ability to create films. In our opinion, further research in the sphere can focus on assessing biological impacts exerted by environmental factors with complex chemical, physical, and biological nature [22].

Summary.

1. Microbial profile of opportunistic pathogenic microbiota is different for different environmental objects. Thus, the leading roles belong to staphylococci in air inside medical and preventive organizations (44 %); to bacteria from *Enterobacteriaceae* family, in wash-offs from technological equipment and objects inside medical and preventive organizations (64 % and 69 % of the total opportunistic pathogenic bacteria accordingly);„ to bacteria from *Pseudomonas* stem, in water objects (46 %).

2. In our research 60 opportunistic pathogenic bacteria isolates out of examined 167 (36 %) had obvious morphologic and tinctorial signs that were modified in comparison to those typical for a specific stem including tint variability as per Gram, cells polymorphism etc. Most isolates from object inside medical and preventive facilities, food productions, and water objects located in recreational zones had a set of modified properties regarding their pathogenicity potential such as hemolytic and lecitinase activity, apparent persistence factors, and ability to create biofilms. Differences in pathogenicity potential of opportunistic pathogenic microorganisms isolated from different environmental objects can be due to quantitative parameters of biomarkers that create this potential depending on multiple complicated interactions between anthropogenic selection factors in the environment.

3. Our analysis revealed that opportunistic pathogenic bacteria strains isolated from wash-offs from objects located at food productions and inside medical and preventive facilities were the most aggressive. Isolates of the same stems detected in water objects located in recreational zones and air inside medical and preventive facilities had less apparent phenotypic properties that characterized pathogenicity potential.

Conclusion. Several works contain data on such a phenomenon as microorganisms modifying their phenotypic properties under exposure to anthropogenic environmental factors; however, previously there has been no comparison between signs of opportunistic pathogenic bacteria isolates detected in different environmental objects. Experimental data in our work provide necessary material for examining and analyzing this phenomenon and it should be taken into account when detecting hazards, creating their profiles, and minimizing uncertainties within microbiological risk analysis procedures. We revealed peculiarities in microbial profiles and phenotypic properties of opportunistic pathogenic microbiota existing on and in different environmental objects. It was shown that 60 isolates (36 %) out of examined 167 had modified hemolytic and lecitinase activity, apparent persistent factors, and

ability to create biofilms. Microbiota existing in and on examined objects had different structures: staphylococci accounted for the greatest share (44 %) in air inside medical and preventive facilities; bacteria from *Enterobacteriaceae* family, in wash-offs from equipment installed at food productions and objects located inside medical and preventive facilities (64 % and 69 % accordingly); bacteria from *Pseudomonas* stem, in water objects (46 %). Opportunistic pathogenic bacteria strains detected in wash-offs from equipment installed at food productions and objects located inside medical and preventive facilities were potentially the most aggressive. Further research on the phenomenon related to modification of microbiota phenotypic properties in the environment can enrich an existing list of opportunistic and emergent pathogenic bacteria, give scientific grounds for developing the most efficient measures aimed at managing microbiological risks associated with different environmental factors. Besides, microorganisms' strains with apparent aggressive potential are quire efficient and relevant test-models for detecting and quantitative assessment of antimicrobial impacts via creating aggravated conditions of significant microbial load in a model experiment.

Funding. The research was not granted any sponsor support.

Conflict of interests. The authors declare there is no any conflict of interests.

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Received: 17.05.2019
Accepted: 03.06.2020
Published: 30.06.2020

MEDICAL AND BIOLOGICAL ASPECTS RELATED TO ASSESSMENT OF IMPACTS EXERTED BY RISK FACTORS

UDC 612.017.2 + 517
DOI: 10.21668/health.risk/2020.2.11.eng

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ASSESSING TENSION COEFFICIENT OF BODY ADAPTATION RESERVES UNDER CHRONIC EXPOSURE TO FACTORS EXISTING IN POLAR REGIONS

E.A. Lugovaya, I.V. Aver'yanova

«Arctica» Scientific and Research Center, the Far Eastern Branch of the Russian Academy of Sciences, 24 Karla Marksa Ave., Magadan, 685000, Russian Federation

When northern territories are divided into different zones, it is conventionally done as per a geographic approach. However, according to some researchers, the issue is to be considered within a more complex approach. Experts at «Arktika» Scientific Research Center of the RAS Far East Division suggested a procedure for determining a degree of environment discomfort; the procedure included assessing several factors: natural and climatic, economic-geographic, socioeconomic ones and factors related to the environment on a territory being suitable for living.

Our research goal was to assess tension coefficients of basic physiological systems and functional state of young people living in the North, in different Far East regions.

We applied random sampling and examined 1,632 young males aged from 17 to 21 who permanently resided in Magadan region. Similar groups made up of Caucasian young males were examined in Susuman settlement (n = 88) and Anadyr in Chukotka Autonomous Area (n = 65). We analyzed basic functional parameters of the cardiovascular system, microcirculation, external breath functioning, gas analysis, biochemical and microelement profile of a body.

Comparative analysis of all the obtained data reveal that Magadan city territory which is considered to belong to Zapolyarye (extreme climatic conditions) is no less uncomfortable, and in some relation even more uncomfortable, as per medical and biological parameters than subarctic territories in Magadan region (Susuman) or arctic zone (Anadyr, Chukotka) as it is shown by calculated discomfort coefficient. Accordingly, aggregated discomfort coefficients amounted to 3.21 arbitrary units in Magadan; 3.42 arbitrary units, in Susuman; 2.90 arbitrary units; in Anadyr (Chukotka); 0.46 arbitrary units, in Central Russia.

Given all the above stated, we believe that Magadan region territory can be considered a territory with a high discomfort degree.

Key words: *young males living in north-eastern Russia, functional reserves, adaptation, cardiovascular system, external breath, gas analysis, microelements.*

Ecological-climatic conditions in the arctic zones produce specific effects on functional systems in a human body as they require considerable efforts aimed at preserving its internal environment. Special attention should be paid to external breath as being the first system in a body exposed to negative impacts exerted by cold air as well as to possible changes in metabolism in people who have been residing under extreme climatic conditions for a long time. The cardiovascular system is among the most significant ones that reflect how well a person is adapted to extreme conditions in the arctic zones.

The cardiovascular system is a complicated transport structure and its main function is supplying metabolizing tissues with oxygen. Microcirculation is aimed at providing oxygen delivery in accordance with metabolic demands of an overall body; perfusion pressure is a key element in the microcirculatory system [1]. Functional properties of microcirculation primarily depend on its angioarchitecture (vessels morphology and location). Microcirculation undergoes constant dynamic structural adaptation (remodeling) that is controlled by hemodynamic and metabolic stimuli [2]. Func-

Elena A. Lugovaya – Candidate of Biological Sciences, Associate Professor, temporarily acting as the Director (e-mail: elena_plant@mail.ru; tel.: +7 (914) 853-93-44; ORCID: http://orcid.org/0000-0002-6583-4175).

Inessa V. Aver'yanova – Candidate of Biological Sciences, leading researcher at the Laboratory of Extremal State Physiology (e-mail: Inessa1382@mail.ru; tel.: +7 (924) 691-11-46; ORCID: http://orcid.org/0000-0002-4511-6782).

tional state of the capillary lumen and lability of microcirculation dynamic properties create conditions that are necessary for circulation being able to adapt to external loads [3].

People's live activities are closely interconnected with chemical structure of the environment and contents of various macro- and microelements in it; these elements participate in formation of several most significant adaptive mechanisms in a human body [4]. Assessment of chemical elements metabolism that occurs in a body allows making precise judgments on how efficient its morphologic systems are and on risks of various pathologic states. It gives an opportunity to use such assessment as a pre-nosologic diagnostic tool [5].

Here it is necessary to take into account the fact that environmental factors can exert different impacts, starting from moderate cold pressure to extreme combined influence on a whole body. Specific climate in the arctic zones undoubtedly makes adaptation «much more expensive» and not all people can adapt successfully [6]. Northern-Eastern regions in Russia are vast territories that differ significantly in terms of ecological and climatic conditions as well as effects produced by abiotic factors on people. Magadan region (MR) can be divided into several subzones that are significantly different from each other; there is a coastal subzone (Magadan city) which is cyclonal, with constant winds and relatively high temperature during cold season (-15 ^{o}C); and then there is a continental subzone (Susuman city) where there are practically no winds but there are extreme temperatures, both in summer (+36 ^{o}C) and in winter (-53 ^{o}C) and relatively low humidity [7]. We should also mention a coastal subzone in the Chukotka Autonomous Area (Anadyr) that belongs to the subarctic climatic zone [8, 9]. These unfavorable conditions make people use additional protection from influence exerted by environmental factors [10].

Starting from the 2nd half of the last century, there has been a permanent trend in the North-Eastern Russia, namely, creation of a permanent population consisting of people born in other parts of the country and belonging to eastern Slavs ethnic group. The existing demographic situation in Magadan region is predetermined by two phenomena; the first one is persisting decrease in population (by 6.04 % from 2014 to 2019); the second one is creation of permanent population that is a positive demographic factor necessary for industrial development of the region.

Young people aged 17−23 who don't have any diagnosed chronic diseases, with already stabilized sexual development and their health being «conditionally good» are the most interesting for researchers as a model for assessing influence exerted by a set of natural and social factors on population living in northern regions.

Therefore, **our research goal** was to assess tension coefficients for basic physiological systems responsible for the overall functional state among young people living in different Far East regions in the country.

Data and methods. We examined 1,632 young males aged 17−21 who were selected via random sampling; they all permanently resided in Magadan region. The same group of young male Caucasians was examined in Susuman (n = 88) and Anadyr in the Chukotka Autonomous Area (n = 65).

External breath functional parameters (EBFP) were registered in an open system built according to «volume – flow» principle with «Diamant-S» KM-AP-01 computer spiroanalyzer (Russia). Due values were calculated in accordance with the conventional standards for spirography samples assessment accepted in the Russian Federation [11]. We applied several parameters to assess tension intensity in the respiratory system; they were instantaneous volume velocity 25 % or IVV25 %, a velocity occurring at a point 25 % from FVC; IVV59 %, at a point 50 % from FVC; and IVV75 %, at a point 75 % from FVC;. The parameters were compared with due values with «Diamant-S» KM-AP-01 computer spiroanalyzer (Saint Petersburg, Russia).

To assess tension in gas exchange parameters in young males being in a rest state, we applied MedGraphics VO2000 metabolic system (the USA); the device operates according to «indirect calorimetry» procedure [12]. We determined energy expenses in a rest state per day (REE, kcal/day) and compared with a due value (REE/Ped, %).

Tension in the cardiovascular system functioning was assessed basing on its parameters via measuring systolic (SBP, mm Hg) and diastolic (DBP, mm Hg) blood pressure with Nessei DS–1862 automatic tonometer (Japan) as well as on examining capillary structure and microcirculation in skin swelling near the nail bed with «Capillaroskan-1» computer capillaroscope («New Energy Technologies» LLC, Skolkovo, Moscow). The device was equipped with an optic probe with x200-400 magnification. All the tests were performed on sitting participants under comfortable temperature that varied from 22 to 25; all participants had their arms used for measuring located at the same level as their hearts [13]. Morphologic properties were calculated with software installed on the devices. We analyzed several morphofucntional parameters of microcirculatory vessels, namely arterial section diameter (μm), venous section diameter (μm), capillary length (μm), and deformation coefficient (arbitrary units).

Tension in the biochemical profile was assessed via determining dextrose contents (mmol/g) in capillary blood taken on an empty stomach in the morning 10–12 hours after the last meal; the test was performed with Cardio-Chek PA potable biochemical express-analyzer (The USA).

A promising trend in up-to-date medicine is examining an elemental "profile" of people living in specific biogeochemical regions in order to develop and implement activities aimed at eliminating detected disorders in microelement balance [14]. Changes in elemental state that are short-term regarding exposure to them but significant in terms of deviations from normal elemental state can be estimated with microelements concentrations in liquid media in a human body. Solid tissues (hair, nails, or bones) can be used to estimate elemental state that exists over a long-term period (weeks, months, or years); they are also applicable in clinical and hygienic pre-nosologic diagnostics, including assessment and monitoring performed at population level.

We estimated excess or deficient concentrations of chemical elements in a body via examining concentrations of the following micro- and macro-elements: Ca, Mg, Cr, I, Mn, Co, Se, Zn, Cu, Fe, K; the concentrations were estimated in hair taken from the occipital region with ICP-MS on NexION 300 ICP-MS device (Perkin Elmer, Shelton, CT, USA) at a laboratory of «Micronutrients» LLC (Moscow).

Data were statistically processed with Microsoft Excel standard software, StatSoft Statistica 6.0, Statistica 7.0, and IBM SPSS Statistica 21 applied software. We calculated mean values (M), error of the mean (±m), and median (Me). Distribution of measured variables was tested in order to determine whether it was normal basing on Shapiro-Wilk test. Significance of discrepancies was estimated as per non-parametric Mann-Whitney test for samplings with abnormal distribution. All deviation parameters were reduced to uniformity in order to make comparisons more comfortable and were measured in % of the physiological standard or conventional reference values. Then, coefficients showing «adaptation costs» were calculated as per a total share of deviations for each functional system separately and for the regions as a whole.

To make comparisons, we included literature data on several central regions in the country (Moscow, Yaroslavl, Vladimir, Tambov regions as well as Kazan and Groznyy cities) into our calculation [15–20].

All the examinations were performed in conformity with the principles stated in Helsinki Declaration and the Federal Law «On the basics of citizens health protection in the RF» issued on November 21, 2011 No. 323[1], and the Federal Law «On personal data» issued on July 27, 2006 No. 152[2]. Before being included into the research, all participants voluntarily gave their written informative consent.

[1] On the basic of citizens' health protection in the RF: the Federal Law issued on November 21, 2011 No. 323. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_121895/ (09.01.2020) (in Russian).

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Results and discussion. To examine tensions in cardiovascular system functioning basing on blood pressure, all participants were divided into 4 groups according to recommendations given by the European Society of Cardiologists (ESC) 2018 [21]. Having distributed young males from Magadan as per their blood pressure, we revealed that 19 % had optimal blood pressure; 30 %, normal; 27 %, high normal blood pressure (pre-hypertension); and 24 % had stage 1 arterial hypertension. 21 % of young males from Susuman had optimal blood pressure; 42 %, normal; 21 %, high normal blood pressure (pre-hypertension); and 16 % had stage 1 arterial hypertension. Optimal and normal blood pressure was detected in 29 % examined young males from Anadyr; 34 % had high normal blood pressure (pre-hypertension); and 8 % had signs of stage 1 arterial hypertension. Frequency of young males with high normal blood pressure and stage 1 arterial hypertension was taken as tension in cardiovascular system functioning; it amounted to 51 % among young males from Magadan; 37 %, from Susuman; and 42 %, from Anadyr. Figure 1 shows the results.

We assessed tension in capillary structure and microcirculation via comparing the obtained results with standard values given in the following works [13, 22]; standard ranges taken from them are as follows: arterial section diameter should be from 7 to 17 μm (11.91 ± 1.87 μm on average); venous section diameter, from 11 to 20.6 μm (15 ± 2.42 μm on average); capillary length, from 92 to 295 μm (240 ± 38.3 μm on average).

Arterial section diameter amounted to 8.4 ± 0.1 μm in examined young males from Magadan and it was 29 % lower than the standard value mentioned above. Venous section diameter was equal to 12.1 ± 0.20 μm and it was 19 % lower than the standard, but capillary length was 310.0 ± 5.3 μm or 30 %, higher than the standard and it was accompanied with deformation coefficient amounting to 35.0 ± 0.9 arbitrary unties. A sum of these deviations from standards values amounted to 113 % without taking negative or positive sign into account; we considered it as tension in the microcirculation system.

Young males from Susuman had the following average microcirculation parameters: artery section diameter being equal to 8.1 ± 0.1 μm (by 32 % lower than the standard value); venous section diameter, 11.8 ± 0.2 μm (by 21 % lower); capillary length, 325.7 ± 5.6 μm (by 35 % higher than the standard value); deformation coefficient, 35.0 ± 0.9 arbitrary units. A total sum of deviations in morphofucntional vessels parameters amounted to 123 % for young males from Susuman. The same sum for young males from Anadyr also amounted to 123 %; it resulted from artery section diameter being by 21 % lower than the standards value (9.33 ± 0.3 μm); venous section diameter, by 5 % lower (17.3 ± 0.4 μm); capillary length being by 65 % longer (398.0 ± 14.3 μm), and deformation coefficient being equal to 32.5 ± 0.1 arbitrary units.

Figure 2 shows tension of body functional reserves regarding gas analysis parameters, external breath function, and biochemical profile in people living in different regions located in the Far East Federal District. Thus, tension in the external breath system becomes apparent via volume-velocity lung properties exceeding the due values; these parameters allows estimating patency of upper (IVV25, %), middle (IVV50, %), and lower bronchial tubes (IVV75, %). Having analyzed these properties, we revealed that young males from Magadan, Susuman, and Anadyr tended to have their IVV25 by 9 %, 4 %, and 8 % higher than the due values accordingly; IVV50, by 13 %, 11 %, 6 %; and IVV70, by 31 %, 50 %, and 14 %. A sum of deviations in IVV25, IVV50, and IVV75 from due values amounted to 53 % for young males from Magadan; 65 %, young males from Susuman; and 28 %, young males from Anadyr. Detected increase in REE/Ped % that amounted to 17 % against the due value for young males in Magadan, 31 % for young males from Sususman, and 15 % for young males from Anadyr was thought to be tension in the basic metabolism.

29 % young males from Magadan had their hyperglycemia higher than the standard value (5.6 mmol/l); the same was true for 48 % young males from Susuamn, and 57 % young males from Anadyr; we considered it to be apparent tension in biochemical profiles of the examined young males from different regions.

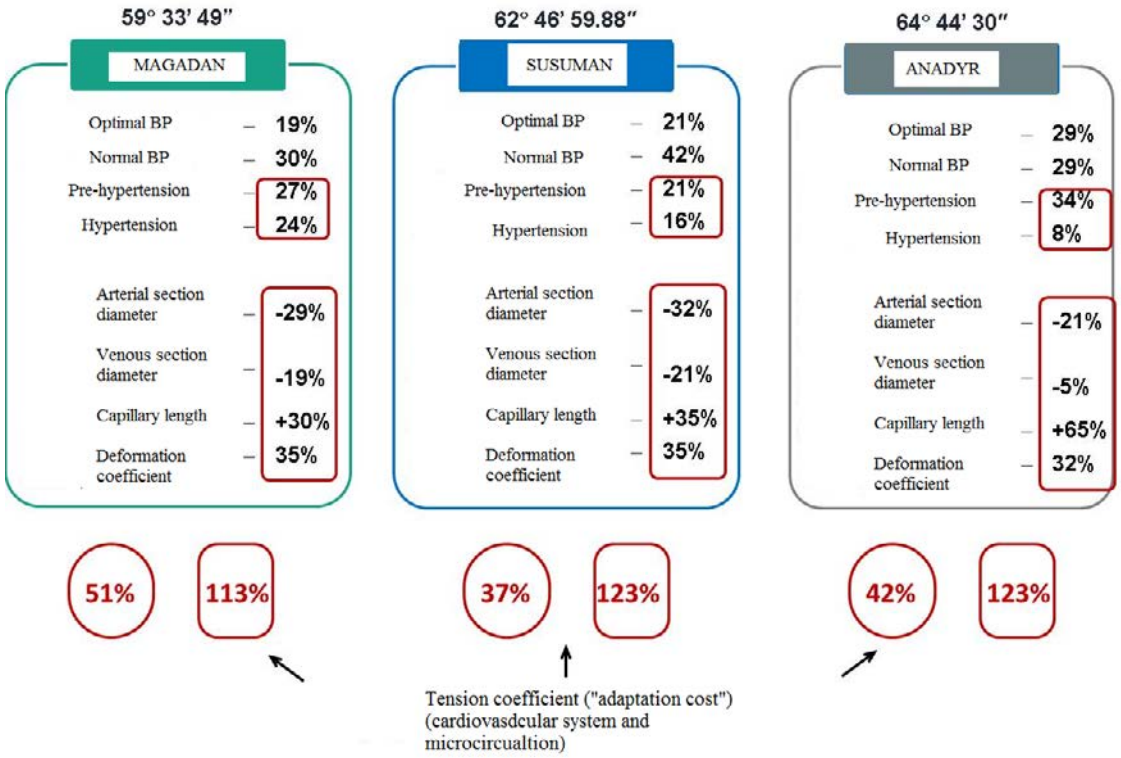

Figure 1. Tension in the cardiovascular system and microcirculation in young males from different regions in the Far East

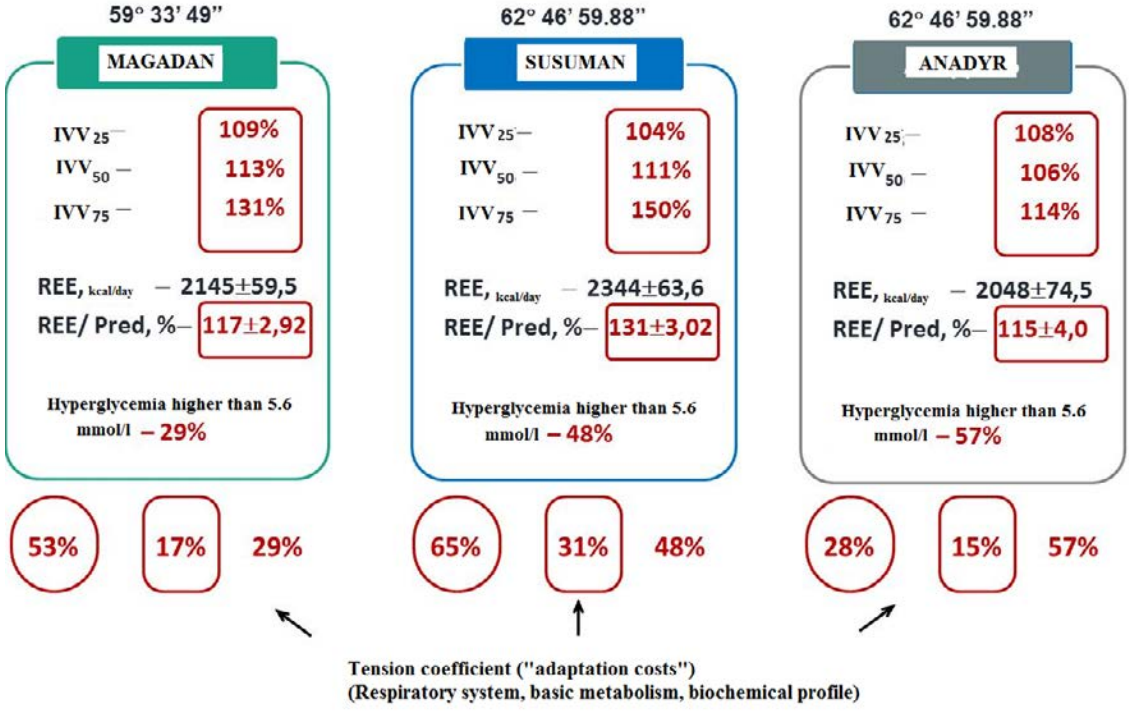

Figure 2. Tension in certain parameters of the external breath function, gas exchange, and biochemical profile in young males from different regions in the Far East

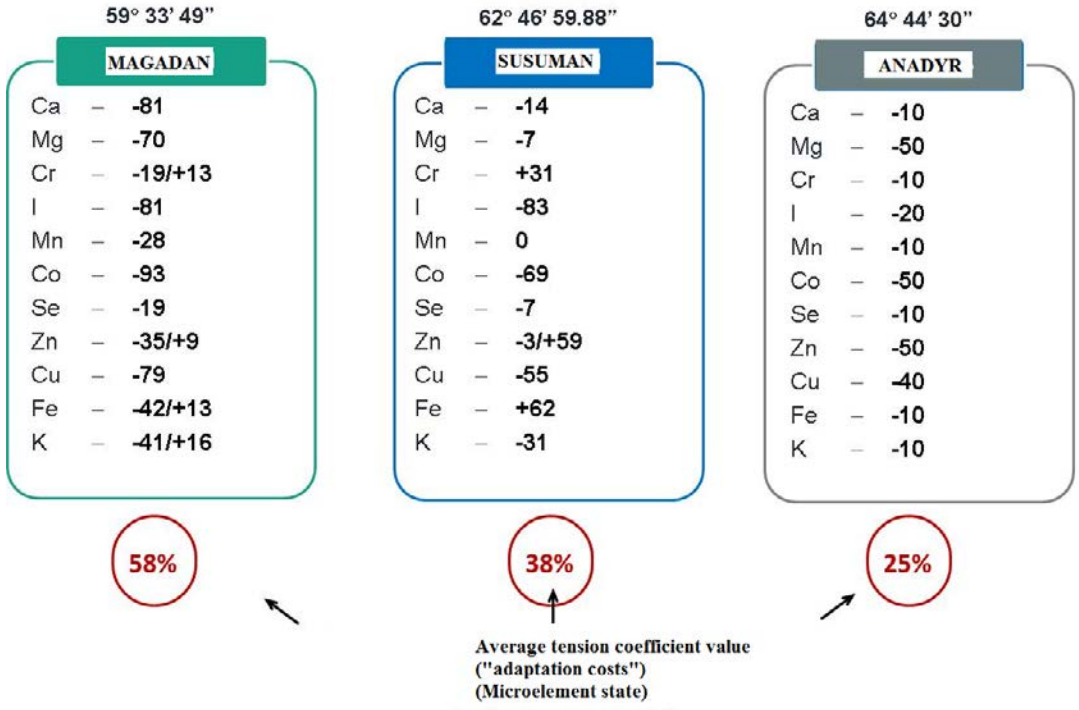

Figure 3. Tension in microelement profile of young males from different regions in the Far East

Figure 3 shows deviations from the standard values in microelement profiles of young males from different regions in the Far East; tension in the parameters was given as a sum of surpluses and deficiencies (divided by 100 to make calculations more convenient). It amounted to 58 % for young males from Magadan; 38 %, for young males from Susuman; and 25 %, for young males from Anadyr. All the examined young males had Co, Ca, Mg, and Se in their bodies in concentrations lower than the lower limit of reference values [23].

Figure 4 shows a combined profile of allosteric tension in body functional reserves of young males who live in zones with more favorable climatic conditions; the profile is drawn up as per results given by authors who performed their research in the Central regions in Russia [15–20]. Average tension as per analyzed parameters amounted for 45 % for people living in those regions and we took this value as a conditional standard.

Basing on the data shown in Figure 4, we calculated «adaptation costs» as a sum of tension coefficients for physiological systems; it was a sum of deviations from the physiological standards divided by 100 (Figure 5). A coefficient calculated for young males from Magadan amounted to 3.2 arbitrary units; young males from Susuman, 3.4 arbitrary units; young males from Anadyr, 2.9 arbitrary units; young males from central regions, 0.46 arbitrary units. Therefore, our data clearly indicate that more extreme climatic factors result in tension occurring in functioning of basic physiological systems in a body; it becomes apparent via apparent deviations from physiological standards.

To sum up, we performed complex estimating of basic parameters that described functional activities of body systems being in the greatest tension under exposure to unfavorable or extreme environmental factors. The results indicate that even people living in different northern regions have different functional state of their bodies. These differences are even more apparent when the examined parameters are compared to those of people living in the central part of the country. Our approach is based on determining tension in basic physiological systems functioning that becomes apparent via deviations in the examined parameters from physiological standards. We can recommend using it as a tool to determine an extent to which a body is adapted to extreme conditions in the arctic zones

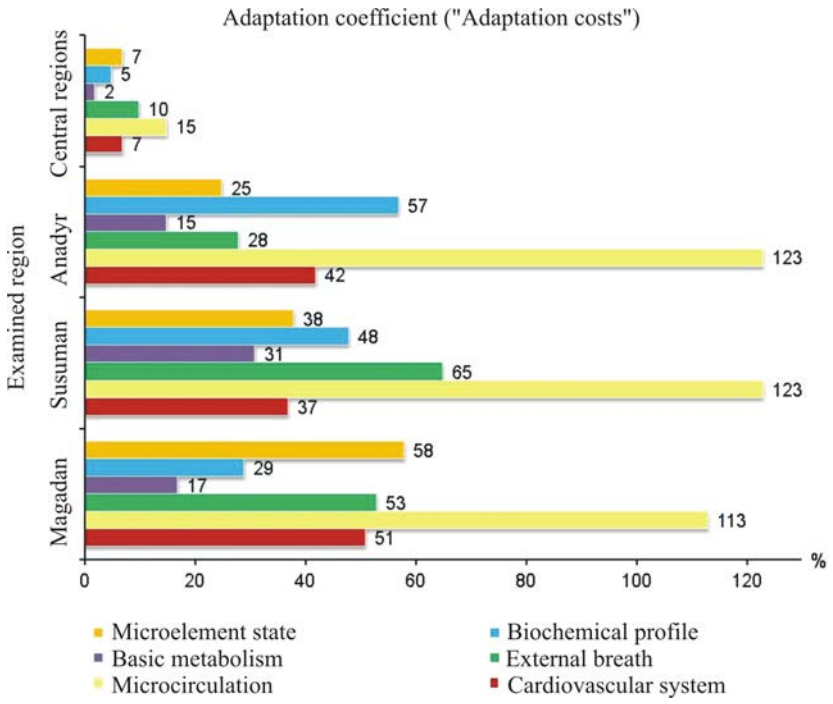

Figure 4. Aggregated pool of tension coefficients for the functional state of basic systems in young males from the Far East region in comparison with young people living in central regions in the country

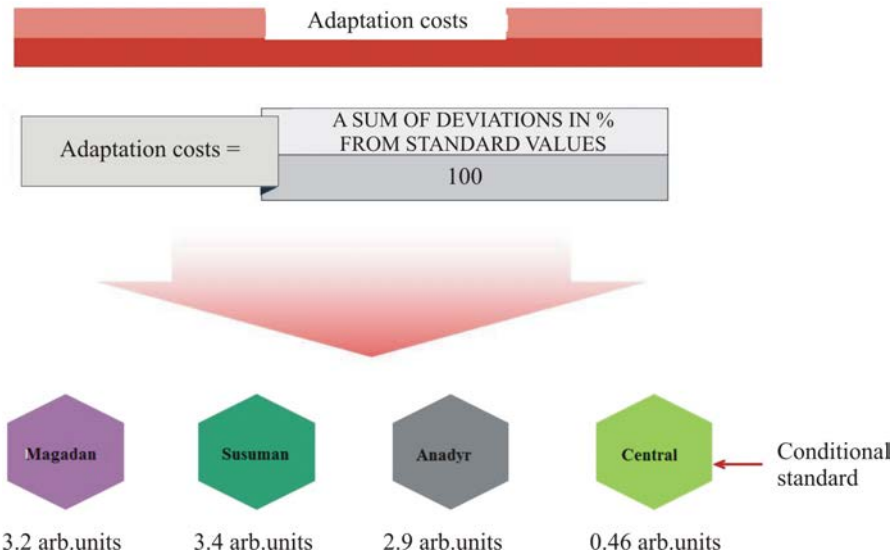

Figure 5. «Adaptation costs» coefficient in young males from Magadan, Susuman, Anadyr, and central regions in the country

(«adaptation costs»). Medical and biological estimation will allow detecting the most vulnerable physiological systems and revealing health risk factors; it will also help create strategies aimed at improving life quality of people living in northern and arctic regions.

Ecologic and climatic conditions in the arctic zones produce specific effects on body systems functioning requiring a lot of efforts aimed at preserving constant internal environment in a body. Our research was performed on different population groups living in Magadan region, all being naturalized Caucasians, borne in the region in the 1st–3rd generation; our participants were young males who attended higher and specialized secondary education establishments. The research revealed that regional peculiarities detected in morpho-

functional characteristics of people living in different climatic geographic zones had certain differences. Specific attention should be paid to the external breath system that is the first to be exposed to negative impacts exerted by cold air; another attention focus should be on probable changes in metabolic processes in people who have long been living under the given extreme climatic conditions. And here we should take into account that exposure to environmental factors can also be different varying from moderate cold pressure to extreme combined effects produced on a whole body. We also performed a comparative analysis of metabolism and external breath functions in young males constantly residing in different climatic geographic zones in the Far East in Russia; the analysis revealed that compensatory-adaptive restructuring in physiological systems functioning occurred in young males from all the examined groups. They were the most apparent in young males from the continental part of Magadan region; adaptation shifts in people from this group were aimed at minimizing apparent effects produced by cold that was typical for that climatic zone. Young males from this group also spent the greatest amount of energy per day as they needed it to maintain elevated heat production. We also detected that they had the highest patency of distal bronchioles among all the examined groups; it was necessary for both adequate oxygen supply and protection from cold temperatures.

Analysis of the obtained data revealed that Magadan city territory that belongs to the Arctic zone is not less and in some cases even more uncomfortable in terms of its medical and biological properties than subarctic zones in Magadan region (Susuman city) and arctic zones (Anadyr, Chukotka Autonomous Area). Accordingly, discomfort coefficients totally amounted to 3.21 arbitrary units in Magadan; 3.42 arbitrary units in Susuman; 2.9 arbitrary units in Anadyr, Chukotka Autonomous Area; and 0.46 arbitrary units in the central regions in the RF. Given all the above stated, we can conclude that Magadan region territory is a zone with considerably uncomfortable conditions and it is the most apparent in its continental part.

Funding. The research was performed due to budgetary funding obtained from «Arktika» Scientific and Research Center, The Far East Branch of the RAS.

Conflict of interests. The authors declare there is no any conflict of interest.

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Received: 29.01.2020
Accepted: 04.06.2020
Published: 30.06.2020

UDC 614.71: 612.017.1-053.6
DOI: 10.21668/health.risk/2020.2.12.eng

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INFLUENCE EXERTED BY INHALATION BURDEN WITH FORMALDEHYDE ON CYTOKINES lEVEL IN TEENAGERS LIVING IN INDUSTRIAL CENTERS

L.B. Masnavieva, I.V. Kudaeva

East-Siberian Institute of Medical and Ecological Research, 12 a the 3rd micro-district, Angarsk, 665827, Russian Federation

The atmospheric air is polluted with formaldehyde and it exerts negative influence on population health; first of all, the immune system suffers as it is the most sensitive to impacts exerted by environmental factors. Our research goal was to examine levels of specific auto-antibodies and cytokines in teenagers depending on an individual inhalation burden with formaldehyde. We calculated a personified hazard index of inhalation exposure to formaldehyde for each school student. A formula for its calculation included data on air pollution with formaldehyde inside school rooms and teenagers' homes, the atmospheric air pollution, anthropometric and spirometry data, as well as data on school students' daily regime. We examined cytokines and specific auto-antibodies in blood serum of teenagers as these two parameters reflected the immune system state. We revealed correlations between a hazard quotient for exposure to formaldehyde and contents of auto-antibodies to β_2-glycoprotein I and to Fc-fragment of IgG, levels of interleukin-2, alpha- and gamma-interferon. We also detected that a share of people with elevated immune reactivity of auto-antibodies to β_2-glycoprotein I and to Fc-fragment of IgG increased as the hazard quotient for exposure to formaldehyde grew. Correlations between the examined parameters of the immune system grew in their strength and number and it proved that pro- and anti-inflammatory processes became more conjugated under inhalation exposure to formaldehyde that was higher than the reference level. Teenagers with their hazard quotient for exposure to formaldehyde was higher than 1 tended to have lower concentrations of interleukin-2, alpha- and gamma-interferons, and there was strain in their system of pro- and anti-inflammatory processes as inhalation burden with formaldehyde became greater.

***Key words**: air pollution, inhalation load, formaldehyde, adolescents, the immune system, interleukins, interferons, autoantibodies.*

Air pollution makes a significant contribution into health risks for people who live in large industrial cities [1, 2]. Emissions from chemical and oil-processing enterprises contain aromatic hydrocarbons, hydrogen sulfide, sulfur and nitrogen dioxides, carbon dioxide. Increased air pollution caused by industrial emission can lead to occurrence of pathologies in organs that are target ones for impacts exerted by pollutants [3–5]. It is well known that when formaldehyde, benzpyrene, phenol, or nitrogen dioxide penetrate a body, it influences the immune system [3, 6, 7], and changes in its activity become apparent via modifications of cytokines synthesis by immune-competent cells. Air pollutants produce their effects on intensity of cell renewal and it can also cause changes in production of auto-anti-bodies (auto-AT) which are known to participate in apoptotic cells clearance.

Our research goal was to examine contents of cytokines and specific auto-anti-bodies in teenagers depending on an individual burden with formaldehyde.

Data and methods. At the initial stage of our research we questioned parents (legal representatives) of 1,150 teenagers aged 11–17 who lived in industrial cities and in rural areas of Irkutsk region. After parents (legal representatives) of 805 children gave their written informative consent, the teenagers were examined by medical experts, and data from their case histories were analyzed. 561 teenagers conformed to all the criteria to be included into

Lyudmila B. **Masnavieva** – Candidate of Biological Sciences, senior researcher at the laboratory for immunological, biochemical, molecular and genetic research in hygiene (e-mail: Masnavieva_Luda@mail.ru, tel.: +7 (964) 657-11-62; ORCID: http://orcid.org/ 0000-0002-1400-6345).

Irina V. **Kudaeva** – Associate Professor, Deputy Director for Research, Head of the clinical and diagnostic laboratory (e-mail: Kudaeva_Irina@mail.ru; tel.: +7 (914) 003-19-76; ORCID: http://orcid.org/0000-0002-5608-0818).

the in-depth research. They belonged to the 1st and 2nd health groups (in other words, they had some minor health disorders or none at all and didn't have any chronic pathologies); they permanently lived and studied at educational organizations on the examined territories; they didn't have any signs of respiratory diseases and exacerbations of somatic pathologies during the examination period and 2 weeks prior to it.

An individual chemical burden on teenagers' bodies was estimated on the basis of data on admixture concentrations in the atmospheric air, and indoor concentrations of priority pollutants (both at home and in an educational organization). We introduced personified data on each school students into a formula for calculating a dose chemical inhalation burden; such data included anthropometric and spirometry parameters, and information about a daily regime. Hazard quotients (HQ) for inhalation exposure to formaldehyde were calculated in accordance with the Human health risks assessment from environmental chemicals [8] taking into account personified data on each individual[1] [9]. Teenagers were divided into two groups according to obtained HQ for exposure to formaldehyde. The first group was made up of 227 school students with HQ lower than 1; the second group was made up of 423 teenagers with HQ equal to 1 or higher. 41.2 % teenagers in the first group were boys (average age was equal to 14.31 ± 0.12), 58.8 % teenagers were girls (average age was equal to 14.79 ± 0.09). The second group was made up of 47.3 % boys and 52.7 % girls (average age was equal to 14.66 ± 0.12 and 15.01 ± 0.10 respectively).

Blood samples were taken from teenagers in the morning on empty stomach. We examined cytokines concentrations in blood serum, namely interleukins-2 and -10, alpha- and gamma-interferons (IL-2, IL-10, INF-α, and INF-γ respectively). Cytokines concentrations were determined via ELISA tests with relevant test-systems («Vector-Best», Novosibirsk). Reference concentrations for IL-2 and IL-10 amounted to 0–10 pg/ml; for INF-α and INF-γ, up to 5 and 15 pg/ml respectively.

We also determined relative concentrations of auto-AT to native DNA (nDNA), Fc-fragment of IgG, and beta2-glycoprotein (β2-ГП I) in teenagers' blood serum as these parameters reflect the immune system state. To determine anti-bodies concentrations with ELISA technique, we applied ELI-Viscero-Test-16 test-systems («Immunkulus», Moscow). A range from -20 up to +10 % is a reference concentration for relative contents of specific auto-AT within the above-mentioned test-system.

We analyzed the results statistically with «Statistica 6.0» applied software and applied such non-parametric tests as Mann-Whitney U-criterion and Spearman rank correlation (r). The research results are given as a median and 25–75 quartiles (Me (LQ-UQ)). We detected discrepancies between groups as regards frequency of elevated values for the examined parameters with a technique for assessing prevalence of a sign in a sampling. A p value equal to 0.05 was considered to be a critical statistical significance of discrepancies.

Results and discussion. Having assessed atmospheric air quality and air quality inside teenagers' homes and classrooms on the examined territories, we detected formaldehyde, particular matter, and nitrogen dioxide in concentrations which were higher than reference ones. Average annual PM concentration in the atmosphere varied from 0.012 to 0.142 mg/m^3; it was within 0.026–0.172 mg/m^3 and 0.033–0.135 mg/m^3 in the air inside homes and classrooms respectively (reference concentration is equal to 0.075 mg/m^3). The same ranges for nitrogen dioxide and sulfur dioxide respectively amounted to 0.007–0.062 mg/m^3 and 0.0004–0.038 mg/m^3 in the atmospheric air; 0.007–0.030 mg/m^3 and 0.0001–0.033 mg/m^3, in the air inside homes; and 0.008–0.044 mg/m^3 and 0.002–0.018 mg/m^3, in the air inside class-

[1] G 2.1.10.1920-04. Guidelines for assessing the risk to public health when exposed to chemicals that pollute the environment. Moscow, Federal Center for State Sanitary and Epidemiological Supervision of the Ministry of Health of Russia, 2004, 143 p. (in Russian).

rooms (reference concentrations for these compounds amount to 0.04 and 0.05 mg/m^3). Average annual concentrations of carbon oxide and formaldehyde respectively amounted to 0.11–2.34 mg/m^3 and 0.000–0.006 mg/m^3 in the atmospheric air; 0.563–0.678 mg/m^3 and 0.0014–0.0066 mg/m^3, in the air inside homes; 0.073–0.340 mg/m^3 and 0.000–0.006 mg/m^3, in the air inside classrooms. Reference concentrations for carbon oxide and formaldehyde are 3.0 and 0.003 mg/m^3 respectively.

As per data obtained via the questioning, teenagers spend from 20 to 23 hours a day at home and at school; therefore, indoor air pollution contributes significantly into an individual chemical burden and HQ for exposure to pollutants. Exposure to formaldehyde made the greatest contribution into a risk of immune disorders as personified HQ for this chemical ranged from 0.60 to 2.03 for the examined teenagers (average value was equal to 1.35 ± 0.02). These elevated hazard quotients for exposure to formaldehyde are caused by the substance penetrating the air inside homes or classrooms out of furniture, construction and finishing materials [10], and the atmospheric air, due to emissions from industrial enterprises [3, 5].

We detected lower average IL-2 concentrations in teenagers from the second group than in those from the first one (Table 1). Since this interleukin determines duration and type of an immune response and participates in regulating IFN-γ contents stimulating its synthesis [11], a decrease in IL-2 concentration can lead to changes in gamma-interferon contents; it is confirmed by lower IFN-γ contents which we detected in the second group. The 1st type T-helpers (Th1) are known to produce IL-2 and IFN-γ; therefore, lower concentrations of these cytokines in school students from the second group can indirectly imply that Th1 are less active in them. We detected significantly lower constitutive concentrations of INF-α (10 times lower) that had antiviral activity in teenagers from the group with HQ ≥ 1. Given all that, we can assume that teenagers with inhalation exposure to formaldehyde within reference concentrations have signs of inflammatory reactions; when teenagers are exposed to higher concentrations of this toxicant, they run significantly greater risks of inflammatory diseases becoming chronic.

This assumption was also confirmed by our analysis of auto-AT contents in groups with different inhalation burden with formaldehyde. High concentration of specific auto-AT is known to be a sign that disorders are occurring in organs and systems and they, among other things, can be caused by bacterial and viral infections and can occur long before any clinical manifestations of a diseases become visible [12]. Elevated concentrations of auto-AT to nDNA were detected in the second group less frequently than in the first group (31.8 and 20.7 % respectively, $p < 0.005$). A share of people with hyper immune reactivity of auto-AT to Fc-fragment of IgG and to β2-GP I was 4.5 times and 9 times higher among those with HQ ≥ 1 (32 %, $p < 0.005$;

Table 1

Cytokines and auto-anti-bodies concentrations in teenagers under inhalation exposure to formaldehyde, Me (LQ-UQ)

Parameters, units	Group I	Group II	*p*
IL-2, pg/ml	4.51 (1.56–7.25)	2.71 (0.01–5.38)	0.000
IL-10, pg/ml	3.42 (0.7–6.76)	3.39 (1.40–6.44)	0.713
INF-α, pg/ml	3.76 (1.43–14.13)	0.36 (0.01–4.87)	0.000
INF-γ, pg/ml	5.91 (4.23–8.32)	2.81 (1.89–4.89)	0.000
Auto-AT to nDNA, %	4.64 (-6.27–20.59)	0.93 (-10.54–11.48)	0.003
Auto-AT to β2-GPI, %	-19.83 (-29.08–-11.75)	-1.56 (-14.55–11.09)	0.000
Auto-AT to Fc-fragment of IgG, %	-7.57 (-13.70–-1.87)	3.97 (-8.25–12.68)	0.000

N o t e: *p* means a level when discrepancies become statistically significant.

28 %, $p < 0.005$ respectively) than in the first group (7 % and 3 % respectively). It proves that infectious and inflammatory processes occurred in teenagers from the second group more frequently than in those from the first one since it is well known that elevated concentrations of auto-AT to DNA and beta-2-glycoprotein 1 indicate there is cell apoptosis in a body which is most frequently induced by an active bacterial or a viral infection, and auto-AT to Fc-fragments of immune globulins reflect protective responses of the immune system aimed at limiting inflammatory processes activity [12]. We should note that previous research revealed an increase in auto-AT contents in children who lived on territories with average atmospheric air contamination; those auto-AT characterized a specific state of the immune system that occurred when inflammatory processes caused by infections were developing in a body; children who lived on territories with significant air contamination ran elevated risks of pathologies in the immune system and their auto-AT had weaker immune reactivity [13].

We analyzed relative auto-AT concentrations depending on personified chemical burden with formaldehyde and revealed that a concentration of auto-AT to β2-GP I and to Fc-fragment of IgG was statistically significantly higher in the second group, and that of auto-AST to nDNA, in the first one. It indicates that weaker resistance of a body to infectious agents in teenagers who lived on environmentally adverse territories was primarily caused by total inhalation burden with formaldehyde coming from both the atmospheric air and the air inside homes or classrooms.

A contribution made by formaldehyde into changes that occur in the humoral immunity parameters in teenagers is confirmed by correlations between chemical burden with the pollutant and cytokines and auto-anti-bodies concentrations (Table 2). We detected that exposure to formaldehyde led to a decrease in concentrations of IL-2, INF-γ, and INF-α, and an increase in concentrations of auto-AT to β2-GP I and to Fc-fragment of IgG.

We should note that correlations detected for the overall examined sampling were characteristic for the teenagers group with $HQ \geq 1$ (Table 2), excluding the correlation between HQ and concentration of auto-AT to Fc-fragment of IgG. This particular correlation was detected in the overall sampling ($R = 0.32$, $p < 0.001$), but it was absent when the first and the second group were considered separately. The fact that there is no correlation between IL-10 concentration and chemical burden with formaldehyde indicates that elevated concentrations of this cytokine in teenagers from the second group are not directly caused by exposure to formaldehyde but they rather result from changes that occur in the immune system at this age.

As we examined correlations between the examined parameters of the immune system, we revealed that a number of these correlations and their strength were higher among teenagers with greater inhalation burden with formaldehyde (the second group) than among those from the first group (Table 3); the nature of these correlations indicated that there was strain in the system of pro- and anti-inflammatory processes. Thus, if we take a correlation between IL-2 and INF-γ concentrations,

Table 2

Correlations between hazard quotients for exposure to formaldehyde, cytokines and auto-anti-bodies concentrations in teenagers

Parameters	Overall sampling		Group I		Group II	
	R	p	R	p	R	p
HQ & auto-AT to β2-GP I	0.44	0.001	-0.04	0.500	0.17	0.010
HQ & IL-2	-0.30	0.001	0.06	0.397	-0.25	0.001
HQ & INF-α	-0.37	0.001	0.09	0.210	-0.28	0.001
HQ & INF-γ	-0.45	0.001	-0.01	0.902	-0.12	0.036

N o t e: R is correlation quotient, p means a level when discrepancies become statistically significant.

Table 3

Correlations between cytokines concentrations in teenagers depending on inhalation exposure to formaldehyde

Parameters	Group I		Group II	
	R	p	R	p
IL-2&INF-γ	-0.06	0.400	0.39	0.0001
IL-2&IL-10	0.17	0.025	0.44	0.0001
IL-2&INF-α	-0.31	0.0001	0.62	0.0001
INF-γ&INF-α	-0.03	0.700	0.51	0.0001
IL-10 &INF-α	0.13	0.070	0.40	0.0001

N o t e: R is correlation quotient, p means a level when discrepancies become statistically significant.

we can note that the 1st type T-helpers increase IL-2 production that stimulates functional activation of T- and B-lymphocytes, NK-cells and monocytes, and these cells play a significant role in protective responses of a body [14]. Since IL-2 synthesis is inducible one, regulation of IL-2-dependent lymphocytes proliferation directly depends on a specific antigen occurrence [15, 16].

INF-γ also has regulatory functions related to the immune systems cells; it is synthesized in a body mostly by antigens-activated T-lymphocytes (primarily Th1) and NK-cells. It activates macrophages and enhances activities of the cell-mediated immunity and plays a significant role in Th1-lymphocytes differentiation acting according to a positive feedback principle [17]. Correlations between IL-2 and INF-γ concentrations prove that such processes occur in bodies of teenagers with higher inhalation burden with formaldehyde. Besides, INF-γ, together with IL-2, is able to control activation of the cell-mediated immunity with T-regulatory lymphocytes participation [18].

IL-10 also performs an immune-regulatory function as regards immune response suppression due to its participation in regulating and performing effector functions of T-regulatory lymphocytes. This interleukin is basically synthesized by such cells as activated CD4+, CD8+, T-lymphocytes, B-lymphocytes, LPS-activated monocytes/macrophages, and Th1. IL-10 negatively regulates synthesis of IL-2, INF-γ, anti-inflammatory cytokines, antigen-representing function of macrophages and dendritic cells as well as switches an immune response from a Th1-depending type to a Th2-depending one [19, 20]. A correlation between IL-2 and Il-10 which we revealed in our research together with lower IL-2 and INF-γ concentrations in children from the second group against those from the first group and with comparable IL-10 concentrations in both groups is an evidence that mechanisms of anti-inflammatory immune response regulation are deregulated. Besides, when IL-10 excessively suppresses production of Il-2 and INF-γ in teenagers with HQ≥1, it can lead to occurrence of susceptibility to allergy, including ecological pollutants allergy. In particular, some previous research revealed that examined children with sensitization to formaldehyde had higher IL-10 concentration in swabs taken from their oral cavity than people who didn't have any reaction to this allergen [21]. Regulatory strain in Th1 lymphocytes system in school students with higher inhalation burden with formaldehyde is also borne out by positive correlation between INF-α concentration and concentrations of cytokines (IL-2, INF-γ) that support differentiation of T lymphocytes into Th1 population.

All the obtained results helped us to create a scheme that reflects influence exerted by inhalation exposure to formaldehyde on cytokines concentrations in teenagers' blood (Figure).

Conclusion. Overall, we detected that occurrence of formaldehyde in the atmospheric air and in air inside homes or classrooms in concentrations higher than reference ones caused elevated risks of pathologies in teenagers' immune system. Personified hazard

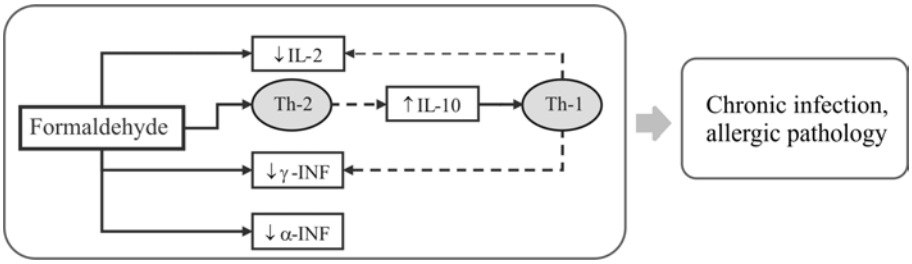

Figure. Influence exerted by inhalation exposure to formaldehyde on cytokines concentrations in teenagers

quotients for exposure to formaldehyde for teenagers living in industrial centers reached 2.03. We revealed that a growth in inhalation burden with formaldehyde was accompanied with more frequent increase in concentrations of specific auto-anti-bodies to β2-GP I and to Fc-fragment of IgG which were signs that pathological processes caused by bacterial and viral agents were developing in organs and systems. When a hazard quotient for exposure to formaldehyde exceeded 1, INF-α, INF-γ, and IL-2 concentrations went down, and strain in the system of pro-and anti-inflammatory processes occurred.

Funding. The work has been accomplished due to financial support provided for completing tasks set by the Government and funds belonging to the East-Siberian Institute for Medical and Ecological Research.

Conflict of interests. There are no apparent or potential conflicts of interests related to publication of the present paper.

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Received: 05.12.2019
Accepted: 03.06.2020
Published: 30.06.2020

UDC 616.127–005.8–053.7–059: [616.12–02: 616.151.5] –07: 616.12–018.74
DOI: 10.21668/health.risk/2020.2.13.eng

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ASSESSING ENDOTHELIUM RESISTANCE TO THROMBUS FORMATION AS A POTENTIAL RISK FACTOR CAUSING RECURRENT CARDIOVASCULAR EVENTS IN YOUNG PATIENTS AFTER CARDIAC INFARCTION

I.A. Novikova, L.A. Nekrutenko, T.M. Lebedeva, A.V. Khachatryan

Perm State Medical University named after Academician E.A. Wagner, 26 Petropavlovskaya Str., Perm, 614000, Russian Federation

Cardiac infarction is considered a disease more common for elderly people; despite that, up to 10 % of all cardiac infarctions occur at a young age. Cardiac infarction has grave consequences both for mental health and future working capability of patients who had it. Approximately 15 % patients who have had cardiac infarction have to face a recurrent cardiovascular event based on thrombus formation in spite of therapy. Our research goal was to assess endothelium homeostasis in patients after cardiac infarction being treated with double anti-thrombocyte therapy during out-patient rehabilitation and to reveal potential risks that could cause recurrent cardiovascular diseases. Overall, we examined 25 people aged from 18 to 45 who had cardiac infarction and were treated with invasive therapy aimed at eliminating ischemic heart disease. The therapy was emergency percutaneous coronary intervention and coronary artery stenting performed at Perm Clinical Cardiologic Clinic during a period from September 2018 to March 2019. Endothelial homeostasis was examined in 12 months after cardiac infarction.

We detected that, together with conventional risk factors, young patients after cardiac infarction had apparent changes in coagulation homeostasis (shorter activated partial thromboplastin time, shorter prothrombin time, an increase in fibrinogen concentration; greater aggregative activity of thrombocytes with adenosine-diphosphate; depressed Hageman-factor-dependent fibrinolysis. Nevertheless, there was no significant difference in aggregative activity of thrombosytes with ristocetin between the test and control groups. Therefore, in 12 months after cardiac infarction, young patients still ran high risks of recurrent cardiovascular events; those risks were caused both by significant prevalence of conventional risk factors and by high thrombogenic risk that persisted in spite of relevant anti-thrombus therapy.

Key words: *cardiac infarction, young patients, recurrent cardiovascular events, risk factors, endothelial homeostasis, hyper-coagulation, thrombosis.*

Cardiovascular diseases remain the leading cause of death all over the world. The forecasts state that by 2030 ischemic heart disease (IHD) will still hold the first place among 15 main reasons for population mortality [1]. Cardiac infarction (CI) is one of the gravest IHD outcomes; it can result in sudden cardiac death.

Up to 10 % of all the infarctions occur at young age even though CI is considered to be more typical for elderly people [2, 3]. When a young patient has CI, it usually leads to grave outcomes both for his or her mental health and for working ability in the future. Mortality risk grows by 74 times in comparison with healthy young people [4].

Over the last years serious progress has been made in treating patients with CI. A considerable decrease in mortality caused by this

Irina A. Novikova – External Researcher at the Department for Hospital Therapy (e-mail: Nurdus@yandex.ru; tel.: +7 (342) 239-31-88; ORCID: http://orcid.org/0000-0002-3968-6498).

Ludmila A. Nekrutenko – Doctor of Medical Sciences, Professor at the Department for Hospital Therapy (e-mail: lunekru@mail.ru; tel.: +7 (342) 239-31-88; ORCID: http://orcid.org/0000-0001-9151-8195).

Tatyana M. Lebedeva – Doctor of Medical Sciences, Professor at the Department for Public Health and Healthcare (e-mail: super.oziz@yandex.ru; tel.: +7 (342) 236-12-56; ORCID: http://orcid.org/0000-0003-3374-8982).

Armenui V. Khachatryan – Postgraduate Student at the Department for Hospital Therapy (e-mail: Khachatryan.armenui@mail.ru; tel.: +7 (342) 239-31-88; ORCID: http://orcid.org/0000-0001-9940-9428).

pathology has been achieved due to widely implemented percutaneous coronary interventions (PCI) and secondary prevention activities that include double anti-thrombocyte therapy. Nevertheless, patients with CI in their case history run 6 times higher risks of recurrent cardiovascular events than patients without it [5]. Approximately 15 % of patients with CI in their case history suffer a recurrent cardiovascular disease that happens due to thrombus formation in spite of anti-thrombocyte treatment [6].

Probability of an acute thrombotic event depends on a balance between susceptibility to thrombus formation and efficiency of endogenous thrombolytic processes. Thus, any disorder in fibrinolysis leads to elevated thrombosis risks [7]. And vice versa, if the fibrinolytic system counterbalances impacts exerted by thrombogenic factors, then a thrombus may not occur at all or, at least, may not result in long-term vessel occlusion [8].

Large vessels endothelium when being in its normal state inhibits adhesion and thrombocytes activation due to various mechanisms, either directly or indirectly via degradation of thrombocytes receptors antagonists. Endotheliocytes produce substances with anti-thrombotic potential such as nitrogen oxide (NO), thrombomodulin, prostanoids, and adenosine. When endothelium doesn't function properly, namely loses its anti-aggregation potential, it makes for atherosclerotic process development [9–12].

Nowadays, a lot of attention is being paid to how thrombocytes interact with intact endothelial surfaces and participate in atherosclerosis development. Thrombocytes may become involved into atherogenesis due to hydrodynamic stress exerting its influence on endothelium cells [13]. A classical way of thrombocytes involvement into blood stasis is interaction between GPIb/IX/V thrombocyte receptor complex components and active A1-domain of von Willebrand factor [14]. Von Willebrand factor is a large multi-dimensional glycoprotein that is synthesized by endothelium cells, sub-endothelial connective tissues, and by thrombocytes themselves though in smaller quantities [15, 16]. After being synthesized large quantities of von Willebrand factor are stored in Weibel-Palade bodies and are released from them after an endothelial cell is stimulated, in particular, as a response to damage, and it can be a sign that endothelial dysfunction has already occurred [17]. Von Willebrand factor production increases under hypoxia and impacts exerted on endothelium by anti-inflammation cytokines [18, 19]. Having bound themselves to von Willebrand factor, thrombocytes activate and a cascade of reaction occurs in them; this cascade ultimately results in thromboxane A2 synthesis and adenosine diphosphate (ADP) release. Thromboxane A2 and ADP initiate talin and αIIbβ3 polymerization thus causing thrombocytes aggregation [20, 21]. Therefore, von Willebrand factor is a key component in blood stasis. Thrombocytes aggregation with ristocetin, a co-factor of von Willebrand factor, indirectly reflects von Willebrand factor quantity in blood plasma.

Endogenous fibrinolysis activation is a function performed by an endothelium cell that prevents local thrombus formation. Fibrinolytic activity violation leads to greater risks of thrombosis in patients suffering from cardiovascular diseases [22]. Research data indicate that patients with early cardiovascular events in their family case histories have denser fibrin clots that are more resistant to lysis [23].

Hageman factor (factor XII) is a glycoprotein that circulates in blood plasma as zymogen; it is activated due to a contact with a negatively charged surface. Hageman factor is structurally similar to other proteins with fibrinolytic activity such as plasminogen, tissue (t-PA) and urokinase (u-PA) plasminogen activator [24]. XII factor activates prekallikrein and thus induces fibrinolysis; prekallikrein in its turn decomposes single-stranded u-PA into active double-stranded u-PA. Kallikrein that occurs in the process releases bradykinin out of high-molecular kininogen. Kallikrein and bradykinin promote t-PA re-

lease [25]. XII factor also can directly activate plasminogen [7]. Disorders in Hageman-dependent fibrinolysis make for thrombotic events development.

Therefore, thrombus formation assessment requires determining thrombocytes reactivity, endothelial function, and activity of endogenous thrombolytic processes.

Endothelium resistance to thrombus in long-term period in young patients with CI in their case history has not been given as much attention in the literature as traditional risk factors. Most research works concentrate on assessing blood stasis parameters only in an acute CI phase. Nevertheless, an attempt to determine individual risks of thrombotic events seems quite promising for treating such patients as it will allow optimizing therapy via targeted selection of medications and treatment duration.

Our research goal was to assess endothelial blood stasis parameters in patients who had CI and were treated with double anti-thrombocyte therapy at an out-patient department; another goal was to reveal potential risks of recurrent cardiovascular events.

Data and methods. We included 25 people aged from 18 to 45 into our research; they all had suffered CI and had been treated against IHD with emergency percutaneous coronary intervention and coronary arteries stenting at Perm Clinical Cardiologic Clinic over a period from September 2018 to March 2019. All the patients were prescribed relevant anti-thrombocyte therapy. Criteria for a patient being excluded from our research were as follows: systemic diseases, grave functional disorders in the liver and kidneys, acute conditions of any concomitant disease, heart rhythm disorders, pancreatic diabetes, thrombocytes concentration being lower than $100 \cdot 10^9$/l, and diagnosed disorders in thrombocytes functioning. Our reference group was made up of 15 practically healthy volunteers aged from 18 to 45.

Initial profiles of research participants are given in Table 1.

The reference group was comparable with the test group as per age and sex. Men prevailed among young patients who had suffered CI. 40 % patients in the test group had overweight and 8 % suffered from obesity; only 26.7 % had overweight in the reference group. It should be noted that smokers accounted for a rather big share among patients with CI, higher than 75 % (whereas it was only 25 % in the reference group); arterial hypertension and burden heredity as per early cardiovascular diseases were also more widely spread among patients with CI.

Table 1

Clinical and demographic profiles of participants in the research

Parameter	Young patients with CI (n = 25)	Reference group (n = 15)
Average age	37.5±7.1	36.3±7.1
Sex	men 84.0 % women 16.0 %	men 80.0 % women 20.0 %
Height, m	1.73±0.08	1.75±0.1
Weight, kg	76.6±14.3	72.4±10.0
Body mass index, kg/m²	25.5±3.3	23.6±1.8
Smoking status	76.0 %	26.7 %
Arterial hypertension	60.0 %	20.0 %
Burdened heredity	72.0 %	33.3 %
Total cholesterol, mmol/l	3.6±0.8	4.5±0.6
LDLP, mmol/l	2.0±0.6	2.4±0.7

16 % out of all the patients had already had CI, and 8 % among them had had even two CIs. Antero-lateral and posterior CIs were the most prevailing in terms of CI localization (Figure 1). CI with ST elevation accounted for 70 % of all cases; CI without ST elevation, 30 %.

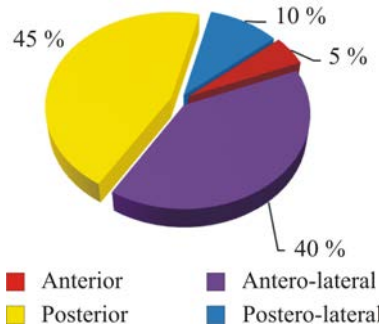

Figure 1. Cardiac infarction localizations

All the patients underwent primary percutaneous coronary intervention; the procedure allowed revealing that 69 % patients had two or more coronary arteries with stenosis exceeding 50 % (Figure 2). Either the anterior inter-ventricular artery or the right coronary artery was symptom-dependent in most patients; those arteries are the largest among all coronary ones.

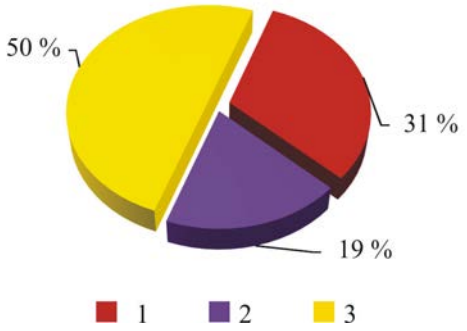

Figure 2. Number of damaged coronary arteries

71.4 % patients also had stenting procedure; in 40 % cases stents covered with a medication were applied. According to some research works, peculiarities of stenting, in particular such parameters as stent diameter and overall length, exert their influence on risks of thrombosis in future [26]. In our research each third patient had a stent with its diameter being less than 3 mm and overall length of applied stents was more than 18 mm practically in all cases.

After being released from hospital, patients were recommended to take medications according to the latest clinical recommendations on treating patients with CI. Thus, angiotensin-converting enzyme (ACE) inhibitors / sartan drugs were prescribed to 80 % patients; beta-blockers, to 88 %; statins in maximum doses and double anti-thrombocyte therapy including acetylsalicylic acid and P2Y12-thrombocyte receptors blocker, to all patients (Table 2).

Perindopril was the most frequently prescribed among all ACE inhibitors / sartans due to its great affinity with tissue ACE and it predetermined additional organ-protective properties of the drug [27]. The greatest share among prescribed beta-blockers belonged to cardioselective Bisoprosol; among P2Y12-thrombocyte receptors blockers, to Clopidogrel; among statins, to Atorvastatin. Commitment to therapy was close to 100 % in our research. Therefore, all the patients were prescribed relevant therapy aimed at improving prognosis for the disease.

Table 2

Принимаемые лекарственные препараты

Medications group	Active ingredient	A share of prescription
ACE inhibitors / sartan drugs	Perindopril	70.0 %
	Ramipril	10.0 %
	Losartan	10.0 %
	Valsartan	5.0 %
	Telmisartan	5.0 %
Beta-blockers	Bisoprosol	59.2 %
	Metoprolol succinate	31.8 %
	Carvediol	4.5 %
	Nebivolol	4.5 %
Acetylsalicylic acid	Acetylsalicylic acid	100.0 %
P2Y12-thrombocytes receptors blocker	Clopidogrel	72.0 %
	Ticagrelor	24.0 %
	Prasugrel	4.0 %
Statins	Atorvastatin	84.0 %
	Rosuvastatin	16.0 %

The research protocol was approved by the Local Ethical Committee at E.A, Vagners' Perm State Medical University of the RF Public Healthcare Ministry according to Helsinki Declaration (2008). All the patients included into the research gave their written voluntary informed consent to take part in it.

CI was diagnosed as per «Fourth Universal Definition of Myocardial Infarction» [28]. According to the WHO classification, age under 45 was considered young. Endothelial blood stasis was estimated 12 months after CI. Blood was taken from a patient on an empty stomach out of a peripheral vein into vacuum systems containing 3.2 % solution of waterless sodium nitrate in ratio 1: 10. To determine aggregation of thrombocytes with ristocetin, we

centrifuged blood samples at 200g for 7 minutes and them collected plasma enriched with thrombocytes. Thrombocytes aggregation was examined as per Born method with «Biola» ALA-T2 laser thrombocytes aggregation analyzer. We determined blood fibrinolytic activity with Hageman-dependent fibrinolysis as per a procedure described by G.F. Eryomin and A.G. Arkhipov (1981, 1982). 12 months after CI frequency of a combined ultimate point was estimated; that point included cardiovascular death, recurrent CI, and unstable stenocardia development.

All the data were statistically processed with Microsoft Excel and Stat Soft Statistica 13.0 applied statistical software. Quantitative parameters are given as simple mean ± standard deviation; qualitative parameters are frequencies given in %. Disprecpancies were considered statistically significant at $p \leq 0.05$.

Results and discussion. Table 3 contains the results obtained in laboratory assessment of blood stasis 12 months after CI.

Table 3

Blood stasis parameters in research participants

Parameter	Young patients with CI ($n = 25$)	Reference group ($n = 15$)	p
APTT, sec	28.5±2.8	33.3±0.7	<0.05
PTT, sec	13.7±0.7	15.07±0.1	<0.05
TT, sec	16.0±1.2	18.53±1.0	<0.05
Fibrinogen, g/l	3.2±0.6	2.94±0.1	<0.05
Aggregation of thrombocytes with ADP, sec	10.3±0.4	14.9±0.2	<0.05
Aggregation of thrombocytes with ristocetin, %	66.2±2.3	64.3±3.1	>0.05
HDF, min	12.0±3.6	9.6±0.4	<0.05

Patients with CI in their case history had more apparent changes in coagulation blood stasis system such as shorter activated partial thromboplastine time (APTT), shorter prothrombin time (PTT), shorter thrombin time (TT), and higher fibrinogen concentration.

Blood stasis disorders are a significant factor that influences rehabilitation after CI. Thus, it was shown in several research works that increased coagulation activity after PCI was related to higher risks of recurrent cardiovascular events such as re-stenosis or recurrent CI [29–31].

We examined aggregation function of thrombocytes with ADP and revealed a significant increase in their activity in patients who had suffered CI against healthy people (OR 4.4; 95 % CI 1.5–12.0; $p < 0.05$). Several prospective studies detected a relation between thrombocytes aggregation activity and cardiovascular event development in patients with diagnosed IHD [32, 33]. TRITON TIMI 38 and PLATO studied revealed that effective ADP-receptors inhibition improved a long-term prognosis for patients' survival rate [34, 35]. A recent ADAPT-DES study showed that high residual thrombocytes reactivity against relevant therapy that included antagonists of P2Y12-thrombocytes receptors resulted in elevated risks of stent thrombosis, recurrent CI, and mortality due to cardiovascular reasons [36].

We didn't reveal any significant differences between two groups regarding aggregation activity of thrombocytes with ristocetin in our research (OR 1.9; 95 % CI 0.2–20.2; $p > 0.05$). Some research works showed that patients with CI had elevated von Willebrand factor concentration. Austrian scientists concluded that elevated von Willebrand factor concentration in patients with CI led to elevated risks of recurrent ischemic events [37]. A. Sambola et al. revealed a correlation between elevated von Willebrand factor concentration in blood plasma and thrombus resistance to fibrinolysis in patients with CI with ST elevation [38]. K. Ozawa et al., in their turn, revealed that an increase in endothelium-associated von Willebrand factor concentration slowed down blood flow in the microcirculatory channel after CI [39]. Chinese researchers performed substantial meta-analysis aimed at estimating von Willebrand factor kinetics af-

ter CI. It was detected that the highest von Willebrand factor concentration occurred during the 1st week after CI and then it decreased gradually. It was detected that high von Willebrand factor concentration had prognostic significance and could be applied to estimate short-term prognosis [37].

Patients who had suffered CI had depressed Hageman-dependent fibrinolysis system. The discrepancy in this parameter was statistically authentic (OR 6.6; 95 % CI 1.1–14.7; $p < 0.05$). Recent works consider weaker endogenous fibrinolysis to be an unfavorable prognostic marker in case there is acute coronary syndrome [40, 41]. M. Farag et al. showed that patients who ran high cardiovascular risks still had functional disorders in their endogenous fibrinolysis 30 days after CI; there was an assumption that endogenous fibrinolysis assessment after CI could help revealing patients who still ran high cardiovascular risks in spite of PCI and double anti-thrombocytes therapy [42]. Researchers from Perm also mention in their works that poorer fibrinolysis parameters in patients after CI have unfavorable prognostic significance [43]. Endogenous fibrinolysis is assumed to become a new target for medication therapy prescribed to patients with high cardiovascular risks [41].

Conclusions. 12 months after CI young patients still run high risks of recurrent cardiovascular events. In addition to traditional risk factors such as smoking, dyslipidemia, overweight, and family case history with early cardiovascular diseases, there is also high thrombogenic risk caused by grave damage to coronary lumen, stenting procedure peculiarities as well as apparent changes in blood stasis. Indirect assessment of von Willebrand factor concentration in patients receiving relevant double anti-thrombocyte therapy allows considering this parameter to become normal during rehabilitation after CI. Nevertheless, there is still a functional disorder in thrombocytes activity, proneness to hyper-coagulation, and endogenous fibrinolysis deterioration.

Funding. The research was not granted any sponsor support.

Conflict of interests. Authors state there is no any conflict of interests.

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Received: 06.04.2020
Accepted: 03.06.2020
Published: 30.06.2020

UDC 617.3
DOI: 10.21668/health.risk/2020.2.14.eng

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SMOKING AND ALCOHOL ABUSE AS RISK FACTORS CAUSING LOW-ENERGY FRACTURES IN MALES SUFFERING FROM PRIMARY OSTEOPOROSIS

S.S. Rodionova[1], U.R. Khakimov[1], A.K. Morozov[1], A.V. Krivova[2]

[1]National Medical Research Center of Traumatology and Orthopedics named after N.N. Priorov, 10 Priorova Str., Moscow, 127299, Russian Federation
[2]Tver' State Medical University, 4 Sovetskaya Str., Tver', 170100, Russian Federation

Osteoporosis is a persistent social and medical issue taking into account moral and material losses related to bone fractures occurring against its background. The disease is more frequently examined in women than in men; still, according to EVOS (European Spinal Osteoporosis Study) 13.5 % men older than 50 and 26 % men older than 60 run high risks of fractures in case they have osteoporosis. Risk factors that cause both the disease itself and fractures as its complications have not been examined profoundly, even though men run 1.6 times higher risk of death after a fracture than women. There is an assumption that a reason for this higher mortality is lack of knowledge about risk factors that cause the disease and a fracture as one of its complications. Growing morbidity with osteoporosis among men indicates it is necessary to perform activities aimed at persuading them to pursue healthy lifestyle. Given that, it seems important to assess impacts exerted by smoking and alcohol abuse on risks of fractures among patients with primary osteoporosis bearing in mind prevention of the disease and fractures as its complications.

We examined a relation between smoking and alcohol abuse and risks of fractures as osteoporosis markers in 231 patients suffering from primary osteoporosis. We revealed that fractures were authentically more frequent among smoking patients, 90.5 % against 68.1 % ($p<0.001$). It was primarily true for fractures of the proximal section in the thigh bone and fractures of vertebral bodies: 20.2 % against 8.8 % and 44.1 % against 27.3 % accordingly. Alcohol abuse also resulted in authentically higher risks of fractures, 89.8 % against 66.2 % accordingly ($p<0.001$). Authentic discrepancies were detected only for fractures of vertebral bodies, 43.9 % against 23.6 % accordingly among those who didn't abuse alcohol ($p<0.001$).

Therefore, we have evidence that there is an authentic relation between smoking and alcohol abuse and risks of fractures of the proximal section in the thigh bone and vertebral bodies. Inclusion of our research results into educational programs may lead to a reduction in frequency of fractures that have the gravest outcomes for health and cause the highest economic losses.

Key words: *primary osteoporosis in men, risk factors of fractures, fractures of vertebral bodies, fractures of the proximal section in the thigh bone, smoking, alcohol abuse, an increase in morbidity with osteoporosis, prevention of the disease.*

Osteoporosis (OP) is a metabolic disease that occurs in bones making them loss their tissue, impairing their structure and strength thus resulting in elevated risks of bone fractures [1]. Annually osteoporosis causes more than 8.9 million bone fractures in various parts of the skeleton [2]. Number of patients that are put into hospital due to osteoporosis is growing and it is already higher than a number of people put into hospital due to cardiac infarction, stroke, and breast cancer [3]. According to some forecasts [4] in 2020 50 % women in menopause will have various bone fractures due to osteoporosis, including 25 % with vertebral bodies' fractures and 15 % with thigh bone fractures. A number of bone fractures caused by osteoporosis in men will also increase; thus, in 2025 a number of thigh bone fractures will be equal to that in women in 1990; by 2050 the figure will grow by 310 % whereas it will rise by 240 % for women [5]. Economically, a growth in num-

Svetlana S. Rodionova – Doctor of Medical Sciences, Professor, Head of the Center for Osteoporosis Treatment (e-mail: rod06@inbox.ru; tel.: +7 (910) 407-59-42; ORCID: http://orcid.org/0000-0002-27-26-87-58).

Umedzhon R. Khakimov – Post-graduate students at the Center for Osteoporosis Treatment (e-mail: umed.05@mail.ru; tel.: +7 (925) 346-37-30; ORCID: http://orcid.org/0000-0002-76-05-94-50).

Aleksandr K. Morozov – Doctor of Medical Sciences, Professor, Head of the X-ray Diagnostics Department (e-mail: cito@cito-priorov.ru; tel.: +7 (916) 604-35-34; ORCID: http://orcid.org/0000-0002-91-98-79-17).

Alla V. Krivova – Doctor of Medical Sciences, Associate Professor at the Traumatology and Orthopedics Department (e-mail: sklif79@yandex.ru; tel.: +7 (905) 600-33-09; ORCID: http://orcid.org/0000-0002-9722-1285).

ber of bone fractures means that there will be a constant growth in social expenses on treating, hospitalizing, and rehabilitating patients with fractures caused by osteoporosis as well as in expenses related to their temporary or constant disability (social pensions). Given that, a study on risk factors that can cause osteoporosis and related bone fractures is a vital component in prevention activities aimed at reducing moral and economic expenses borne by both a patient and a society as a whole.

Such bad habits as smoking and alcohol abuse are distinctive among risk factors that cause osteoporosis and related bone fractures. They are modifiable ones since negative effects produced by them on bone tissue can be reduced [6]. However, impacts exerted by these factors are, as a rule, discussed only when it comes to patients suffering from secondary osteoporosis while there are practically no researches that dwell on assessing their role played in pathological bone fractures occurrence among men with primary osteoporosis.

Our research goal was to estimate contribution made by smoking and alcohol abuse into occurring deficiency of bone mineral density (BMD) and a correlation between these bad habits and risks of bone fractures as markers in men suffering from primary osteoporosis.

Data and methods. We accomplished as open comparative controlled examination; men suffering from primary OP took part in it. The examination was performed in full conformity with ethical principles and Good Clinical Practice rules fixed in Helsinki Declaration. All the patients gave their informed consent to be examined and have their clinical data processed. Overall, we examined 231 patients suffering from primary osteoporosis; they were aged from 17 to 92 and were treated in the Center for Osteoporosis of the N.N. Pirogov's National Medical Research Center for Traumatology and Orthopedics from 2008 to 2018. As our research focused only on primary osteoporosis, we excluded all patients with pathologies that could cause secondary osteoporosis (we examined case histories in order to reveal diseases or prescribed medications that could influence bone tissue). We also excluded patients with hypogonadism from our research (to do that, we assessed sex hormones, examined family case histories, and performed a clinical examination; also, patients had consultations with endocrinologists). Osteomalacia was excluded basing on peculiarities detected via x-ray examinations and assessed homeostasis parameters of calcium, phosphor, and calcium-regulating hormones; hypophosphatasia was excluded as per alkaline phosphatase levels and genetic examinations results.

Primary osteoporosis was diagnosed basing on occurring low energy fractures of vertebral bodies or peripheral bones including fractures in the proximal section of the thigh bone, or on BMD losses being equal to <-2.5 SD as per T-criterion for people older than 50, or <-2.0 SD as per Z-criterion for people younger than 50 [7].

People who were included into the research only basing on a relevant decrease in BMD had first degree relatives who turned out to have low energy fractures. As for patients aged 17–20, 7 out of 26 didn't have any fractures; nevertheless, we took into account an apparent decrease in BMD (higher than -2.0 SD as per Z-criterion) and occurrence of osteoporosis with low energy fractures in their first degree relatives (father or mother); therefore, they were included into our research group. Another reason for including patients aged 17–19 into our research was the fact that healthy men in Russia have their peak bone tissue mass in the lumbar spine and femoral neck completely formed by the age of 15. BMD in these localizations has no authentic discrepancies in young males aged 16–19 whereas there were significant discrepancies revealed between them and 15–year old young males[1]. Bearing these data in mind, we excluded any possibility that BMD could

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change in young people aged 17–20 due to their skeletons still growing; any revealed decrease in BMD against a physiological standard for this age was considered to result from disorders in peak bone mass formation due to osteoporosis.

We applied X-ray densitometry (LUNAR Prodigy) to estimate BMD in L1–L4 and the femoral neck (we took a database collected for this device obtained in NHANES research). To detect symptomless fractures in the vertebral bodies, we performed X-ray examinations of the thoracic and lumbar spine; the examination was performed on each patient included into our research group.

Patients were divided into 3 age groups (Table 1) that corresponded to the following primary OP types: age 17–20 years, juvenile OP; age 21–50 years, idiopathic OP; age 51 and older, both idiopathic and senile primary OP.

Table 1

Patients being distributed into age groups

Group	Age (years)	Number of patients	Average age (years)
1	17–20	26	18.02+1.43
2	21–50	103	33.68+9.3
3	51 and older	102	63.5+8.1

We examined such bad habits as smoking and alcohol abuse in each patient included into our research group.

A patient was considered to abuse alcohol in case he daily consumed 30 grams of spirit or totally 200 grams of spirit per week [8].

Smoking was considered to be a habit in case a patient had been smoking for more than three months prior to the research (this term was taken as a minimal one to judge on whether the examined patients actually had this bad habit).

To assess impacts exerted by a bad habit on BMD, we compared its absolute values in g/cm^2 in patients who had this bad habit and their counterparts who didn't.

To assess effects produced by the same factors on risks of fractures, we divided all the patients into 5 groups, 4 out of them according to fracture localizations, and 1 group included patients without any fractures and was denominated Group 0. Group 1 included patients with low energy fractures of foot and hand bones; Group 2, patients with fractures in the proximal section of the humeral bone, shin bones, forearm bones, and ribs; Group 3, patients with fractures in the proximal section of the thigh bone; Group 4, patients with fractures in the vertebral bodies. We sequentially assessed bad habits of patients included into these groups that could cause a pathologic fracture in patients with various primary OP types.

Statistical analysis. We applied contingency tables to estimate interval variables and exact Fischer's test to reveal any correlations between the examined parameters. Critical significance was taken as 0.05 [9, 10].

Results and discussion. Tables 2 and 3 contain the results of influence exerted by bad habits on BMD.

The performed analysis didn't reveal any authentic discrepancies in BMD deficiency between smoking and non-smoking patients in these groups.

We also didn't detect any effects produced by alcohol abuse on BMD deficiency value.

Therefore, we didn't reveal any correlations between absolute BMD values (g/cm^2) and such bad habits as alcohol abuse and smoking. Table 4 contains data on effects produced by smoking on risk of fractures.

Table 2

Comparing BMD (g/cm^2) in L1–L4 and the femoral neck In smokers and non-smokers (Mann – Whitney test)

Groups of patients	Number of patients	BMD L1–L4 (g/cm^2)	Neck BMD (g/cm^2)
Smokers	82	0.93±0.16	0.80±0.13
Percentiles	25 %	0.84	0.72
	50 %	0.94	0.79
	75 %	1.01	0.88
Non-smokers	149	0.93±0.16	0.84±0.15
Percentiles	25 %	0.82	0.75
	50 %	0.90	0.80
	75 %	1,00	0,92

Table 3

Influence exerted by alcohol abuse on BMD (g/cm²) in L1–L4 and the femoral neck (Mann – Whitney test)

Groups of patients	Number of patients	BMD L1–L4 (g/cm²)	Neck BMD (g/cm²)
Abusing alcohol	91	0.93±0.16	0.93±0.16
Percentiles	25 %	0.84	0.72
	50 %	0.93	0.81
	75 %	1.02	0.89
Not abusing alcohol	140	0.81±0.15	0.83±0.15
Percentiles	25 %	0.82	0.74
	50 %	0.90	0.80
	75 %	1.00	0.90

Table 4

Estimating correlations between fractures and smoking (exact Fischer's test, $p < 0.001$)

Gropus of patients	Division into groups as per fractures					Total
	0	1	2	3	4	
Smokers	8 9.5 %	9 10.7 %	13 15.5 %	17 20.2 %	37 44.1 %	84 100 %
Non-smokers	47 31.9 %	17 11.5 %	30 20.5 %	13 8.8 %	40 27.3 %	147 100 %

As we can see from the Table, smoking patients tended to have more frequent fractures in the proximal section of the thigh bone, 20.2 % against 8.8 % accordingly, and fractures in the vertebral bodies, 44.1 % against 27.3 % accordingly. 31.9 % non-smoking patients didn't have any fractures whereas only 9.5 % of their smoking counterparts managed to avoid them. Discrepancies between smoking and non-smoking patients were authentic ($p < 0.001$).

To get more precise data on a correlation between fracture localizations and smoking, we sequentially divided patients into three groups for each localization; it was done in the following way: Group 1 included patients without fractures; Group 2, patients with fractures of all localizations except the one being estimated in this contingency table; Group 3 included patients with the fracture localization being estimated.

Sequential analysis revealed that there were authentic discrepancies between patients without fractures (their number was authentically ($p < 0.001$) higher among non-smokers) and patients with fractures of the vertebral bones (their number was authentically higher among smokers ($p < 0.001$). These data are given in Table 5.

Table 5

Contingency of vertebral bodies fractures with smoking (exact Fischer's test, $p < 0.001$)

Gropus of patients depending on smoking status	Division into gorups as per fractures			Total
	1	2	3	
Smoking	8 9.5 %	39 46.4 %	37 44.1 %	84 100 %
Non-smoking	47 31.9 %	60 40.8 %	40 27.3 %	147 100 %

We didn't reveal any correlations between other localizations of fractures and smoking.

Table 6 contains data on a correlation between fractures and alcohol abuse.

Table 6

Assessing a correlation between fractures and alcohol abuse (exact Fischer's test, $p < 0.001$)

Groups of patients	Division into gorups as per fractures					Total
	0	1	2	3	4	
Abusing alcohol	10 10.2 %	14 14.3 %	16 16.3 %	15 15.3 %	43 43.9 %	98 100 %
Not abusing alcohol	45 33.8 %	12 9.0 %	27 20.3 %	15 11.3 %	34 25.6 %	133 100 %

We assessed a correlation between fractures and alcohol abuse and revealed that fractures occurred among alcohol abusers authentically more frequently than among those who didn't have this bad habit ($p < 0.001$). There were only 10.2 % patients without any fractures among those who abused alcohol

whereas there were 33.8 % patients without fractures among those who didn't do it.

The next stage was to get more precise data on a correlation between fracture localizations and alcohol abuse. Patients were divided into groups in the same way as it was done when assessing influence exerted by smoking. Group 1 were patients without fractures; Group 2, patients with fractures of all localizations except the one being estimated in this contingency table; Group 3 included patients with the fracture localization being estimated.

We sequentially assessed all fracture localizations and revealed authentic discrepancies only for fractures of the vertebral bodies (Table 7). Fractures of the vertebral bodies authentically more frequently occurred among patients who abused alcohol, 43.9 % against 23.6 % accordingly ($p < 0.001$).

Table 7

Assessing a correlation between fractures of the vertebral bodies and alcohol abuse (exact Fischer's test, $p < 0.001$)

Groups of patients	Division into gorups as per fractures			Total
	1	2	3	
Abusing alcohol	10 10.2 %	45 45.9 %	43 43.9 %	98 100 %
No abusing alcohol	45 33.8 %	54 40.6 %	34 25.6 %	133 100 %

At present osteoporosis holds a very specific place among non-communicable diseases due to high prevalence and significant risks of fractures; prior to their occurrence the disease is mostly symptomless and its clinical picture is not at all apparent. Frequently fractures not only give a clear signal the disease has already developed but also cause grave health disorders or even death [11]. Over many years, the disease has been considered as being exceptionally a female one. However, over the last 20 years, it has become quite obvious that 30 % low energy fractures of the thigh bone among men occur due to osteoporosis; its prevalence among men older than 50 varies from 2 to 8 %, and additionally from 33 to 47 % men in this age group can be put a diagnosis «decreased bone mineral density» and it also results in higher risks of low energy fracture [12, 13]. 1 out of 5 male patients has a fracture associated with OP [14]. When analyzing risk factors that can cause fractures, experts mostly discuss secondary osteoporosis cases without giving special attention to influence exerted by these factors on risks of fractures in case of primary osteoporosis [15–17]. At the same time, according to certain data [18] 80 % osteoporosis cases among men older than 50 are exactly primary osteoporosis. These are the cases when it is impossible to reveal any somatic pathology or intake of medications that could cause metabolic changes in the bone tissue [19]. Primary osteoporosis among men can be juvenile, idiopathic, or senile depending on age at which the disease is detected [20]. Our research group included 231 patients with different types of primary osteoporosis; some patients had fractures of different localizations. In all cases fractures were spontaneous or low energy ones and were considered to be pathologic fractures caused by osteoporosis.

Fractures caused by OP occur among male patients 10 years later than among female ones but they tend to have much graver outcomes [21]. According to available data, risks of such fractures and mortality due to them is higher among men older than 60 than among women from the same age group [22, 23]. Thus, in case of thigh bone fractures mortality among men during the 1st year after a fracture was 2 times higher than among women [24–26]. As life expectancy grows both among men and women, a number of fractures also increases and this growth is considered to be related not only to age but also to bad habits. Thus, in the research work by Mariola Janiszewska [27] that concentrated on risk factors causing osteoporosis, 71.25 % respondents mentioned alcohol abuse, and 56.6 % stated they were smokers. In another research work that also dwelled on issues related to osteoporosis among male patients [28], 38 % respondents mentioned smoking as a risk factor that can cause osteoporosis and more than one third of

respondents considered alcohol abuse to be another risk factor. Negative effects produced by smoking on BMD deficiency are also being discussed, among other things, in relation to BMI and physical activity [6]. Thus, a decrease in BMD among men aged 40–80 varied from 14 % (non-smoking and physically active men with BMI equal to 30 kg/m^2) to 30 % (smoking and not physically active men with BMI starting from 18 kg/m^2). A separate analysis of BMD among men older than 80 revealed that non-smoking and physically active men (4 hours of physical activity per week) had BMD that was by 1–2.0 SD higher than BMD among their smoking and not physically active counterparts from the same age group. However, among other modifiable causes of osteoporosis, smoking has long been accepted as a factor that, regardless of any other reason, produces negative effects on a balance between bone resorption and bone formation and it results in an increase in BMD deficiency [29]. Disorders in bone tissue metabolism influenced by smoking are also thought to be related to influence exerted on calcium homeostasis (calcium absorption declines) and on parathyrin-D-hormone endocrine chain [30]. Previously, P.D. Broulik et al. [31] made a point on a direct impacts exerted by nicotine on bones. There are some data on smoking exerting more adverse effects on bone tissue among men than among women [32]. Thus, smoking causes a 13 % increase in risks of spine fractures among women and a 32 % increase in the same risks among men; a 31 % and 40 % increase accordingly in risks of thigh bone fracture.

We didn't dwell on influence exerted by smoking on BMD value; still, we obtained some evidence that this bad habit authentically caused elevated risks of fractures for those who had it against those who didn't; 31.9 % non-smoking patients didn't have any fractures whereas there were only 9.5 % smoking patients who managed to avoid them, discrepancies being authentic at $p < 0.001$. Smoking patients more frequently had fractures in the proximal section of the thigh bone, 20.2 % against 8.8 % accordingly, and fractures of the vertebral bodies, 44.1 % against 27.3 % accordingly; discrepancies in frequency of vertebral bone fractures were authentic ($p < 0.001$). When it comes to such bad habit as alcohol abuse, we should mention that effects produced by alcohol on risks of osteoporosis and fractures caused by the disease are considered to be related both to calcium homeostasis disorders and pathological changes in the liver that result in D-hormone metabolism disorders. Besides, alcohol abuse makes people more prone to falling [33]. In our research alcohol abuse, just as smoking, wasn't revealed to exert any influence on BMD deficiency value but it had certain influence on risk of fractures. Only 10.2 % patients among those who abused alcohol didn't have fractures whereas there were 33.8 % patients without any fractures among those who didn't do it; discrepancies between two groups were authentic ($p < 0.001$). First of all, it was the case with frequency of vertebral bodies' fractures, 43.9 % alcohol abusers against 23.6 % of those who didn't had this bad habit ($p < 0,001$).

Therefore, despite absence of any direct influence exerted by smoking and alcohol abuse on BMD value, our research allowed obtaining certain evidence that there was a correlation between these bad habits and fractures frequency; first of all, it was true for fractures of the vertebral bones and it was similar to effects produced by these bad habits on risks of fractures in case of secondary osteoporosis. These data are significant for working out measures aimed at preventing fractures in patients with primary osteoporosis hence previously several cross-over studies included into meta-analysis by D. Kenneth et al. [32] contained data on ex-smokers having BMD similar to BMD of those people who never smoked. In the authors' opinion, these data indicate that giving up smoking produces favorable effects on BMD. And though mechanisms of these effects are still not clear, we can assume that it is quite advisable to promote healthy lifestyle among men with primary osteoporosis who have such bad habits as smoking and alcohol abuse. Such promotion can result in lower risks of fractures in the proxi-

mal section of the thigh bone and vertebral bodies. There is other evidence that this trend in prevention is significant; it is related to people being hardly aware of smoking and alcohol abuse as risk factors that can cause osteoporosis and related fractures. It is especially vital when it comes to teenagers. Thus, the research work [27] contains a reference to the work by S. Wahba et al. [34], mentioning results of a questioning with 494 participants aged 16–24 living in Cairo; only 6 % teenagers and young people knew that smoking can cause osteoporosis. And though 41.7 % adult women [35] among the examined ones realized that smoking was a risk factor that could cause osteoporosis, more than a half questioned women didn't see any relations between the disease and this bad habit.

Since reducing risks of fractures is a vital component in a healthcare strategy aimed at improving life quality of patients suffering from osteoporosis, we believe that our data on contributions made by smoking and alcohol abuse should be included into educational programs for patients with the disease. It will result in lower frequency of pathologic fractures in the proximal section of the thigh bone and vertebral bodies; these fractures have the gravest consequences for patients' health and result in the highest economic costs.

Funding. The research was not granted any sponsor support.

Conflict of interests. The authors declare there is no any conflict of interests.

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Received: 12.01.2020
Accepted: 17.03.2020
Published: 30.06.2020

UDC 616.91: 614.446: 578.825.1
DOI: 10.21668/health.risk/2020.2.15.eng

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ASSESSING RISKS OF INFECTION WITH HERPES VIRUSES DURING TRANSFUSION OF DONOR BLOOD AND ITS COMPONENTS

T.V. Solomay[1], T.A. Semenenko[2,3], N.V. Karazhas[2], T.N. Rybalkina[2], M.N. Kornienko[2], R.E. Bosh'yan[2,3], S.A. Golosova[4], I.V. Ivanova[4]

[1]Inter-regional Office No. 1 of the Federal Biomedical Agency of Russia, 6A 1st Pekhotnyi lane, Moscow, 123182, Russian Federation
[2]Honor Academician N.F. Gamalei's National Research Center for Epidemiology and Microbiology, 18 Gamalei Str., Moscow, 123098, Russian Federation
[3]I.M. Sechenov First Moscow State Medical University, 2 Bld., 2 Bol'shaya Pirogovskaya Str., Moscow, 119435, Russian Federation
[4]Blood Center of the Federal Biomedical Agency of Russia, 2 Bld., 6 Shchukinskaya Str., Moscow, 123182, Russian Federation

A primary task transfusion medicine should solve is to provide infection safety of donor blood and its components.

Our research goal was to assess potential risks of a recipient being infected with herpes viruses during transfusion of donor blood and its components and to suggest a set of activities aimed at the risk reduction.

We examined blood samples taken from 142 donors who permanently resided in Moscow; our task was to detect markers of active infections caused by herpes simplex viruses, types 1 and 2, Epstein-Barr virus (EBV), cytomegalovirus, and human herpes type 6 virus. Immunoglobulins M and G were determined with ELISA test; antigens, via an indirect immune fluorescence reaction combined with rapid cultural technique. All the donors successfully passed all the selection procedures and were accepted for donation.

Active forms were most frequently detected for infections caused by EBV (11.97 ± 2.73 per 100 examined) and human herpes type 6 virus (9.86 ± 2.51 per 100 examined), and it was accordingly 10 and 8.96 times higher than data given by other authors. It indicates there was high epidemic activity of these infectious agents in Moscow city in November-December 2019 and higher risks of recipients being infected with EBV and human herpes type 6 virus with donor blood and its components. Frequency of detecting donors with active infections caused by herpes simples, types 1 and 2, EBV, cytomegalovirus, and human herpes type 6 virus amounted to 27.46 ± 3.76 per 100 examined. Frequency of detecting donors bearing antigens to herpes viruses in their blood amounted to 20.42 ± 3.39 per 100 examined. Risk of potential infecting with examined herpes viruses during blood transfusions amounted to 40.85 per 100 recipients.

In order to reduce this risk, we suggest wide implementation of leuko- and pathogen reduction of stored donor blood and its components.

Key words: *risk assessment, infection risk, herpes viruses, blood examination, donors, donor blood and its components, infection safety, transfusion.*

Tat'yana V. Solomay – Candidate of Medical Sciences, Deputy Director (e-mail: solomay@rambler.ru; tel.: +7 (499) 720-49-17; ORCID: https://orcid.org/0000-0002-7040-7653).

Tat'yana A. Semenenko – Doctor of Medical Sciences, Professor, RANS Academician, Head of the Epidemiology Department, professor at the Infectiology and Virology Department (e-mail: semenenko@gamaleya.org; tel.: +7 (499) 190-72-56; ORCID: https://orcid.org/0000-0002-6686-9011).

Natal'ya V. Karazhas – Doctor of Biological Sciences, Professor, Head of the Laboratory of Opportunistic Infections Epidemiology (e-mail: karazhas@inbox.ru; tel.: +7 (499) 193-43-89; ORCID: https://orcid.org/0000-0003-3840-963X).

Tat'yana N. Rybalkina – Candidate of Medical Sciences, Senior researcher at the Laboratory of Opportunistic Infections Epidemiology (e-mail: rybalkinatn@mail.ru; tel.: +7 (499) 193-43-89; ORCID: https://orcid.org/0000-0003-2083-5307).

Mariya N. Kornienko – Candidate of Biological Sciences, Senior researcher at the Laboratory of Opportunistic Infections Epidemiology (e-mail: kornienko2011@gmail.com; tel.: +7 (499) 193-43-89; ORCID: https://orcid.org/0000-0002-5694-0435).

Roman E. Bosh'yan – Candidate of Medical Sciences, Researcher at the Laboratory of Opportunistic Infections Epidemiology, Associate Professor at the Microbiology, Virology, and Immunology Department (e-mail: rbrm@mail.ru; tel.: +7 (903) 160-29-85; ORCID: https://orcid.org/0000-0003-4789-4964).

Sofiya A. Golosova – Chief physician (e-mail: sgolosova@bloodfmba.ru; tel.: +7 (495) 122-20-13; ORCID: https://orcid.org/0000-0001-5405-1282).

Irina V. Ivanova – Head of the Laboratory Diagnostics Department (e-mail: iivanova@bloodfmba.ru; tel.: +7 (495) 122-20-13; ORCID: https://orcid.org/0000-0003-4491-8123).

Up-to-date medical technologies are being implemented into every sphere in health care including transfusion medicine; it allows increasing quality and efficiency of medical services rendered to population. Annually, volumes of whole donor blood that are stored up in the Russian Federation grow by 7–10 %; in 2018 they amounted to approximately 1.5 million liters and the figure didn't include plasma obtained via plasmapheresis in volumes exceeding 700 thousand liters [1, 2]. Given that, a most vital problem the domestic transfusion medicine in Russia has to tackle is providing safety of donor blood and its components; that means, among other things, minimizing risks related to recipients being infected with hemotransmissive infections [3, 4]. The existing legislative and regulatory documents stipulate that donors are to be checked in order to reveal whether they have type B hepatitis virus (BH), type C hepatitis virus (CH), HIV, or syphilis infectious agents in their blood. It allows a substantial reduction in risks of infections; however, being only a single activity, it can't provide complete biological safety of donor blood and its components as the above mentioned pathogens are not the only ones that can potentially occur in blood [5–7].

There are cases mentioned in literature when recipients got infected with herpes virus infections after transfusion of donor blood and its components [8, 9]. At present an epidemiologic situation as per these infections is considered to be rather unfavorable. According to official statistic data, in the RF over the recent years there has been a growth in morbidity with cytomegalovirus infection and infectious mononucleosis. It is rather difficult to reliably assess a situation regarding morbidity with infections caused by simple herpes viruses, types 1 and 2, and human herpes type 6 virus, due to absence of its official registration [10, 11]. Nevertheless, results obtained in research both in our country and abroad indicate that infectious pathology associated with herpes viruses is widely spread and occurs everywhere [7, 12–14]. It creates additional health risks for recipients of donor blood and its components.

Our research goal was to assess potential risks of a recipient being infected with herpes viruses during transfusion of donor blood and its components and to suggest a set of activities aimed at the risk reduction.

Research problems to be solved:

– to detect frequency of active infections caused by herpes viruses including simple herpes types 1 and 2 virus, Epstein-Barr virus, cytomegalovirus, and human herpes type 6 virus in donors from Moscow city;

– to detect frequency of donors with active mono- and mixed herpes virus infections;

– to calculate frequency of donors with herpes viruses antigens in their blood indicating an infectious agent occurred in their circulatory system;

– to calculate potential risks of recipients being infected with herpes viruses during transfusion of donor blood and its components;

– to give recommendations on activities aimed at reducing risks.

Data and methods. To achieve our goal, over a period from November 05, 2019 to December 02, 2019 we examined blood taken from 142 donors aged from 22 to 55 (average age was 36.68 ± 9.11; 89 males and 53 females) who permanently lived in Moscow, had negative results regarding markers of syphilis infectious agent, HIV, HB and HC viruses, and negative results after a molecular-biologic examinations aimed at detecting syphilis infectious agent, HIV, HB and HC viruses in their blood. All the examined donors had alanine aminotransferase, hemoglobin, PCV, ESR, crude protein and protein fractions, and cellular formula within reference values fixed in the Order by the RF Public Healthcare Ministry issues on September 14, 2001 (last edited on June 06, 2008) No. 364 «On approving a procedure

for a medical examination for a donor of blood and its components»[1]. All the donors gave their consent in conformity with conventional procedures. After blood was taken, all the samples were encoded. No personal data were processed during the present research.

We identified immunoglobulin M (IgM) and G (IgG) to antibodies to simple herpes viruses type 1 and 2 (HHV-1 and HHV-2); Epstein-Barr virus (EBV); cytomegalovirus (CMV); human herpes type 6 virus (HHV-6); to do that, we applied ELISA test with a reagent set provided by «Vector-Best». Antigens (AG) of viruses were detected via an indirect immune fluorescence reaction (IIFR) with human hyper-immune serums, FITS conjugate and Evans blue dye test. Early antigens and herpes viruses' reproduction were detected via rapid cultural technique (RCT) on Veru, U937, and M-19 cells (human fibroblasts) with the subsequent repeated AG identification with IIRF. Virus accumulation on a cellular culture allowed achieving higher sensitivity in detecting antigens with a viral load being low.

All the results were interpreted in conformity with instructions issued for applied reagent sets and procedures. An active herpes virus infection (primary acute and reactivated one) caused by HHV-1, HHV-2, CMV, and HHV-6 was considered to be present in case AG were detected; also, IgM, including cases when it was detected together with AG and/or IgG; an infection caused by EBV was considered to be present in case AG were detected; also IgM to capsid antigen (IgMVCA), including cases when it was detected together with AG and/or IgG to capsid (IgGVCA) and/or nuclear (IgGEBNA) antigens; also IgG to an early antigen (IgGEA), including cases when it was detected together with IgMVCA, IgGVCA, IgGEBNA.

Potential risks that a recipient of donor blood and its components would be infected with herpes viruses were calculated as per the following formula (1)

$$R = M \cdot Nd/Nr, \quad (1)$$

where M is frequency of donors with herpes viruses' antigens in their blood indicating they had a pathogen in their circulatory system;

Nd is a number of blood component doses taken from one donor;

Nr is a number of blood components transfused form one donor to one recipient.

Results were treated according to conventional statistic procedures with licensed Microsoft Excel package for Microsoft Windows. We calculated frequency of herpes viruses' markers per 100 examined donors, error of the mean (m), and Student's t-test (t). Discrepancies were considered to be valid at confidence probability $p \leq 0.05$.

Results and discussion. Our research revealed that an infection caused by EBV was the most frequently detected one, both in its primary acute and reactivated forms (Table 1). The 2nd place belonged to an infection caused by HHV-6; the 3rd place, CMV; the 4th place, HVV-1. Active infections caused by HHV-2 were the most rarely detected. There were authentic discrepancies in detected frequencies of active infections caused by EBV and HVV-2 ($t = 3.64$; $p \leq 0.01$); HHV-6 and HVV-2 ($t = 3.13$; $p \leq 0.01$); CMV and HVV-2 ($t = 2.6$; $p \leq 0.05$); HHV-1 and HHV-2 ($t = 2.18$; $p \leq 0.05$). Discrepancies were not valid in all other cases ($t < 2$; $p > 0.05$).

[1] On approving a procedure for a medical examination for a donor of blood and its components: The Order by the RF Public Healthcare Ministry issued on September 14, 2001 No. 364 (last edited on June 06, 2008). *Garant: information and legal database*. Available at: http://base.garant.ru/4177987/ (08.02.2020) (in Russian).

Table 1

Frequency of active infections (primary acute and reactivated) caused by EBV, HHV-1, HHV-2, CMV and HVV-6 in donors (per 100 examined)

Markers of active infections	HHV-1	HHV-2	EBV	CMV	HVV-6
$M \pm m$	6.34 ± 2.05	1.4 ± 0.99	11.97 ± 2.73	7.74 ± 2.24	9.86 ± 2.51

Table 2

Frequency of active mono- and mixed infections caused by HHV-1, HHV-2, CMV, HVV-6 and EBV in donors (per 100 examined)

Overall 142 people examined		Number of donors with active infections	Per 100 examined ($M \pm m$)
Active mono-infection	HHV-1	6	4.23 ± 1.69
	HHV-2	1	0.7 ± 0.7
	CMV	7	4.93 ± 1.82
	HHV-6	8	5.64 ± 1.94
	EBV	7	4.93 ± 1.82
Active mixed infection	HHV-1 + EBV	1	0.7 ± 0.7
	HHV-1 + HHV-2 + EBV	1	0.7 ± 0.7
	HHV-1 + EBV + CMV + HHV-6	1	0.7 ± 0.7
	CMV + HHV-6	1	0.7 ± 0.7
	EBV + CMV	2	1.41 ± 0.99
	EBV + HHV-6	4	2.82 ± 1.39
Total		39	27.46 ± 3,76

As the same donor can simultaneously have several active herpes virus infections, we made an additional assessment aimed at detecting frequency of active mono- and mixed infections (Table 2).

Markers of active mono-infection were detected for all the examined infectious agents; they were most frequently detected for an infection caused by HHV-6; and the least frequently, for an infection caused by HHV-2. Authentic discrepancies were detected for frequency of active mono-infection caused by HHV-6 and HHV-2 ($t = 2.4$; $p \leq 0.05$); CMV and HHV-2 ($t = 2.17$; $p \leq 0.05$); EBV and HHV-2 ($t = 2.17$; $p \leq 0.05$).

Apart from detecting markers of an active mono-infection, we revealed that examined donors had active mixed infections. In one case a donor was infected with three viruses (HHV-1 + HHV-2 + EBV); and in another one, with four (HHV-1 + EBV + CMV + HHV-6). A combination of two viruses was authentically more frequent (5.64 ± 1.94 per 100 examined donors), $t = 2.4$; $p \leq 0.05$.

There were totally 39 donors out of 142 examined with various combinations of active herpes virus infections detected in their blood (27.46 ± 3.76 per 100 examined). Virus antigens including virus replication in a cellular culture were detected in 29 donors (20.42 ± 3.39 per 100 examined).

To calculate risks related to recipients being infected, we applied frequency of donors with herpes viruses' antigens in their blood that indicated they had a pathogen in

their circulatory system. Given that one donor on average usually gives blood for two doses of blood components per one donation, and one recipient on average gets one dose, a potential risk that a recipient would be infected with the examined pathogens amounted to 40.85 per 100 recipients.

Despite the fact that donors are often used in epidemiologic research as a reference group, at present there are very few available works on prevalence of active herpes virus infections in them. Experts from Russia and Belarus give some data that frequency of active infections caused by simple herpes viruses varied from 0.0 to 30.2 per 100 examined donors; CMV, from 2.2 to 16.5; EBV and HVV-6, 1.1 per 100 examined donors [15, 16]. Hence, our data on frequency of active infections caused by simple HVV and CMV were quite comparable with data taken from literature. We detected active EBV and HHv-6 infections accordingly 10 and 8.96 times more frequently in our research and it indicates that these infectious agents were highly epidemically active on the examined territory in November and December 2019; consequently, a risk that a recipient would be infected with the said viruses during blood transfusion was higher than calculated basing on data given by other authors.

Our research revealed a possibility that a recipient would be infected simultaneously with several herpes viruses with transfused donor blood and its components; it is a real challenge for clinical medicine [17–19] that can't be faced without applying a wider set of preventive and anti-epidemic activities.

An existing system that ensures infectious safety of donor blood and its components in the RF is based on proper selection of donors including medical examinations and laboratory instrumental research. Additional procedures include leuko- and pathogen reduction of blood components stipulated by the Rules for taking, storing up, transporting and clinical use of donor blood and its components (approved by the RF Government Order issued on June 22, 2019 No. 797[2]). However, the procedures are not obligatory and are applied to discretion of an organization that stores up donor blood and its components. At the same time, these procedures are widely used in other countries and they play an important role in providing donor blood safety as there are a lot of pathogens that potentially circulate in blood including those that are not indentified with up-to-date tools for laboratory diagnostics [5]. Leuko-reduction is especially relevant when it comes to cellular-associated pathogens, and herpes viruses belong exactly to this category. Several research works revealed that a risk related to CMV infection is significantly reduced after leuko-reduction performed with leuko-filters [5, 8, 9]; EBV is not at all detected after leuko-filtration has been performed on knowingly infected doses of thrombocytes concentrations [20]. Pathogen reduction is also a significant preventive procedure as it is efficient against most bacteria, protozoa, and viruses with lipid membranes [21–23]. The procedure is aimed at inhibiting infectious agents' reproduction; however, it can be insufficient for protecting a recipient from being infected in case viruses are already present in blood [24].

Our results indicate that recipients run a considerable risk of being infected with herpes viruses; to reduce it, it is necessary to widely implement both leuko- and pathogen reduction into storing up donor blood and its components. Another fact that

[2] On Approval of the Rules for taking, storing up, transporting and clinic use of donor blood and its components and on certain RF Government Orders being no longer valid: The RF Government Order issued on June 22, 2019 No. 797. *Garant: information and legal database*. Available at: https://www.garant.ru/products/ipo/prime/doc/72184110/ (08.02.2020) (in Russian).

proves the necessity of these procedures is that all the donors who took part in our research had been selected according to all the existing legal and regulatory documents and had been accepted for donation. They didn't have any clinical signs of infections and their clinical and biochemical parameters revealed via laboratory research were within reference values.

Conclusions.

1. Active infections (both in their primary acute and reactivated forms) caused by EBV and HHV-6 were the most frequently detected (11.97 ± 2.73 per 100 examined and 9.86 ± 2.51 per 100 examined accordingly), and it was respectively 10 and 8.96 times more frequent than according to data given by other authors. It indicates that those infectious agents were highly epidemically active in Moscow in November and December 2019 and recipients ran high risks of being infected with EBV and HHV-6 with donor blood and its components.

2. Frequency of donors with active infections caused by simple herpes type 1 and 2 viruses, Epstein-Barr virus, cytomegalovirus, and human herpes type 6 virus amounted to 27.46 ± 3.76 per 100 examined.

3. Frequency of donors with herpes virus antigens detected in their blood amounted to 20.42 ± 3.39 per 100 examined.

4. Risk of a recipient being infected with the examined herpes viruses during blood transfusions amounted to 40.85 per 100 recipients.

5. To reduce risks of a recipient being infected with the examined infectious agents, it is necessary to widely implement leuko- and pathogen reduction and perform these procedures on stored donor blood and its components.

Funding. The research was not granted any sponsor support.

Conflict of interests. The authors declare there is no any conflict of interests.

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Received: 10.02.2020
Accepted: 04.06.2020
Published: 30.06.2020

UDC 616-099
DOI: 10.21668/health.risk/2020.2.16.eng

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PROCEDURE FOR PREDICTING PROGRESSING HEPATIC FIBROSIS IN PATIENTS WITH HUMAN IMMUNODEFICIENCY AND HEPATITIS C COINFECTION

V.V. Maslyakov, M.S. Aristanbekova

«Reaviz» Medical University, 227 Chapaevskaya Str., Samara, 443001, Russian Federation

Our research goal was to develop a system for predicting nature of fibrosis processes in patients infected with HIV and Hepatitis C virus and to assess its efficiency bearing in mind peculiarities of anti-virus therapy applied for treating the infections.

Research was performed on 459 patients with confirmed HIV/viral hepatitis C who had been treated for 1 year at Saratov Regional Center for AIDS Prevention and Elimination. Most patients were males younger than 36. 72–78 % patients had 3–4A HIV infection stages. The rest had 4B–C stages. 32 % were treated only with sets of anti-retroviruses medications made up of nucleoside and non-nucleoside inhibitors of reverse transcriptase, inhibitors of protease, and inhibitors of integrase in different combinations. 14 % patients infected with both HIV and Hepatitis C virus were treated only with antiviral medications aimed for treating hepatitis C and made up of pegylated interferon α and ribavirin or medications with direct effects such as sofosbuvir and daclatasvir. 19 % patients were prescribed both antiviral therapy aimed at treating Hepatitis C and anti-retrovirus therapy.

Research results allowed establishing risk criteria for progressing hepatic fibrosis; they included fibro scanning of liver, number of CD3+CD4+ cells in blood, and immune regulatory index. Basing on the research data, we created an integral parameter for assessing quantitative risk criteria that could be used when a patient was examined for the first time or during a short-term observation period.

Key words: *HIV/Hepatitis C co-infection, infection process, progressing hepatic fibrosis, fibro scanning, T-lymphocytes subpopulations, antiviral therapy, high risk index, risk criteria.*

HIV/hepatitis C virus (HCV) coinfection doesn't only tend to have more severe clinical course but also predetermines high lethality among patients due to rapidly developing damage to the liver. It is also known that HIV-infected patients who also have hepatitis C run higher risks of extrahepatic symptoms [1] and hepatotoxic effects produced by anti-retrovirus (ARV) medications [2]. Given all that, an issue related to progressing liver fibrosis is becoming most outstanding together with problems that doctors have to face when treating chronic hepatitis C (CHC) in patients coinfected with HIV/HCV. Over the recent years, a new strategy has been developed regarding CHC treatment exactly in case there is HIV/HCV coinfection. Up to now, a combination of pegylated recombinant interferon α (IFNα) and Ribavirin has been considered the only anti-virus therapy against CHC; a procedure for applying it depended on HCV genotype. This treatment usually involves multiple side effects. A large group of patients who suffered from neuropsychological or cardiovascular disorders could not be treated with interferons due to serious contraindications [3, 4]. Use of this treatment scheme usually results in persistent anti-virus response only approximately in 40 % when it comes to people who simultaneously have HIV and HCV [5].

In 2011 a new era began as innovative anti-virus medications with direct effects on HCV were first implemented into treatment practices. Infectiologists started to use NS3/4A inhibitors of HVC proteases (Telaprevir and Boceprevir) to treat HVC infection caused by a virus with genotype 1 combined with pegylated interferon α and Ribavirin [6, 7]. As the trend developed, new medications were created with a wider range of effects produced on HCV and it was possible to use them without IFN [8]. However, a new problem occurred; there was a probability that anti-retrovirus agents and medications with direct effects applied to treat HCV infection would interact with each other [9].

Vladimir V. Maslyakov – Doctor of Medical Sciences, Professor, Vice Rector responsible for research (e-mail: maslyakov@inbox.ru; tel.: +7 (903) 023-71-69; ORCID: https://orcid.org/0000-0002-1788-0230).

Maira S. Aristanbekova – Post-graduate student at the Department for Clinical Medicine (e-mail: saratov@reaviz.ru; tel.: +7 (4952) 74-27-21; ORCID: https://orcid.org/0000-0003-2119-5225).

All the above mentioned problems are extremely urgent for the contemporary infectiology and finding solution to them sets another task that clinical medicine has to solve, namely, the necessity to create a system for precise prediction on how fast liver fibrosis will progress in patients infected with both HIV and HCV. Such a system should be based on existing diagnostic techniques and its goal should be subsequent development of recommendations on relevant treatment procedures. Nowadays it is obvious that HCV progresses much more rapidly in HIV-infected people [10, 11] hence HIV-infection considerably (by 2–5 times) increases frequency of acute hepatitis C transforming into chronic one, makes for development of liver cirrhosis, hepatocellular carcinoma, and liver decompensation up to total loss of all its vital functions [12]. And approximately 60 % lethal outcomes in case of HIV/HCV coinfection are exactly due to fatal damage to the liver [13]. To estimate efficiency of anti-virus therapy applied to treat HIV/HVC coinfection is rather complicated; it can also be due to interactions between anti-retrovirus and anti-HCV medications [9, 14–20]. A system was created for detecting high risks of progressive liver fibrosis in patients with HIV/HCV coinfection; it included creating a quantitative integral parameter for risk assessment as well as an algorithm that could be used to calculate it and provide ways to apply it for determining relevant anti-retrovirus and anti-HCV therapy.

Our research goal was to develop a system for predicting fibrosis development in patients with HIV/HCV coinfection and to estimate its efficiency bearing in mind peculiarities related to anti-virus therapy applied to treat the infectious process.

Data and methods. Over 1 year we observed 459 patients with verified HIV/HCV coinfection who were treated at Saratov Regional Center for AIDS Prevention and Elimination (AIDS Center). We applied the following criteria to select patients for our research: verified HIV-infection and chronic hepatitis C; absence of etiotropic therapy against HCV at the moment the research was accomplished; 3–4B HIV infections stages acceding to V.I. Pokrovskiy's classification; more or less apparent drug addiction in patients; age from 25 to 57; given informed consent to take part in the research.

We also applied several criteria for excluding a patient from the research; they were severe concomitant somatic and mental diseases, obesity; concomitant autoimmune and allergic diseases, a patient being often sick for a long period of time; viral hepatitis of other etiology (not CHC), autoimmune hepatitis, damage to the liver caused by medications, liver steatosis; a refusal to take part in the research. Most examined patients were males younger than 36. 72–78 % had 3–4A HIV infection stages; the rest had 4B–4C. Approximately 67 % patients had HCV 1b genotype; 1 %, 2a genotype; the rest, 3a genotype. All the patients underwent transient liver elastography throughout the research; the results were given in kPa. A stage in fibrosis was estimated according to METAVIR scale. As per initial data, 40 % patients didn't have any fibrosis changes in their liver (F0 stage); 20 % had the first stage when fibrosis just occurred (stage F1); 16 % had significant fibrosis (stage F2); 8 % has apparent fibrosis (stage F3); and 16 % already had cirrhosis (stage F4). 35 % patients were not treated with anti-virus medications. 32 % had only anti-retrovirus therapy that involved applying medications from groups of nucleoside and non-nucleoside reverse transcriptase inhibitors, inhibitors of protease and integrase in different combinations. 14 % patients with HIV/HCV coinfection were treated only with anti-HCV therapy based on pegylated interferon α and Ribavirin or direct effect medications, such as Sofosbuvir and Daclatasvir. 19 % patients received both anti-HCV therapy and anti-retrovirus therapy. All the patients had their HIV/HCV coinfection verified via laboratory research (serologic examinations with ELISA test, immune blotting, and PCR diagnostics); besides, throughout the research, they underwent laboratory monitoring that involved clinical and biochemical blood tests, determination of HIV and HCV viral load in blood with PCR in real time mode, and immunologic examinations with flow cytofluorometry.

ELISA test was performed to determine antibodies – HIV and viral hepatitis C infection markers in blood serum; it was done with «Dynex MRX II» microplate reader (Dynex-technologies, the USA) basing on «Abbot» diagnostic test-systems (the USA). The exami-

nation was accomplished in conformity with the user guide provided for the device and test systems. Immune blotting was performed to determine HIV-1 proteins in blood serum; it was done with electrophoresis equipment together with «GelDoc» software package (Bio-Rad, the USA) and «Genescreen Plus HIV Ag-AB» test system (Bio-Rad, USA) in conformity with the user guide provided for the device and test systems. Polymerase chain reaction (PCR) was applied to determine HIV and HCV RNA in blood, viral load with HIV and HCV, and HCV genotype; it was done with «COBAS 50 TaqMan 48» PCR analyzer with an automated device for sample preparation «COBAS® AmpliPrep» (Roche Diagnostic Systems, the USA). The research included the following stages: RNA extraction (sample preparation), reverse transcription reaction, PCVR-amplification to HIV DNA in real time mode in order to quantitatively determine viral load in conformity with the user guide provided for the device and reagents. Qualitative and quantitative determination of HCV RNA in blood plasma was performed with Hoffman-La-Roche test-system with its sensitivity being equal to 15ME/ml. Transient liver fiber elastography was made with «Fibroscan» (France). All the patients underwent the procedure prior to treatment and 48 weeks after (when treatment was over) with determining fibrosis stage according to METAVIR scale and results given in kPa. We also performed clinical examination of peripheral blood that involved calculating blood corpuscles per 1 unit of volume; it was done with «SWELAB AlfaBasic» automated hematologic analyzer (Sweden). We applied thrombocytes* number equal to 109/l in our research. Biochemical blood analysis was performed with «FURUNO 270» automated biochemical analyzer (Japan); it involved determining aspartate aminotransferase (AST), μmol/min.l; alanine-51-aminotrasferase (ALT), μmol/min.l; alkaline phosphatase (AP), μmol/min.l; lactate dehydrogenase (LDG), μmol/min.l; total protein, g/l; albumin, g/l; overall and conjugated bilirubin, μmol/l; cholesterol, g/l; dextrose, g/l. Flow cytofluorometry was performed to determine immunologic parameters with «FACS Calibur» device (Beckton Dickinson, the USA) after blood sample were automatically prepared with BD FACS SamplePrepAssistant II device (Becton Dickinson, the USA) in conformity with the user guide provided for the devices and monoclonal antibodies. We processed all the obtained data with FACS Diva software. Determination was accomplished basing on BD Multitest 6- Color TBNK Reagent, a standardized monoclonal antibodies set (BD Biosciences, the USA). We analyzed absolute number of CD3+CD4+ lymphocytes (T-helpers and CD3+CD8+ cells (cytotoxic T-lymphocytes) in blood. Immune regulatory index (IRI) was calculated as per the following formula basing on the research results: IRI = CD3+CD4+ / CD3+CD8+.

All the data were statistically processed with SPSS software (Version 21) in conformity with the user guide provided for it.

Results and discussion. To assess liver fibrosis development in patients with HIV and HCV coinfection, we distributed all the patients into several groups according to fibrosis process each of them had (progressive, stable, or regressive). The examination was based on data obtained via transient elastography performed for each patient, both at the moment the observation started and when it ended 1 year after. The disease was considered to be progressing in case liver elastography parameters increased by more than 10 % 1 year after and fibrosis moving on to the next stage; the disease was regressive if elastography parameters decreased by more than 10 %, and a patient returned to the previous stage in fibrosis process. Fibrosis was considered to be stable in all other cases. As a result, it turned out that 16 % out of 459 observed patients coinfected with HIV/HCV had progressive fibrosis; 65 %, stable; and 19 %, regressive (Table).

Relevance of this approach to fibrosis process estimation found its statistical confirmation. Thus, in case the disease was progressive, there was a statistically authentic transition from initial median in elastography parameters equal to 6.7 kPa to 7.7 kPa 1 year after (approximately 15 % growth). There were practically no changes in median when the disease was stable as it was equal to 5.8 kPa in both tests. In case the disease was regressive, median went down authentically, from 7.7 kPa to 5.8 kPa, that is, approximately by 13 %. We were the first to apply such an approach to data consolidation and there are no analogues to our research in available scientific literature.

Table

Dynamics of elastography parameters in compliance with fibrosis course in patients coinfected with HIV/HCV

Liver fibrosis course	Elastography parameters (kPa): median [min; max]		*p*
	initial	1 year after	
Progressive (*n* = 73)	6.7 [4.0; 12.9]	7.7 [4.0; 28.0]	<0.001
Stable (*n* = 297)	5.8 [2.8; 75.0]	5.8 [3.0; 75.0]	0.950
Regressive (*n* = 89)	7.7 [4.7; 22.5]	5.8 [3.5; 15.4]	<0.001

Note:

n is a number of patients in a group;

p is probability of discrepancy between initial data and data obtained 1 year after;

Validity of discrepancy as per Mann-Whitney test at $p < 0,05$ is colored grey.

The next stage in the research focused on determining instrumental and laboratory-immunologic criteria that could be used to identify patients coinfected with HIV/HCV who ran high risks of adverse fibrosis course. Our quantitative parameters were those obtained via elastography as well as routine hematologic, biochemical, virologic, and immunologic data that are conventionally applied to monitor liver fibrosis in patients with CHC or HIV infection including those coinfected with both viruses. These parameters included disorders in liver tissue elasticity given in kPa; number of thrombocytes; ALT; AST; alkaline phosphatase; LDH; total protein and albumin; total bilirubin; cholesterol; dextrose; viral load with HIV; viral load with HCV; number of CD3+CD4+ and CD3+CD8+ lymphocytes; immune regulatory index. Our statistical analysis revealed that elastography parameters allowed determining groups with high and low risks quite precisely. In particular, values higher than 7 kPa were typical for patients with high risks. There weren't any routine hematologic or biochemical data that would show statistically authentic differences between coinfected patients with different fibrosis course. As for immunologic blood parameters, we should note that they all authentically deviated from the control but their differences depending on a risk of progressive fibrosis were limited to only two parameters, namely number of T-helpers (CD3+CD4+) and immune regulatory index. We statistically estimated whether deviations in these parameters had any predictive value and revealed that in case a number of T-helpers is lower than 400 cells/ml, it allows predicting that a patient belongs to a group with high risks; predictive value is quite high (AUROC = 0.818). The same goes for IRI being lower than 0.45 (AUROC = 0.793).

Therefore, several parameters can be considered risk criteria that indicate there are high risks of progressive fibrosis. They are liver elastography parameters, number of CD3+CD4+ cells in blood, and immune regulatory index. Basing on these data, we developed an integral parameter for assessing quantitative risk criteria that could be used in case a patient applied for medical aid for the first time or was observed by a doctor over a short period of time. To do that, we performed regression analysis of all obtained quantitative data in determined groups with high and low risks of progressive fibrosis. When performing this analysis, we took the following data as our independent variables: initial liver elastography parameters, number of T-helpers, and immune regulatory index; our dependent variable was a score estimate of risk factors; and a variable showing selection of observations was a patient belonging to a group with high risks of progressive fibrosis. We got the following regression equation: $HRI = 4.070 + 0.099 \cdot kPa + 0.476 \cdot CD4 - 0.518 \cdot IRI$, where kPa is initial elastography parameter, CD4+ is an absolute number of CD3+CD4+ cells/ml of blood, and IRI is immune regulatory index. Finding solution to this equation gave us «high risk index» (HRI) for progressive liver fibrosis. We determined 95 % confidence interval of HRI in groups of patients coinfected with HIV/HCV with high and low risks and revealed its high predictive value (AUROC = 0.846) in case it was lower than 180. This stage in our research is top priority.

Two last stages in the research involved testing the high risk index for adverse fibrosis course in patients coinfected with HIV/HCV in order to prescribe or adjust anti-retrovirus therapy, anti-virus therapy for treating CHC, or to correctly combine anti-retrovirus therapy and anti-virus therapy for treating CHC.

Let us give several clinical cases from a pool of our own observations.

Clinical case No.1. The following data were taken from a case history of a patient with HIV/HCV who was treated with anti-retrovirus therapy. They illustrate that liver fibrosis progressed rapidly against a combination of

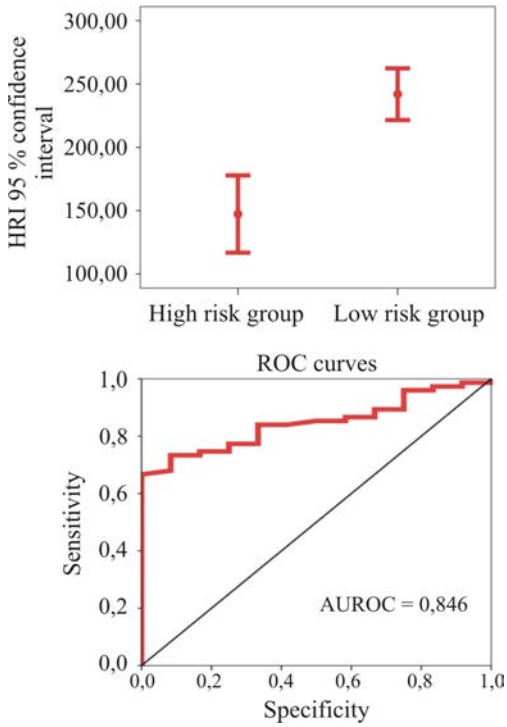

Figure. 95% -confidence intervals and ROC-curves of HRI in groups of patients coinfected with HIV/HCV with high and low risks of progressive liver fibrosis

nucleoside reverse transcriptase inhibitors and non-nucleoside reverse transcriptase inhibitors. Patient Z. was 36 years old and was treated at an outpatient department at «AIDS Center». The diagnoses were «HIV-infection, stage 4A» and «Chronic hepatitis C, virus reproduction stage». The patient got infected with both viruses due to intravenous injections of psychoactive drugs (PAD). At the moment the patient was included into our research, it was established that he had got infected with hepatitis C in 2002 and with HIV even earlier, in 2000. At present the patient states that he doesn't take any PAD and drinks only beer, 1.0–1.5 liters per week. He has not been given any antivirus therapy before. His height and weight were last measured on August 01, 2015, 169 cm and 57 kg accordingly. He feels rather satisfactory but still complaints about weakness and rapid fatigue. Objective data obtained via a medical examination are as follows: skin and visible mucosas have normal color and are clean. Peripheral lymph nodes (cervical, submaxillary, and axillary) are enlarged. Vesicular breath can be heard in the lungs and there are no rales there. Heart sounds are muffled, heart rhyme is normal, there are no noises, and heart rate is 78 strokes per minute. Blood pressure is 125/75 mm Hg. Body temperature is 36.7^0 C. Stomach is soft with no pains in any section during palpation; the liver goes beyond the coastal margin by 1 cm, its edge is smooth and even and its surface is elastic. The spleen is enlarged. The patient feels no pains when being punched slightly at both sides. Defecation and urination are normal. Consciousness is clear. There are no focal or meningeal symptoms. Blood test results are as follows: hemoglobin is 146 g/l; thrombocytes, $175.0 \cdot 10^9$/l; leukocytes, $7.3 \cdot 10^9$/l. Urine test hasn't revealed any pathology. Biochemical blood test results are as follows: ALT is 53 IU/l; AST, 51 IU/l; total bilirubin, 13.6 mmol/l; LDH, 231 IU/l. Immunity parameters are as follows: CD4+ lymphocytes, 95 cells/ml; CD8, 741 cells/ml; IRI is 0.26. PCR test revealed HCV RNA in quantity equal to $1.7 \cdot 10^6$ IU/ml, virus genotype 1b, and HIV RNA in quantity equal to 121,300 copies/ml. Ultrasound scanning of the abdominal cavity has revealed hepatomegaly, diffuse changes in liver parenchyma, and splenomegaly. Performed liver elastography showed first stage fibrosis (F1) with the parameter being 6.1 kPa as per METAVIR scale. A board of doctors, having taken into account immunologic parameters, viral load, and liver elastography results, prescribed the patient anti-retrovirus therapy (ARVT) as a combination of nucleoside reverse transcriptase inhibitors (Zidovudine + Lamivudine) and non-nucleoside reverse transcriptase inhibitors (Efavirenz). ARVT was applied for 6 months and it resulted in a decrease in viral load with HIV RNA down to indefinable level (less than 20 copies/ml); also, immunologic parameters improved as CD4+ grew to 240 cells/ml, and CD8+, to 857 cells/ml, IRI rose to 0.28. But biochemical blood test showed deterioration in ALT, 199 IU/ml; AST, 201 IU/ml, total bilirubin rose to 26 mmol/L, and direct bilirubin, to 5.8 mmol/L. Overall blood test showed a decrease in thrombocytes concentration down to 110·10 g/L; hemoglobin, 115 g/L. Liver elastography revealed that fibrosis had progressed to stage F3 and the parameter was equal to 11.8 as per METAVIR scale. We applied a formula for calculating an index showing adverse fibrosis course in patients coinfected with HIV and HCV in order to prescribe

new therapy or correct the existing one; the value was less than 180 and it indicated that the patient belonged to a group with high risks of progressive fibrosis.

$$HRI = 4.070 + 0.099 \cdot 11.8 \text{ kPa} + \\ + 0.476 \cdot 240 \text{ cells/ml} - 0.518 \cdot 0.28 = 119.33$$

Given that, a board of doctors took a decision to change ARVT scheme and apply a combination of nucleoside reverse transcriptase inhibitors (Zidovudine+Lamivudine) and protease inhibitors (Kaletra). The patient was being observed during the next 6 months after the scheme had been changed to the above said medications; 6 months after there was regress in fibrosis process to stage F2 with the parameter going down to 7.4 kPa; another 6 months after fibrosis regressed to stage F1 and the parameter was 6.3 kPa. Immunologic parameters improved as there was 38 % growth in CD4+ quantity up to 240 cells/ml. HIV RNA concentration was still indefinable (less than 20 copies/ml) and viral load with HCV RNA remained the same at $1.5 \cdot 10^6$ IU/ml. In this case it is impossible to prescribe any anti-viral therapy against hepatitis C due to low immunological parameters, namely quantity of CD4+ cells in blood being less than 500 cells/ml. But we can apply HRI formula to select an optimal anti-viral therapy scheme that in future will allow reaching such parameters that will make anti-viral therapy against CHC possible and, consequently, will secure regress in fibrosis process.

Clinical case No.2. The following data were taken from a case history of a patient with HIV/HCV who was treated with anti-retrovirus therapy. They illustrate that liver fibrosis regressed due to a combination of nucleoside reverse transcriptase inhibitors and protease inhibitors. Patient T. was 45 years old and was treated in an outpatient department at «AIDS Center». The diagnoses were «HIV-infection, stage 4A» and «Chronic hepatitis C, virus reproduction stage». The patient got infected with both viruses due to intravenous injections of psychoactive drugs (PAD). At the moment the patient was included into our research, it was established that he had got infected with hepatitis C in 2001 and with HIV even earlier, in 2000. At present the patient states that over the last 5 years he hasn't been taking any PAD and hasn't been drinking alcohol. Previously in 2006 he was prescribed anti-retrovirus therapy but he ceased taking the prescribed medications one month after and was excluded from the treatment program. His height and weight were last measured on December 17, 2014, 178 cm and 67 kg accordingly. He feels rather satisfactory but still complaints about weakness and heaviness in the right hypochondrium that sometimes appears under physical loads and/or when he doesn't stick to a healthy diet. Objective data obtained via a medical examination are as follows: skin and visible mucosas have normal color and are clean. Peripheral lymph nodes (cervical, submaxillary, and axillary) are not enlarged. Vesicular breath can be heard in the lungs and there are no rales there. Heart sounds are muffled, heart rhyme is normal, there are no noises, and heart rate is 78 strokes per minute. Blood pressure is 120/80 mm Hg. Body temperature is 36.7^0 C. Stomach is soft with no pains in any section during palpation; the liver goes beyond the coastal margin by 2 cm, its edge is smooth and even and its surface is elastic. The spleen is enlarged. The patient feels no pains when being punched slightly at both sides. Defecation and urination are normal. Consciousness is clear. There are no focal or meningeal symptoms. Blood test results are as follows: hemoglobin is 137 g/l; thrombocytes, $109.0 \cdot 10^9$/l; leukocytes, $6.3 \cdot 10^9$/l. Urine test hasn't revealed any pathology. Biochemical blood test results are as follows: ALT is 186 IU/l; AST, 98 IU/l; total bilirubin, 15.2 mmol/l; LDH, 211 IU/l. Immunity parameters are as follows: CD4+ lymphocytes, 555 cells/ml; CD8, 1,664 cells/ml; IRI is 0.33. PCR test revealed HCV RNA in quantity equal to $8.8 \cdot 10^5$ IU/ml, virus genotype 3a, and HIV RNA in quantity equal to 108,231 copies/ml. Ultrasound scanning of the abdominal cavity has revealed hepatomegaly, diffuse changes in liver parenchyma, and splenomegaly. Performed liver elastography showed the third stage fibrosis (F3) with the parameter being 9.6 kPa as per METAVIR scale.

A board of doctors, having taken into account immunologic parameters, viral load, and liver elastography results, prescribed the patient anti-retrovirus therapy (ARVT) as a combination of nucleoside reverse transcriptase inhibitors (Abacavir + Lamivudine = Kivexa) and protease inhibitors (Prezista). ARVT was

applied for 6 months and it resulted in a decrease in viral load with HIV RNA down to indefinable level (less than 20 copies/ml); also, immunologic parameters improved as CD4+ grew to 680 cells/ml, and CD8+, to 1,458 cells/ml, IRI rose to 0.46. Biochemical blood test showed the following; ALT, 68 IU/ml; AST, 52 IU/ml, total bilirubin fell to 10.3 mmol/L, and direct bilirubin, to 5.2 mmol/L. Overall blood test showed an increase in thrombocytes concentration up to 137·10 g/L; hemoglobin, 135 g/L. Liver elastography revealed that fibrosis had regressed from stage F3 (9.6 kPa as per METAVIR scale) to F1 with the parameter falling to 7.2 kPa. We applied a formula for calculating an index showing adverse fibrosis course in patients coinfected with HIV and HCV in order to prescribe new therapy or correct the existing one; the value was 323.24 (higher than 180) and it indicated that the patient belonged to a group with low risks of progressive fibrosis.

$$HRI = 4.070 + 0.099 \cdot 7.2 \text{ kPa} + \\ + 0.476 \cdot 680 \text{ cells/ml} - 0.518 \cdot 0.46 = 323.24$$

Patient didn't need any corrections in ARVT scheme; he continued taking nucleoside reverse transcriptase inhibitors (Abacavir + Lamivudine) combined with a protease inhibitor (Prezista). The patient was being observed during the next 6 months; there was regress in fibrosis process to stage F0 with the parameter going down to 5.3 kPa. Immunologic parameters improved with CD4+ quantity up to 720 cells/ml. HIV RNA concentration was still indefinable (less than 20 copies/ml) and viral load with HCV RNA was equal to $8.5 \cdot 10^5$ IU/ml. In December 2015 the patient was prescribed anti-virus therapy against hepatitis C and treated with pegylated interferon and Ribavirin for 48 weeks; as a result, a persistent virologic response occurred. 24 weeks after anti0vrus therapy was over, HCV RNA was not detected and liver elastography parameter was F0 = 5.1 kPa; biochemical blood parameters were as follows: ALT was 40 UI/ml; AST, 38 UI/ml; total bilirubin, 8.9 mmol/l; direct bilirubin, 1.5 mmol/l; but immunologic blood parameters went down a bit due to interferon therapy, quantity of CD4+ being equal to 514 cells/ml.

Therefore, doctors managed to achieve complete regress in fibrosis process due to ARVT that combined nucleoside reverse transcriptase inhibitors (Abacavir + Lamivudine) with a protease inhibitor (Prezista) with subsequent addition of double antivirus therapy against hepatitis C (interferon + Ribavirin).

Clinical case No. 3. The following data were taken from a case history of a patient with HIV/HCV who was not given any anti-retrovirus therapy. They illustrate liver fibrosis progress against absence of any therapy. Patient A. was 34 years old and was treated at an outpatient department at «AIDS Center». The diagnoses were «HIV-infection, 3rd sub-clinic stage» and «Chronic hepatitis C, minimal activity». The patient got infected with both viruses due to intravenous injections of psychoactive drugs (PAD). At the moment the patient was included into our research, it was established that he had got infected with hepatitis C in 2002 and with HIV much later, in 2015. At present the patient states that he doesn't take any PAD and doesn't drink alcohol. Previously he has not been prescribed antivirus therapy against HCH or HIV infection. His height and weight were measured on April 02, 2015 when he was first included into a treatment program, 171 cm and 59 kg accordingly. He feels rather satisfactory but still complaints about weakness and heaviness in the right hypochondrium that sometimes appears under physical loads and/or when he doesn't stick to a healthy diet. Objective data obtained via a medical examination are as follows: skin and visible mucosas have normal color and are clean. Peripheral lymph nodes (cervical, submaxillary, and axillary) are not enlarged. Vesicular breath can be heard in the lungs and there are no rales there. Heart sounds are muffled, heart rhyme is normal, there are no noises, and heart rate is 78 strokes per minute. Blood pressure is 120/85 mm Hg. Body temperature is 36.7 °C. Stomach is soft with no pains in any section during palpation; the liver goes beyond the coastal margin by 2 cm, its edge is smooth and even and its surface is elastic. The spleen is not palpated. The patient feels no pains when being punched slightly at both sides. Defecation and urination are normal. Consciousness is clear. There are no focal or meningeal symptoms. Blood test results are as follows: hemoglobin is 131 g/l; thrombocytes, $208.0.0 \cdot 10^9$/l; leukocytes, $6.8 \cdot 10^9$/l. Urine test hasn't revealed any pathology. Biochemical blood test results are as follows: ALT is 87 IU/l; AST, 78 IU/l; total bilirubin, 5.8 mmol/l; LDH,

242 IU/l. Immunity parameters are as follows: CD4+ lymphocytes, 635 cells/ml; CD8, 1,432 cells/ml; IRI is 0.44. PCR test revealed HCV RNA in quantity equal to $8.7 \cdot 10^3$ IU/ml, virus genotype 3a, and HIV RNA in quantity equal to 9,007 copies/ml. Ultrasound scanning of the abdominal cavity has revealed hepatomegaly, diffuse changes in liver parenchyma, and splenomegaly. Performed liver elastography showed the first stage fibrosis (F1) with the parameter being 6.3 kPa as per METAVIR scale.

A board of doctors, having taken into account immunologic parameters, viral load, and liver elastography results, decided the patient didn't need any anti-retrovirus therapy (ARVT). According to the standards for medical aid provision the patient was to be periodically examined at «AIDS Center». A year after the observation started, viral load with HIV RNA increased to 15,167 copies/ml, and immunologic parameters deteriorated as CD4+ went down to 355 cells/ml, and CD8+, to 806 cells/ml, IRI was 0.44. Biochemical blood test showed the following; ALT, 137 IU/ml; AST, 80 IU/ml, total bilirubin was up to 20.3 mmol/L, and direct bilirubin, to 6.23 mmol/L. Overall blood test showed a decrease in thrombocytes concentration down to $197 \cdot 10^9$ g/L; hemoglobin, 125 g/L. Liver elastography revealed that fibrosis had progressed from stage F1 (6.3 kPa as per METAVIR scale) to F3 with the parameter rising to 9.4 kPa. We applied a formula for calculating an index showing adverse fibrosis course in patients coinfected with HIV and HCV in order to prescribe new therapy or correct the existing one; the value was 173.75 (lower than 180) and it indicated that the patient belonged to a group with high risks of progressive fibrosis.

$$\text{HRI} = 4.070 + 0.099 \cdot 9.4 \text{ kPa} + \\ + 0.476 \cdot 355 \text{ cells/ml} - 0.518 \cdot 0.44 = 173.75$$

The patient was immediately offered to take anti-retrovirus therapy but he refused it. In 2017 a scheduled medical check-up revealed liver fibrosis progress from 9.4 kPa to 10.3 kPa (F3). But still, the patient didn't give his informed consent to HIV/HCV treatment and was not committed to take any therapy.

Therefore, it is advisable to apply ARVT in case of HIV/HCV coinfection not only in order to treat HIB-infections but also to influence fibrosis that occurs under HCH as it allows inhibiting its active progress.

Conclusions.

1. There are several quantitative risk criteria for determining risks of progressive liver fibrosis; they were determined basing on work models for high and low risks. They are initial elastography parameters being higher than 7 kPa; number of CD3+CD4+ T-lymphocytes in blood being lower than 400 cells/ml; immune regulatory index being lower than 0.45; predictive value of these criteria is either moderate or high (AUROC varying from 0.79 to 0.83).

2. The greatest predictive value in determining probable adverse fibrosis course (AUROC = 0.846) belonged to high risk index (HRI) that was determined as per the following linear regression equation: HRI = = 4.070–0.099·kPa + 0.476·CD4 – 0.518·IRI, where kPa is initial elastography parameter, CD4–is an absolute number of CD3+CD4+ cells/ml in blood, IRI is immune regulatory index CD3+CD4+/CD3+CD8+.

3. HRI value being ≤ 180 indicates that a patient coinfected with HIV/HCV runs high risks of adverse fibrosis course and its predictive value is high; determination of this value is a key component in the algorithm applied for diagnostics and treatment of patients coinfected with HIV/HCV.

4. HRI value being ≤ 180 in patients coinfected with HIV/HCV indicates that antiretrovirus therapy is required and it should combine HIV reserve transcriptase inhibitors and HIV protease or integrase inhibitors.

Funding. The research was not granted any sponsor support.

Conflict of interests. The authors declare there is no any conflict of interests.

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Received: 18.07.2019
Accepted: 03.06.2020
Published: 30.06.2020

UDC 616-008,6; 612.2
DOI: 10.21668/health.risk/2020.2.17.eng

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DEVELOPING NEW APPROACHES TO HYPERLIPIDEMIA CORRECTION TAKING INTO ACCOUNT CHANGES IN FATTY ACIDS STRUCTURE OF BLOOD SERUM

D.M. Azizova[1], I.R. Mavlyanov[2], R.A. Sabirova[1], M.U. Kulmanova[1], A.B. Soliev[2], G.Zh. Zharylkasynova[3]

[1]Tashkent Medical Academy, 2 Farobi Str., Tashkent, 100109, Uzbekistan
[2]Republican Scientific and Practical Center for Sport Medicine at the National Olympic Committee of Uzbekistan, 6 Almazar Str., Tashkent, 100027, Uzbekistan
[3]Bukhara State Medical Institute named after Abu Ali ibn Sino, 1 Navoi Ave., Bukhara, 200118, Uzbekistan

It is still a pressing issue in contemporary medicine to examine pathogenesis mechanisms and update procedures aimed at treating atherosclerosis. Developments by domestic and foreign researchers revealed that complex molecular and cellular studies on a mechanism of impacts exerted by vegetative-based medications, produced both domestically and abroad and used to treat atherosclerosis, were of primary importance in practical medicine in terms of educing population health risks. It is assumed that disorders in formation and transfer of non-esterified fatty acids (NEFA) in blood plasma are a major reason for hypertriglyceridemia occurrence.

The article contains research data on lipid metabolism parameters taken in dynamics of experimental hypercholesterolemia development. Performed research allowed revealing hypolipidemic effects produced by a biologically active additive called Biomays. We developed theoretical grounds for recommendations that should be given to patients suffering from hyperlipidemia and not getting proper therapeutic effects form treatment with statins. We recommend a complex approach which includes a BAA (biologically active additive) Biomays made of dried wheat sprouts in order to reduce risks caused by complications related to treatment with statins.

Our research goal was to develop new approaches to correcting hyperlipidemia basing on changes in fatty acids structure of blood serum.

The experiments were performed on 30 male rabbits belonging to chinchilla breed with initial body mass equal to 2,500–3,00 grams; animals were divided into 5 groups, 6 animals in each, depending on a research goal and treatment procedures. We started a 30-day treatment of experimental animals with ultrox and Biomays in doses equal to 0.6 mg/kg and 142 mg/kg accordingly after they had been given cholesterol for 2 months. We determined fatty acids structure of blood serum with a triple quadrupole chromato-mass-spectrometer with gas chromatographer (GC-MS/MS) TRACE 1310 TSQ 8000 and automated autosampler CTC TriPlus RSH produced by Thermo Fisher Scientific (the USA).Combined application of ultrox and Biomays led to more significant hypolipidemic effects. Use of statins and wheat sprouts had a distinct positive effect on contents of saturated and poly-unsaturated fatty acids n blood such as linoleic acid and linolenic acid.

Key words: *fatty acids, water-soluble vitamins, policosanol, Biomays biologically active additive, mass-spectrometry, gas chromatography, hyperlipidemia.*

Cardiovascular diseases, especially ischemic heart disease (IHD), remain the most widely spread ones all over the world; more than 50 % mortality cases occur due to these pathology. A considerable increase in cardiovascular morbidity and mortality among young people and employable population is especially alarming [1–3]. These pathologies are caused by numerous risk factors; it makes them even graver and undoubtedly requires

Dilzoda M. Azizova – Doctor of Philosophy, Senior lecturer at the Medical and Biological Chemistry Department (e-mail: dilzoda89@yandex.ru; tel.: +9 (98901) 78-12-21; ORCID: https://orcid.org/0000-0002-4824-0834).

Iskandar R. Mavlyanov – Doctor of Medical Sciences, Professor, Head of the Clinical Pharmacology Department (e-mail: iskandar.mavlyanov@inbox.ru; tel.: +9 (98946) 08-78-95; ORCID: https://orcid.org/0000-0001-5470-3498).

Rikhsi A. Sabirova – Doctor of Medical Sciences, Professor at the Medical and Biological Chemistry Department (e-mail: sabirovara@yandex.ru; tel.: +9 (98901) 87-53-84; ORCID: https://orcid.org/0000-0001-6119-5225).

Munozhat U. Kulmanova – Doctor of Medical Sciences, Head of the Medical and Biological Chemistry Department (e-mail: Munojat.kulmanova@mail.ru; ORCID: https://orcid.org/0000-0001-9131-7393).

A"zamzhon B. Soliev – Doctor of Medical Sciences, Head of the Research Laboratory (e-mail: 1136001@gmail.com; tel.: +9 (98712) 41-52-49, ORCID:https://orcid.org/0000-0002-3596-6628).5.

Gaukhar Zh. Zharylkasynova – Candidate of Medical Sciences, Associate Professor at the Department for Skills Development for general practitioners at the Skills Development Faculty, Deputy Rector responsible for education (e-mail: gavhar72@inbox.ru; tel.: +9 (98914) 48-48-26; ORCID: https://orcid.org/0000-0001-5376-3034).

correction. Therefore, activities aimed at preventing cardiovascular diseases have national significance [4–6]. Today, it is still vital to develop highly efficient prevention techniques, pre-clinic diagnostics, and therapy aimed at treating atherosclerosis; this scientific and medical-social task is hard to solve [7, 8]. At present it is obvious that hypercholesterolemia has become a global non-communicable epidemic. As per data provided by the Uzbekistan Public Healthcare Ministry, in 2014 circulatory system diseases amounted to approximately 5,800 cases per 100 thousand people and tended to grow. Ischemic heart disease (IHD) was the most frequent cause of death accounting for 22,300 deaths per year [9–11].

Hypercholesterolemia (HCS) plays an important role in atherosclerosis and IHD pathogenesis [12–14]. Prescribing medications that reduce cholesterol is a priority in IHD and HCS treatment. Inhibitors of 3-hydroxy-3-methyl-glutaril-CoA reductase are the most efficient in reducing low density lipoprotein cholesterol (CS-LDLP) and mortality caused by atherosclerosis and IHD [15–17]. Effective therapeutic daily dose of many statins causes side effects such as an increase in liver enzymes concentrations, aspartate and alanine transaminase (ALT and AST), myalgia, and myopathy with an increase in creatinine phosphokinase (CPK) concentration.

Every year there is a growth in number of research works focusing on searching for alternative hypolipidemic remedies. Leading role among them belongs to natural preparations. Over the last years, researchers have shown certain interest in wheat germ and wheat germ flour. Some data obtained by foreign researchers on effects produced by wheat germ oil and wheat germ flour on cholesterol contents in blood and liver have become a precondition for testing them in treating various cardiovascular diseases. As we can see from the data given in Figure 1, cholesterol contents in rats' blood and liver apparently goes down significantly due to use of wheat germ oil against use of cotton or soya oil [14, 15, 18–21].

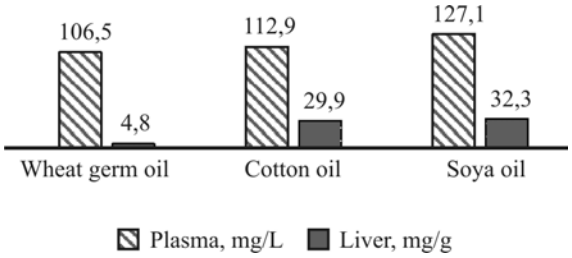


Figure 1. Effects produced by wheat germ oil on cholesterol contents in rats' blood and liver[1]

Other researchers revealed that a diet with 7 % wheat germ resulted in 5–10 % decrease in cholesterol contents in blood against the reference group. Besides, wheat germ flour consumption didn't cause any side effects or allergic reactions. Researchers at the Therapy and Neurology Department of the Kharkov Medical Academy for Postgraduate Studies examined effects produced by wheat germ oil on patients with ischemic heart disease (angina pectoris, II and III functional category). Analysis of changes in blood biochemical structure revealed that when wheat germ oil was applied for treating patients with ischemic heart disease, it resulted in a more valid hypolipidemic effect (a decrease in lipids and β-lipoproteins contents). Positive results were also yielded as regards clinical course of the disease. Thus, when clinical picture was assessed in those patients who were additionally given wheat germ oil, it was revealed that a number of angina pectoris attacks went down by 4 times (by 2.5 times only in the reference group), and, accordingly, nitroglycerine doses also decreased. And patients from the test group endured physical loads better than their counterparts from the reference one. It was also noted that use of wheat germ oil in treatment was accompanied with a decrease in elevated coagulability that was very important from pathogenetic point of view [18–20].

Similar research performed by N.S. Radionova and O.A. Sokolova also showed that there was positive dynamics in blood lipid spectrum when a patient took wheat germ oil; it was confirmed by lower contents of choles-

[1] L.A. Shpagina. Use of wheat germ oil and Vitasar in treating internal diseases: methodical guidelines for doctors. Novosibirsk, Novosibirsk printing house Publ., 2008, 80 p. (in Russian).

terol and cholesterol in low density lipoproteins, and, more importantly, by higher contents of anti-atherogenic high density cholesterol [21, 22].

In Novosibirsk Medical Academy L.A. Shpagina supervised assessment of wheat germ oil efficiency in treating workers with cardiovascular diseases [23, 24]. The results revealed that patients who were prescribed a combined hypolipidemic diet and wheat germ oil had authentic improvement in their health, weaker clinical symptoms, and positive dynamics in blood lipids spectrum. Hypolipidemic effects were persistent and remained even 3 months after the therapy was over. Consequently, this analysis of research works that focused on examining effects produced by wheat germ oil and flour on levels and spectra of blood lipids in case of hyperlipidemia shows that these products exert apparent and persistent hypolipidemic impacts and it is a precondition for conducting further targeted studies in the sphere.

Our research goal was to develop new approaches to correcting hyperlipidemia basing on changes in fatty acid structure of blood serum.

Data and methods. Given all the above stated, we conducted an experimental study on effects produced by Biomays food additive on blood lipids spectrum and fatty acids structure in animals with modeled experimental hypercholesterolemia.

Our experiments were performed on 30 male «Chinchilla» rabbits with initial body mass being 2,500–3,000 grams; the animals were divided into 5 groups, 6 animals in each, depending on research goals and a chosen therapy. Experimental animals started to receive their treatment after 2-month cholesterol intake [25]. To comparatively assess effects produced on blood serum by Biomays vegetable preparation and ultrox statin, we determined contends of triglycerides (TG), total cholesterol (TCS), high density lipoproteins cholesterol (CS HDLP), low density lipoproteins (LDLP), very low density lipoproteins (VLDLP) with an automated biochemical analyzer (RX Daytona/Randox, Great Britain) and calculated atherogenicity coefficient (AC).

A procedure for determining fatty acids structure in blood plasma. Fatty acids structure in blood serum was determined at the scientific laboratory of the Republican Scientific and Practical Center for Sport Medicine at the Uzbekistan national Olympic Committee; to do that, we applied TRACE 1310 TSQ 8000, a triple quadrupole chromate-mass-spectrometer with a gas chromatographer (GC-MS/MS) and autosampler CTC TriPlus RSH produced by Thermo Fisher Scientific (the USA).

Blood serum was first separated from red corpuscles via whole blood centrifuging at 2,000 turns per minute for 6 minutes. Then 0.5 ml of supernatant (blood serum) were put into 1.5-ml calibrated eppendorf vials and added with 0.4 ml acetone in order to sediment protein fraction in them. The mixture was thoroughly mixed in a vortex for 0.5–1 minute and then centrifuged at 15,000 turns per minute for 10 minutes. After that supernatants with their volume being 0.3–0.4 ml were put into new eppendorf vials and added with 0.25 ml hexane for fatty acids extraction. The mixture was again thoroughly mixed in a vortex and left for several minutes in order to achieve complete separation between water and hexane layers. Hexane layer was put into new eppendorf vials and extraction was repeated two more times in order to completely extract chemicals with lipid essence. Obtained hexane layers were evaporated in a microconcentrator until dry and then obtained sediments were dissolved in 0.5 ml hexane and put into glass vials for further GC-MS/MS analysis.

Chromatography conditions were as follows: there was a capillary column (0.2 μм · 0.25 mm · 30 m) impregnated with 5 % - biphenyl-dimethylsiloxane; helium was chosen as a carrier gas with constant flow equal to 1 ml/min. Initial temperature of the column thermostat was 40 ºC with 1-minute delay. Then thermostat was heated to 280 ºC at a rate 20 ºC/min with a 3-minute delay at 280 ºC and a consequent temperature fall to its initial state during 6 minutes at a rate 40 ºC per minute. Injector and mass spectrometer detector temperatures were set at 250 ºC. Extract was input in a volume equal to 1 μl in a split flow mode.

Ionization was performed with an electron impact at 20 eV. A chromatographic profile was registered 3 minutes after the start in order to remove a signal belonging to a solvent. Chromatography was controlled with XCalibur program within values limits range being m/z 50–1,500. Components were identified with etalon lass-spectra taken from «NIST» library for etalon mass-spectra of natural substances.

All the obtained data were statistically processed with applied computer software for statistical analysis.

Results and discussion. Table 1 contains all the obtained data. A cholesterol diet the experiment animals were put on for 60 days resulted in apparent hypercholesterolemia (295.0 ± 1.45 mg/dL). Treatment with ultrox and Biomays food additive led to a decrease in cholesterol contents, by 2.08 and 1.49 times accordingly ($p < 0.05$). When ultrox and Biomays were taken together, it resulted in a more apparent decrease in TCS contents.

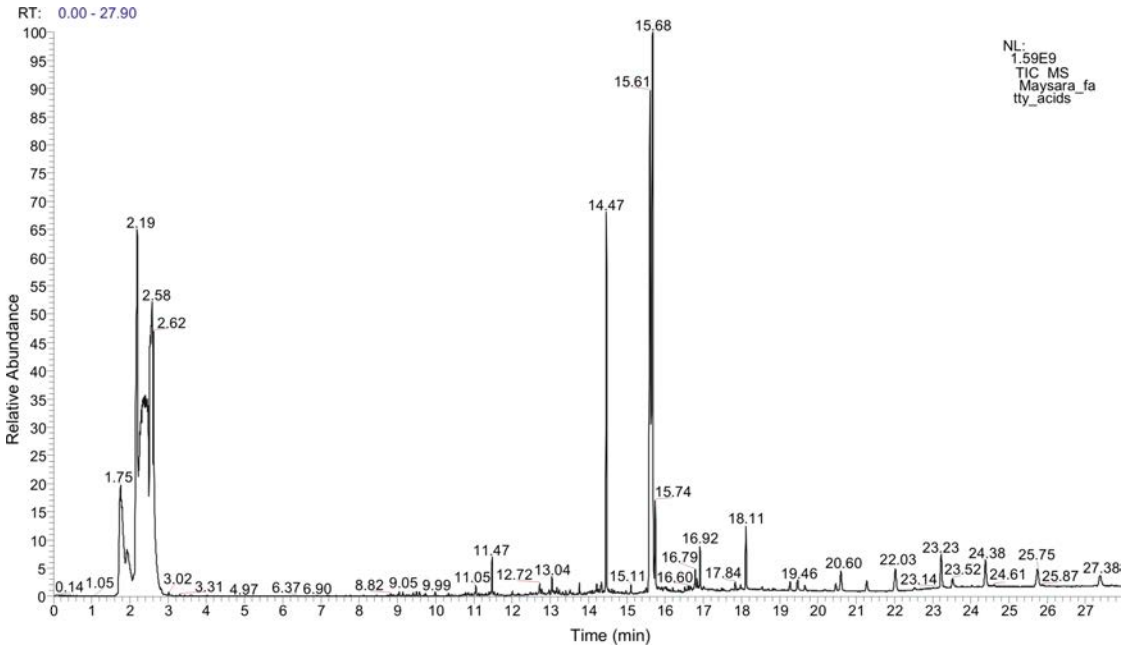
It should be noted that a decrease in TCS contents in animals that were given ultrox and Biomays were quite comparable. There was an authentic difference in TCS levels between animals from all the experimental groups and from the reference one 30 days after combined intake of two preparations, by 7.75–26.8 % ($p < 0.05$); it indicates that combined intake of ultrox and Biomays is efficient in terms of cholesterol contents reduction.

Table 1

Lipid metabolism parameters in rabbits with experimental HCS, $n = 6$

Parameter	Reference group	Animals with experimental HCS	After treatment		
			Ultrox	Byomais	Both preparations combined
TCS, mg/dL	71.8 ± 0.78	295 ± 1.45	142 ± 0.66	179 ± 1.77	131 ± 1.2
TG, mg/dL	14.6 ± 0.6	28.1 ± 0.36	29.4 ± 0.66*	37.3 ± 0.54	25.6 ± 0.12
CS HDLP, mg/dL	26.7 ± 0.98	17.8 ± 0.8	29.6 ± 0.7	25.3 ± 1.08	34.8 ± 0.75
CS VLDLP mg/dL	2.92 ± 0.07	6.98 ± 0.15	5.9 ± 0.22	7.46 ± 0.21*	5.12 ± 0.68
CS LDLP mg/dL	40.78 ± 0.86	270.3 ± 2.8	106.7 ± 0.68	146 ± 1.88	91.08 ± 0.14
AC	1.37 ± 0.02	15.6 ± 0.43	3.83 ± 0.14	6.16 ± 0.12	2.76 ± 0.44

N o t e: * means $p < 0.05$ against the animals that were not given any treatment.



If we look at other blood lipids parameters in animals with HCS, in particular, TG contents, we can see that it was 1.92 times higher than in the reference group ($p < 0.05$). There were no authentic changes in TG contents after treatment with ultrox[2] [26–31].

Therefore, it seems vital to create a poly-component biologically active substance with hypolipidemic properties; it can potentially be useful not only for treating mild lipid metabolism disorders but also for combined therapy when it is taken with statins in order to decrease their doses and, consequently, reduce their side effects.

To examine impacts exerted by Biomays on fatty acids contents in blood serum, we first of all examined fatty acids structure of Biomays food additive itself. The results are given in Figure 2.

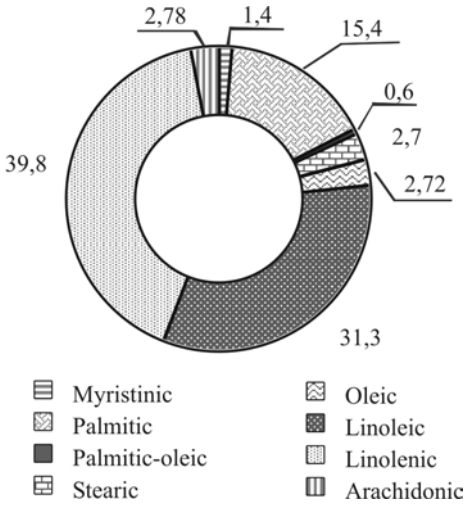


Figure 2. Biomays fatty acid structure in % per 1 mg

Saturated fatty acids in Biomays are mostly palmitic and stearic acids. At the same time, the greatest specific weight in fatty acids structure belongs to linoleic (31.3 %) and linolenic acids (39.8 %). Consequently, a substantial amount of fatty acids, including unsaturated ones, are linoleic and linolenic acids that have great physiological significance for a body [32–36].

Linoleic acid is well known to be the basic one as regards physiological effects; the acid is transformed into arachidonic acid in a body and the latter is an important component in lipid metabolism. The process occurs with vitamins A and E participating in it [37–39].

Besides, linoleic acid belongs to Omega-6 family, while linoleic acid – to Omega-3, although both families, Omega-6 and Omega-3 consist of 11 poly-unsaturated fatty acids (Table 2 and 3).

Fatty acids within Biomays structure (analysis):

– 9.73 min; methyl ether of decanoic acid;
– 11.05 min; eicosan;
– 13.04 min; tetra-decanoic acid;
– 13.76 min; penta-decanoic acid;
– 14.34 min; 9-hexane acid;
– 14.47 min; palmitic acid;
– 15.61 min; linoleic acid;
– 15.68 min; linolenic acid (α-form) (Omega-3);
– 15.74 min; stearic acid;
– 16.52 min; 9-cys, 11-trans, 13-transc-octadecatrienoic acid;
– 16.79 min; 10.13-eicosadienic acid;
– 16.84 min; 6,9,12,15-docosatetraenoic acid;
– 16.92 min; eicosan acid.

Our study on fatty acid structure of Biomays food additive revealed that some other poly-unsaturated fatty acids from Omega-3 and Omega-6 families could be found there, for example docosatetraenic (arachidonic) acid (Omega-6), eicosapentadienic acid (Omega-3), and octadecatrienic acid (Omega-6). But still, it should be noted that the greatest specific weights among them belong to linoleic and linolenic acids. These polyunsaturated fatty acids as components in Biomays food additive have certain physiological significance for a body. Indeed, polyunsaturated fatty acids produce positive effects, first of all, on fat metabolism as they accelerate lipid oxidation intensity [40, 41]. Besides, they participate in detoxification of a body, support immunity

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Table 2

Structure of Omega-6 family containing poly-unsaturated fatty acids

№	Poly-unsaturated fatty acids	Chemical structure
1	Linoleic acid	18: 2ω6, cys,cys-9,12-octadecadienoic acid
2	γ-linolenic acid	18: 3ω6, cys, cys, cys-6,9,12-octadecatrienoic acid
3	Calendic acid	18: 3ω6, 8-trans,10-trans,12-cys- octadecatrienoic acid
4	Eicosadienic acid	20: 2ω6, cys,cys-11,14-eicosadienic acid
5	Dihomo-γ-linolenic кислота	20: 3ω6, cys,cys,cys-8,11,14-eicosatrienic acid
6	Arachidonic acid	20: 4ω6, cys,cys,cys,cys-6,9,12,15- eicosatrienic acid
7	Docosadienic acid	22: 2ω6, cys,cys-13,16-docosadienic acid
8	Adrenic acid	22: 4ω6, cys,cys,cys,cys-7,10,13,16- docosadienic acid
9	Docosapentaenic acid	22: 5ω6, cys,cys,cys,cys,cys-4,7,10,13,16-docosapentaenic acid
10	Tetracosatetraenic acid	24: 5ω6, cys,cys,cys,cys,cys-6,9,12,15,18-tetracosapentaenic acid
11	Tetracosapentaenic acid	24: 5ω6, cys,cys,cys,cys,cys-6,9,12,15,18- tetracosapentaenic acid

Table 3

Structure of Omega-3 family containing poly-unsaturated fatty acids

№	Poly-unsaturated fatty acids	Chemical structure
1	Hexadecatrienic acid	16: 3ω3, cys,cys,cys-7,10,13-hexadecatrienic acid
2	α-linoleic acid	18: 3ω3, cys,cys,cys-9,12,15-octadecatrienic acid
3	Stearic (stioridic) acid	18: 4ω3, cys,cys,cys,cys-6,9,12,15-octadecatetraenic acid
4	Eicosatrienic acid	20: 3ω3, cys,cys,cys-11,14,17-eicosatrienic acid
5	Eicosatetraenic acid	20: 4ω3, cys,cys,cys-8,11,14,17-eicosatetraenic acid
6	Eicosapentaenic acid	20: 5ω3, cys,cys,cys,cys,cys-5,8,11,14,17-eicosapentaenic acid
7	Geneicosapentaenic acid	21: 5ω3, cys,cys,cys,cys,cys-6,9,12,15,18- geneicosapentaenic acid
8	Docosapentaenic acid	22: 5ω3, clupanodonic acid, cys,cys,cys,cys,cys-7,10,13,16,19-docosa-pentaenic acid
9	Docosahexaenic acid	22: 6ω3, cys,cys,cys,cys,cys,cys-4,7,10,13,16,19- docosahexaenic acid
10	Tetracosapentaenic acid	24: 5ω3, cys,cys,cys,cys,cys-9,12,15,18,21- docosahexaenic acid
11.	Tetracosahexaenic acid	24: 6ω3, cys,cys,cys,cys,cys,cys-6,9,12,15,18,21- tetracosahexaenic acid

and hormonal balance in it thus exerting favorable influence on functions performed by many organs and systems, for example, the digestive, cardiovascular, endocrine, and nervous systems etc. Moreover, polyunsaturated fatty acids become involved into energy formation and turn out to be basic energy suppliers for a body just as any other fatty acids. The promote decrease in total cholesterol contents in blood, increase in high density lipoproteins contents, and decrease in low density lipoproteins contents [42–44]. It is probably due to this mechanism that positive shifts in lipid blood spectrum were revealed in our research. Together with hypolipidemic effects Omega-3 fatty acids also produce positive effects on coagulation via reducing thrombocytes aggregation as well as increase oxygen inflow to tissue and reduce arterial hypertension [45].

Omega-6 polyunsaturated fatty acids, just as Omega-3 ones, have a lot of benign physiological properties. Their derivatives accelerate regeneration in tissues, participate in immune system regulation and, above all, reduce cholesterol contents in blood that makes for a reduced risk of atherosclerosis. It is probably these effects that predetermined positive dynamics in blood lipids spectrum that we obtained for animals with experimental hypercholesterolemia.

Biomays food additive, apart from comparatively large amounts of polyunsaturated

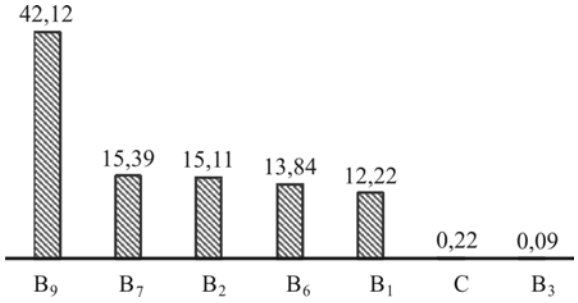

Figure 3. Structure and contents (in %) of water-soluble vitamins in Biomays food additive

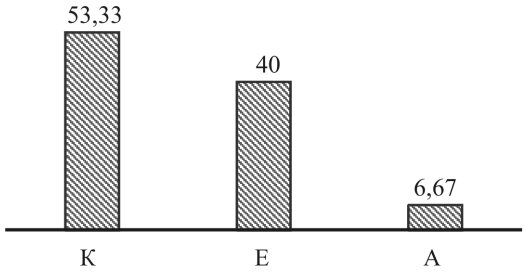

Figure 4. Structure and contents (in %) of fat-soluble vitamins in Biomays food additive

fatty acids, also contains many water-soluble and fat-soluble vitamins. Their contents and structure are given in Figures 3 and 4. As we can see, Biomays food additive contains quite a significant number of different vitamins. The greatest share among water-soluble vitamins belongs to B_9 or folic acid, namely 2/5 of all the water-soluble vitamins. At the same time, other vitamins from group B have almost identical shares. Thus, specific weight of biotin (B7) amounts to 15.39 %, specific weight of B_2, 15.11 %; B_6 and B_1, 13.84 % and 12.22 % accordingly. So, water-soluble vitamins structure is quite diverse in this food additive and it is good for physiological processes in a body. At the same time, fat-soluble vitamins are mostly K, E and A, and 90 % belong to vitamins K and E (Figure 4). Rather high specific weight of vitamin E is necessary for transforming linoleic acid into arachidonic one. Still, vitamin structure of the examined food additive indicates it is quite good for a body.

Vitamin B_9 or folic acid has the biggest share among water-soluble vitamins and takes active part in synthesis of many biologically active substances that are important for vital activities performed by cells and tissues [46].

Results of our research revealed effects produced by Biomays food additive on fatty acids structure of blood taken from animals with hypercholesterolemia. The chromatograms show that treatment with this product results in considerable shifts in fatty acid spectrum in experimental animals against the initial one (Figure 5). It becomes especially apparent by the end of the 2nd month after treatment started (Figure 2).

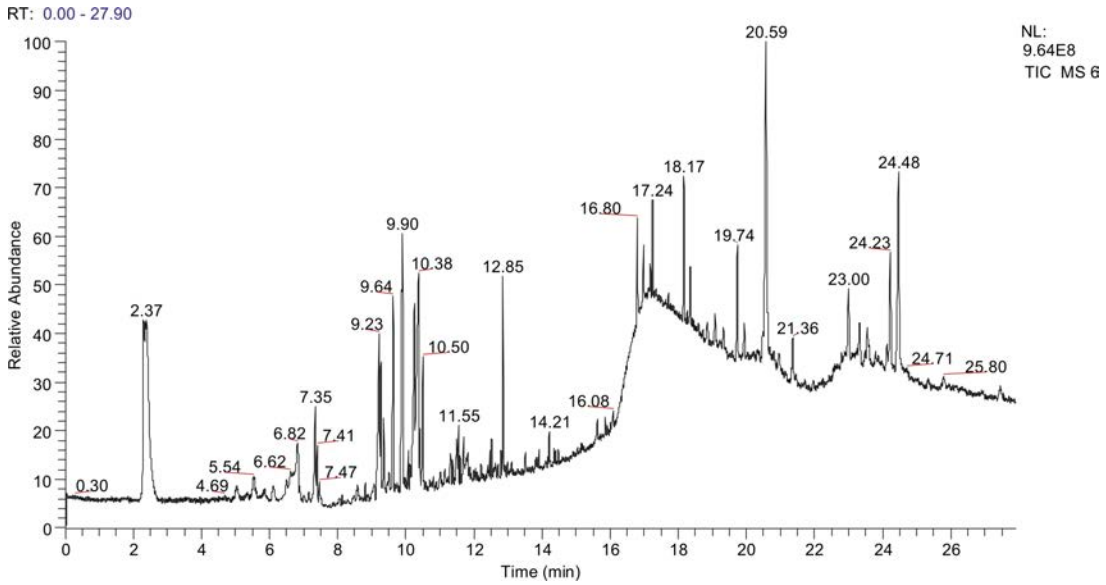

Figure 5. Fatty acids structure of blood taken from experimental animals with hypercholesterolemia prior to preparations intake

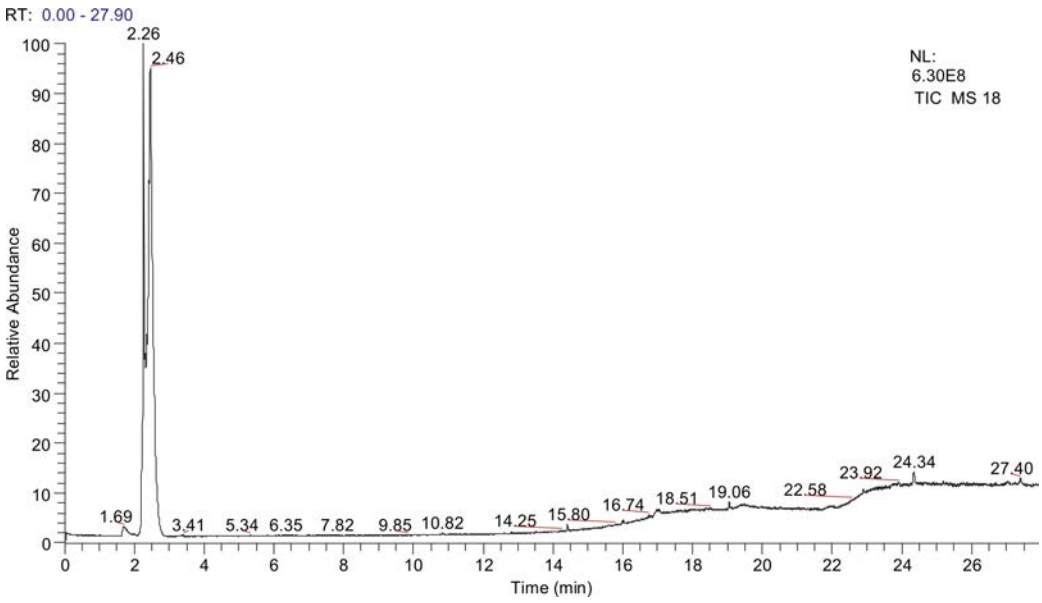

Figure 6. Fatty acids in blood of experimental animals with hypercholesterolemia after 1 month of Biomays intake

We quantitatively analyzed certain fatty acids in animals with hypercholesterolemia that were given Biomays food additive and compared the results with animals that weren't given it (Figure 7). The analysis revealed that contents of such saturated and monounsaturated fatty acids as palmitic, palmitic-oleic, stearic, and oleic acid went down by 46.0 %, 64.0 %, 37.7 %, and 20.0 % accordingly in animals that received Biomays against animals that didn't. At the same time concentrations of such polyunsaturated fatty acids as linoleic and linolenic on the contrary increased by 29 % and 141 % accordingly. Hence, treating animals with hyperlipidemia with Biomays food additive promoted a considerable decrease in concentrations of saturated fatty acids in blood and an increase in polyunsaturated ones such as linoleic and linolenic acid. Bearing in mind that these acids belong to Omega-3 and Omega-6 fatty acids, it becomes obvious that they play an important role in metabolism in a body as a whole and cholesterol metabolism in particular. Shift which we revealed in fatty acids structure of blood taken form experimental animals with hypercholesterolemia underlie positive shifts in spectra of low and high density lipoproteins against Biomays food additive intake.

We also performed a study on effects produced by Biomays food additive on practically healthy people; the results also revealed quite a similar fatty acids structure in blood.

As we can see from Figure 8, quantitative analysis of certain fatty acids in blood of practically healthy people who were given Biomays food additive revealed that palmitic acid contents decreased by almost 2 times after 2 months of Biomays intake. At the same time, contents of polyunsaturated fatty acids, such as linoleic and linolenic acid, increased by 3.5 and 2.6 times accordingly. Arachidonic acid concentration also grew (Figure 8), but this growth was less apparent.

Therefore, our research revealed that the examined food additive, when given to practically healthy people, promoted an increase in polyunsaturated fatty acids in blood, in particular linoleic, linolenic, and arachidonic acid; it again confirms that Biomays produces positive effects on lipid metabolism.

Therefore, our research results indicate that both hypolipidemic medication ultrox and Biomays food additive made of wheat germ produced obvious positive effects on high and low density lipoproteins spectra in animals with hypercholesterolemia; their combined intake promoted more apparent hypolipidemic effects.

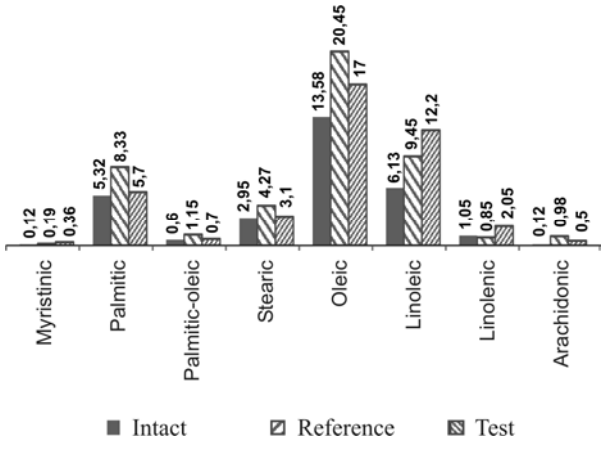

Figure 7. Comparative contents of certain fatty acids in blood of experimental animals with hypercholesterolemia after 1 month of Biomays intake

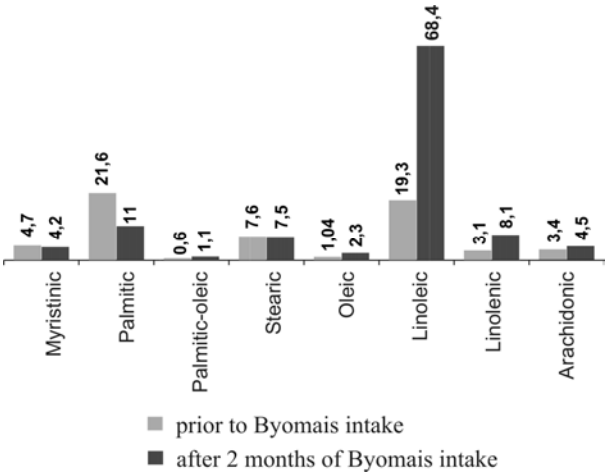

Figure 8. Comparative contents of certain fatty acids in blood of practically healthy people after 2 month of Biomays intake

Conclusion. Experimentally induced hyperlipidemia resulted in higher concentrations of atherogenic very low density and low density lipoproteins (VLDLP and LDLP) and a decrease in concentration of anti-atherogenic high density lipoproteins in blood plasma of rabbits form the test group against intact animals. Mono-therapy with ultrox in a dose equal to 0.5 mg/kg and Biomays statistically significantly reduced TCS and LDLP contents in comparison with animals that were not given any treatment. When both preparations were taken together, there was an authentic decrease in LDLP and VLDLP contents.

Basing on the accomplished research, we developed theoretical grounds for recommending treatment with Biomays food additive to patients receiving anti-hyperlipidemia therapy who had troubles with statins. Application of this biologically active additive helps reducing statins doses.

Funding. The research was not granted any sponsor support.

Conflict of interests. The authors declare there is no any conflict of interests.

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Received: 24.03.2020
Accepted: 13.06.2020
Published: 30.06.2020

ANALYTICAL REVIEWS

UDC 616.61-008.64
DOI: 10.21668/health.risk/2020.2.18.eng

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CHRONIC KIDNEY DISEASE: PREVALENCE AND RISK FACTORS (LITERATURE REVIEW)

A.M. Aringazina[1], O.Zh. Narmanova[2], G.O. Nuskabaeva[3], Zh.A. Tagaeva[3], E.S. Mendybaev[4]

[1]Kazakhstan's medical university «Kazakhstan School of Public Health», 19 A Utepov Str., Almaty, 050060, The Republic of Kazakhstan
[2]Astana medical university, 49A Beibitshilik Str., Nur-Sultan, 010000, The Republic of Kazakhstan
[3]Akhmet Yassawi International Kazakh-Turkish University, 29 B Sattarkhanova Ave., Turkestan, 161200, The Republic of Kazakhstan
[4]Kazakh medical university of continuing education, 34 Manasa Str., Almaty, 050057, The Republic of Kazakhstan

Chronic kidney disease (CKD) is a complex of syndromes that occurs as an outcome of various kidney diseases or as a complication caused by diseases of other organs; it often exerts maximum influence on prognosis for a primary disease. It seems an urgent task to improve early CKD diagnostics and reveal risk factors that can cause unfavorable clinical course and development of the pathology. Finding solution to this task will allow reducing terms and improving organization of specialized medical aid provided for patients. The issue related to detection of health risk factors is especially pressing in countries with low and middle incomes. National and international efforts aimed at preventing, detecting, and treating chronic kidney diseases are necessary for decreasing worldwide mortality and morbidity.

The article presents a review of literature data accumulated in PubMed, Elsevier, and Google Scholar databases on epidemiologic issues concerning chronic kidney diseases. We managed to find more than 150 materials; more than 40 articles out of them were analyzed and they turned out to dwell on different aspects of the issue. Special attention is paid to CKD prevalence among population depending on a country, ethnic group, age, and sex as well as to examining risk factors occurring in a specific region or a country.

Literature analysis allowed concluding that CKD prevalence has grown substantially over the last 10 years. Among risk factors there are medical parameters (prevalence of chronic cardiovascular diseases and endocrine system diseases) and social and demographic conditions. It is shown that CKD tends to occur more frequently among people from black race than those from other races. But black people have higher survivability after dialysis than their white counterparts from the same age groups. Awareness about CKD risk factors among population and doctors providing primary medical assistance predetermines efficiency of early diagnostic and further treatment of the disease in low income countries.

Key words: *chronic kidney disease, glomerular filtration rate, terminal kidney failure, prevalence, risk factors, epidemiology.*

Non-communicable diseases are among leading death causes all over the world. Chronic kidney disease (CKD) is among those pathologies that cause mortality including untimely deaths. Over the last decade CKD prevalence has been growing steadily simultaneously with a rapid growth in number of people suffering from cardiovascular diseases and pancreatic diabetes. In 2016 CKD resulted in 1.19 million death cases all over

Altyn M. Aringazina – Doctor of Medical Sciences, Head of the Department for Public Health and Social Sciences (e-mail: altyn.aringazina@gmail.com; tel.: +7 (777) 277-46-07; ORCID: https://orcid.org/0000-0002-9056-2394).

Oryngul' Zh. Narmanova – Doctor of Medical Sciences, Professor at the Department for Public Health and Social Sciences (e-mail: oryngul.winner@gmail.com; tel.: +7 (701) 575-55-95; ORCID: https://orcid.org/0000-0002-4957-1475).

Gul'naz O. Nuskabaeva – Candidate of Medical Sciences, acting as Associate Professor, Head of the Department for Specialized Clinical Courses (e-mail: g_nuskabaeva@mail.ru; tel.: +7 (705) 285-31-31; ORCID: https://orcid.org/0000-0003-2139-3221).

Zhanat A. Tagaeva – doctoral candidate (e-mail: zhanet16-16@mail.ru; tel.: +7 (702) 336-00-75; ORCID: https://orcid.org/0000-0001-7087-8474).

Ermek S. Mendybaev – doctoral candidate (e-mail: mendybayev@gmail.com; тел.: +7 (702) 544-81-59; ORCID: https://orcid.org/0000-0002-7616-8497).

the world that was by 28.8 % higher than in 2006. It allowed CKD to take the 11th rank place among death causes in 2016 against the 13th and 27th rank place in 2013 and 1990 accordingly. The WHO predicts that in 2030 CKD will hold the 13th rank place among death cases [1].

Apart from effects produced on mortality growth, CKD also exerts significant influence on population life quality and economic results achieved in a country or a region. Hence, fighting against global CKD epidemic is a vital and complicated task that requires, among other things, early detection of people with arterial hypertension, pancreatic diabetes, and other risk factors. In this case screening as a procedure aimed at detecting potential patients with CKD is important and economically efficient [2]. Experts revealed differentiated inverse dependence between cardiovascular risks and glomerular filtration rate (GFR) that was not dependent from age, sex, and other risk factors [3]. Kidney functional reduction is a predictor of hospitalization, cognitive dysfunction, and low life quality [4–8]. Low awareness about CKD in many countries can crate obstacles for early intervention and some researchers recommend raising this awareness about the disease among people [2].

CKD doesn't only result in deaths but also leads to a significant decrease in life quality and disability. Cross-questioning performed in the USA allowed revealing that difficulties in everyday life were much more frequently mentioned by patients with CKD than by those who didn't suffer from it [9]. Besides, CKD frequently aggravates other chronic diseases such as pancreatic diabetes, hypertension, and cardiovascular diseases and it can impose additional limitations on people's functional abilities. The latest WHO report on global diseases burdens stated that over the last 10 years overall number of lost healthy years due to CKD grew significantly from 29.2 thousand to 35.0 thousand. This calculated amount is higher than one calculated for many neurological disorders including dementia, Parkinson disease and chronic renal failure as well [10].

Remarkably, CKD is also related to substantial expenses on medical services. In the state register in Sweden annual expenses on medical aid rendered to patients suffering from CKD (without dialysis) were 4 times higher than those rendered to an average patient; in case hemodialysis was applied, the difference grew to 45 times [11].

According to KDOQI (Kidney Disease Outcomes Quality Initiative), CKD can be classified into five stages [12] using CKD parameters and data on structural changes in the kidneys (for example, proteinuria). Other recommendation as per NICE allows dividing the stage 3 into 3a and 3b that reflect a growth in cardiovascular risks [13]. As per data obtained via a retrospective study performed in Great Britain, the highest CKD stage is stage 3 determined in more than 90 % cases. 84 % out of them are stage 3a (glomerular filtration rate (GFR) varies from 45 to 59 ml / min/ 1 · 73 m ^{2}) and 16 % are stage 3b (GFR is from 30 to 44 ml / min / 1 · 73 m^2) [14].

CKD reasons vary depending on a country, ethnic group, and age.

Changes in CKD prevalence over time are rather controversial. Data obtained via the Third National Health and Nutrition Examination Survey revealed that over a period from 1999 to 2004 CKD stage 1–4 prevalence grew considerably in comparison with a period from 1988 to 1994 (13.1 % against 10.0 %) [15–17]. Although this high prevalence is partially due to population becoming older, it is also related to growth in hypertension and pancreatic diabetes prevalence [3]. However, results obtained via representative cross-studies performed in Great Britain allowed revealing that prevalence decreased over time within national borders [18].

Diabetic nephropathy is the most widely spread kidney disease that results in renal replacement therapy (RRT) in the USA (44 %) and Great Britain (27.5 %) [19, 20]. On the contrary, primary glomerulonephritis is a basic reason for kidney failure or end-stage renal disease (ESRD) in China [21]. However, approximately 10–15 % patients who had ESRD didn't have any specific renal diagnosis [19, 22].

N.R. Hill et al., researchers at Oxford Universality, performed a systematic review and meta-analysis on the subject; they revealed that average CKD prevalence was higher from stage 1 to 5 (13.4 % against 11.0 %). CKD cases distribution as per stages performed with the use of all the available data was as follows: stage 1 (GFR> 90) 3.5 % (2.8–4.2 %); stage 2 (GFR 60–89) 3.9 % (2,7–5.3 %); stage 3 (GFR 30–59) 7.6 % (6.4–8.9 %); stage 4 (GFR 29–15) 0.4 % (0.3–0.5 %), and stage 5 (GFR<15) 0.1 % (0–0.1 %). It was impossible to analyze specific data on stages 3a/3b due to absence of reports on them. Besides, the same research revealed that a growth in person's age made a significant contribution into CKD prevalence. A growth in CKD frequency with age can be due to peculiarities of applied formulas where an age is usually inversely proportionate to CKD value [3].

K.T. Mills et al. performed a systematic review on CKD prevalence in the world over a period from 2006 to 2013. The results are given in Table 1 [23].

Table 1

Research performed by K.T. Mills; CKD stages depending on sex, age and country income, %

№	CKD stages	Men	Women
1	*CKD stages 1–5 among adults aged ≥20*	10.4 (9.3–11.9)	11.8 (11.2–12.6)
1.1	High income countries	8.6 (7.3–9.8)	9.6 (7.7–11.1)
1.2	Low and middle income countries	10.6 (9.4–13.1)	12.5 (11.8–14.0)
2	*CKD stages 3–5 among adults aged ≥20*	4.7 (3.4–6.7)	5.8 (4.4–8.1)
2.1	High income countries	4.3 (3.5–5.2)	5.7 (4.4–7.6)
2.2	Low and middle income countries	4.6 (3.1–7.7)	5.6 (3.9–9.2)

When performing their meta-analysis, the authors noted that 51 works out of 100 examined one contained data on CKD prevalence varying depending on sex. Average CKD prevalence among men (95 % confidence interval for research in which 5 CKD stages were determined) amounted to 12.8 % (10.8–11.9 %), and the parameter amounted to 8.1 % (6.3–10.2 %) for research in which stages 3–5 were determined. CKD prevalence among women at stage 1–5 amounted to 14.6 % (12.7–16.7 %), and to 12.1 % for research in which stages 3–5 were determined. N.R. Hill, S.T. Fatoba, and J.L. Oke noted that CKD was more widely spread among women than among men [3].

B. Bowe, Y. Xie, T. Li, and A.H. Mokdad examined morbidity with CKD stage 3–5 detected when patients were rendered primary medical-sanitary aid; over the examined period (2010–2014) it amounted to 71.9 per 1,000 people with huge difference as per geography (urban/rural settlements), socio-demographic factors (age, deprivation), and clinical factors (number and type of concomitant diseases).

Overall CKD prevalence was inversely proportionate to its gravity (3a stage, 31.8 per 1,000; 3b stage, 25.3 per 1,000; stage 4, 11.7 per 1,000; and stage 5, 3.3 per 1,000 thousand). There were no substantial differences in prevalence as per patients' sex.

Graver CKD stages were widely spread among elderly people (≥ 65 years old), especially among people aged from 75 to 80 (345.1 per 1,000) and people older than 80 (397.6 per 1,000).

There was great CKD prevalence among people with 3 or more concomitant diseases; overall, it was equal to 281.7 per 1,000 people, most of them having stages 3a and 3b (98.9 and 109.6 per 1,000 people). CKD prevalence was high among people with comorbid dementia (303.3 per 1,000), pancreatic diabetes and arterial hypertension combined (267.4 per 1,000 people), Parkinson disease (223.7 per 1,000 people), and chronic obstructive lung disease (221.3 per 1,000 people) [24].

In Kazakhstan comorbidity was examined by O.J. Narmanova in 2008. The author revealed high prevalence of factors making for CKD growing progressively worse in patients with glomerular diseases: 23.37 exam-

ined patients had arterial hypertension; 31.73 %, diagnostically significant proteinuria; 56.03 % suffered from anemia; 35.49 % patients had hypoproteinemia. A direct correlation was detected between prevalence of the revealed factors and CKD and an inverse one between CKD and comorbidity. Analysis of CKD prevalence among dispensary patients suffering from AH, pancreatic diabetes, and primary and secondary nephropathy revealed that 71.5 % examined patients had CKD stages 1–2; 17.7 %, stage 3; 1.3 % stages 4–5 that is, functional disorders in the kidneys were irreversible[1].

As regards geography, higher CKD prevalence was detected in rural areas (86.2 per 1,000 people) than in urban ones (68.4 per 1,000 people). Literature contains a lot of data on factors that determine inequality regarding health preservation in remote urban and rural settlements; the most widely spread ones are remoteness from public healthcare organizations, geographical isolation, limited number of medical aid suppliers, and socioeconomic factors [24].

When analyzing chronic diseases burden in the USA, researchers revealed that over a period from 2002 to 2016 CKD burden was growing in the USA and was ahead of other non-communicable diseases. Over the last 15 years in the USA certain changes have occurred in demographic, social, and epidemiologic trends. Those changes probably made for changes in chronic kidney disease (CKD) epidemiology.

In the USA an increase in CKD DALY was related to an increase in susceptibility to risk (40.3 %), ageing (32.3 %), and population growth (27.4 %). CKD parameters standardized as per age increased by 18.6 % with a growth in metabolic risk factors and, to a lesser extent, in diet-related ones that amounted to 93.8 % and 5.3 % accordingly [24].

CKD in the South Asia has the same widely variable prevalence as in developed countries. Reasons that cause CKD are different, and in some regions there is high prevalence of CKD caused by glomerulnephritis and obstructive nephropathy as well as CKD with unknown etiology [25].

When analyzing these collaborators in studies on global diseases burden in the USA over a period from 2002 to 2016, researchers revealed a 52.6 % growth in CKD DALY. CKD burden grew in all the states but rates of change (2002–2016) and burden in 2016 varied depending on a particular state. States on the south (including Mississippi and Louisiana) had burden that was more than 2 times higher than in other states (for example, CKD DALY standardized as per age amounted to 321 per 1,000 in Vermont whereas in Mississippi it amounted to 697 per 1,000 people).

Similar heterogeneity was detected in European countries. For example, prevalence of CKD stages from 1 to 5 varied from 3.31 % in Norway to 17.3 % in the northwest Germany; prevalence of CKD stages from 3 to 5 varied from 1.0 % in the central Italy to 5.9 % in the northwest Germany. Similarly, in Asian countries, for example, in China, prevalence of CKD stages from 1 to 5 varied greatly, from 6.7 % in the southern China to 18.3 % in the southwest China [25].

O.Yu. Gerasimova and L.N. Semchenko noted in their works that in Russia there were no available authentic data on a number of patients who suffered from kidney diseases and chronic renal failure. From 2003 to 2013 a number of urogenital system diseases grew by 31.6 %. In 2013 a number of patients suffering from renal failure on average amounted to 44.6 per 100 thousand people and it was 2.2 times higher than in 2003 [26].

B.T. Bikbov and N.A. Tomilina noted in the first part of the report issued basing on data provided by the Russian register of substitute kidney therapy that annual growth in number of people suffering from CKD was well in line with world trends [27]. O.I Apolikhin et al. stated that a number of patients with CKD on average grew by 9.9 % every year [28].

[1] O.J. Narmanova. Epidemiologic and medical-organizational aspects of improving specialized medical aid rendered to patients with chronic renal failure: abstract of the thesis ... Doctor of Medical Sciences. Astana, 2008, 140 p. (in Russian).

CKD prevalence as per geographical regions was also examined by British researchers. The results revealed that CKD prevalence was higher in developed regions such as Europe, USA, Canada, and Australia, than in regions with developing economies such as African countries located south from Sahara and India, excluding Iran where similar parameters were high. Research results are given in Table 2 [3]. CKD prevalence is probably predetermined with nutritional disorders, high body mass index (BMI), high systolic blood pressure, and concomitant diseases that are spread in a specific country [19].

Table 2

CKD prevalence as per geographic regions

Regions	CKD stages 1–5 % (95 % CI)	CKD stages 3–5 % (95 % CI)
South Africa, Senegal, Congo	8.66 (1.31–16.01)	7.60 (6.10–9.10)
India, Bangladesh	13.10 (11.01–15.19)	6.76 (3.68–9.85)
Iran	17.95 (7.37–28.53)	11.68 (4.51–18.84)
China, Taiwan, Mongolia	13.18 (12.07–14.30)	10.06 (6.63–13.49)
Japan, South Korea, Oceania	13.74 (10.75–16.72)	11.73 (5.36–18.10)
Australia	14.71 (11.71–17.71)	8.14 (4.48–11.79)
The USA, Canada	15.45 (11.71–19.20)	14.44 (8.52–20.36)
Europe	18.38 (11.57–25.20)	11.86 (9.93–13.79)

K.T. Mills et al. reported in their research work that overall CKD prevalence depending on stage 1 to 5 varied from 4.5 to 25.7 % in South Korea; from 4.1 % among men in Salvador and Saudi Arabia to 16.0 % among women in Singapore; CKD stage from 3 to 5 varied from 1.3 % among men in China to 15.4 % among men in Nepal, and from 1.7 % among women In Singapore to 21.3 % among women in Nepal [23]. 12.5 % adults aged 40 and older suffered from CKD in Pakistan [29].

CKD prevalence depending on an ethnic group was examined by Pakistan researchers. In Pakistan CKD prevalence was estimated as per different communities in several research works. T.H. Jafar et al. (2003) estimated proteinuria prevalence as a CKD marker in four ethnic groups. They detected the highest prevalence among Sindhi (9.5 % among men and 10.3 % among women) and Muhajir (8.2 % among men and 4.7 % among women); the lowest prevalence was detected among Baluchi (2.4 % among men and 4.2 % among women) and Pashtun (2.5 % among men and 1.2 % among women) [25].

Arabs account for approximately 20 % of population in Israel. In the country socioeconomic position and other difference regarding Arabs can create a situation similar to that of African Americans in the USA [30]. According to the Register on Kidneys maintained by «Israeli Society of Nephrology and Hypertension» and «Israel Center for Disease Control» by the end of 2007 there were 4,800 patients with CKD in Israel including 23 % ethnic Arabs (both Muslim and Arabian Christians). From 1997 to 2007 in Israel the disease frequency grew by 71 % [30].

Approximately 11 % adults in the USA probably have a chronic kidney disease that is progressing into its irreversible form and at present can't be cured. B.B. Newsome et al. reported in several research works that 125 thousand African Americans, being 6.5 % of the overall examined sampling (1.9 million people), accounted for 14.9 % cases of progressing CKD [31].

«Healthy People 2020», a program existing in the USA, has been focusing on the nation health over the last few years. Its goal is to assess and predict changes in public healthcare. Among other things, assessment includes analyzing specific risk factors that cause CKD and end-stage renal disease (ESRD) [32]. As we can see from Table 3, it was revealed within «Healthy People 2020» implementation that CKD prevalence grew both among African Americans and their white counterparts [33, 34].

Table 3

Patients treated due to CKD as per race/ethnic group, data provided by «Healthy People 2020»

Parameters	Black / African Americans		White		Targets approved within «Healthy People 2020»
	2006	2015	2006	2015	
% of patients with CKD c treated by a nephrologist at least 12 months prior to substitute kidney therapy start	23.2 %	32 %	27.9 %	37 %	30.4 %
New ESRD cases per 1 million people	1114	895	294	312.1	352
% of patients who had kidney transplantation within 3 years time since ESRD was diagnosed	9.1 %	7 %	21 %	16.2 %	20.1 %
Number of deaths per 1,000 patient-years for people on dialysis	170.9	135.8	258.1	207.4	187.4

When estimating patients' health within Composite Health Care System (CHCS) procedures, experts obtained the following results: overall, 8,318 patients were examined, 5,849 (70.3 %) of them were whites, 1,344 (16.2 %) were blacks, and 1,125 (13.5 %) belonged to other races that were not identified. CKD stage 3 was diagnosed in 5,459 white patients (93.3 %), and stage 4, in 390 (6.7 %). CKD stage 3 was diagnosed in 1,205 black patients (89.7 %), and stage 4, in 139 (10.3 %). People belonging to unidentified races had CKD stage 3 in 94.7 % cases (1,065 patients), and stage 4 in 5.3 % cases (60 patients) [35].

There was a study on determining ethnic differences in chronic kidney disease progressing among people suffering from pancreatic diabetes in Great Britain performed with the use of data taken from East London database over a period from 2006 to 2016; the study revealed that 6,274 patients out of 120,591 adults with pancreatic diabetes also had CKD; those patients aged 25-84 were whites, South Asian people, and blacks. 81.5 % white people had CKD stage 3a; 15.7 %, stage 3b; and 2.8 %, stage 4. 82.9 % South Asian people had CKD stage 3a; 13.9 %, stage 3b; and 3.2 %, stage 4. 83.6 % black patients had CKD stage 3a; 13.2 %, stage 3b; and 3.2 % stage 4 [36].

Approximately 25 % people with CKD have very poor literacy regarding health and it to a greater extent influences people with low socioeconomic position and obviously results in greater risks of adverse clinical outcomes [37, 38].

Raising awareness and literacy among population is a basic task in fighting CKD; it is also very important to early detect the disease and provide a patient with treatment by a nephrologist already at its early stages [2]. The latter is especially significant due to CKD developing mostly symptomless at early stages (before major renal failure occurs) [39].

Absence of awareness about CKD all over the world can be partially due to CKD diagnostics being based on laboratory blood tests (creatinine contents in blood serum or cystatin C contents necessary for estimating glomerular filtration rate (GFR)) and urine tests (for urine sediments, especially albuminuria); these tests are probably less available than a tonometer or a glucometer that are used in hypertension and diabetes diagnostics. A wide-scale examination performed in Canada revealed alarmingly low awareness about CKD as only 8 % patients suffering from it knew their diagnosis; elderly people and women less frequently knew

about it [40]. Overall awareness about CKD among population in general and even population groups running high cardiovascular risks amounted to less than 10 % in 12 countries with low and middle incomes [41]. Research performed in Hong Kong revealed that less than a half of its citizens knew that hypertension and diabetes, being the major ESRD causes, could damage kidney functions [42].

T.H. Jafar et al. performed a quantitative study and revealed that not only patients were poorly aware about CKD; doctors working in primary healthcare were also rather ignorant. Doctors who took part in the study mentioned limited knowledge and lack of confidence in a possibility to cure CKD at its early stage. Though doctors working in primary healthcare knew such terms as «urea» and «creatinine», they didn't perform preventive CKD screening among their patients and didn't treat those who suffered from it; instead, they sent such patients to specialized medical organizations. Also some doctors noted that cultural beliefs and standards of their patients often contradicted clinical recommendations and it created additional problems in treating CKD [43–45].

Doctors from two towns in Cameroon took part in a study focusing on determining literacy among medical personnel; the study revealed that only 58.8 % questioned doctors were able to determine CKD correctly. Less than a half (44 %) knew that CKD had 5 stages and 73.8 % wrong answers were given by specialists in the field. It was also revealed that more than 90 % doctors knew basic risk factors that caused CKD; more than 80 % knew basis CKD complications; and more than 90 % knew that hemodialysis and transplantation were basic tools used in substitute kidney therapy. But still, peritoneal dialysis that was not used in the country at that moment was poorly known to questioned doctors. As regards detecting CKD, some doctors (12.7 %) still relied solely on creatinine in blood serum when diagnosing the disease. Accordingly, patients in Cameroon were not aware about CKD and its complications and doctors weren't able to properly slow down the disease progressing up to ESRD in such patients [44].

Therefore, our examination of literature sources on chronic kidney disease prevalence has yielded the following results:

– chronic kidney disease occurs in approximately 12 % of the overall world population. CKD prevalence is growing steadily together with other most significant non-communicable diseases;

– CKD risk factors are pancreatic diabetes, arterial hypertension, cardiovascular diseases, high body mass index, as well as social-demographic factors such as population growing older, low incomes, medical aid being poorly available, and low awareness about CKD among patients and doctors working in primary health care;

– most studies on CKD prevalence concluded that the disease was more frequent among women than among men. Average CKD prevalence among men (95 % confidence interval for studies where 5 CKD stages were determined) amounted to 12.8 % (10.8–11.9 %) and to 8.1 % (6.3–10.2 %) for studies where CKD stages 3–5 were determined. CKD prevalence among women for studied where stages 1–5 were determined amounted to 14.6 % (12.7–16.7 %) and to 12.1 % for studied where stages 3–5 were determined;

– studies perform over a period from 2006 to 2013 revealed that CKD prevalence in countries with middle and low incomes was higher than in countries with high incomes. However, British researchers revealed in their works performed prior to 2014 that CKD prevalence was higher in developed regions such as Europe, the USA, Canada, and Australia that in regions with developing economies such as African countries located south from Sahara and India;

– Composite Health Care System (CHCS) database contained data on a number of new ESRD cases being 2.8 times higher among blacks than among whites in the USA; number

of deaths per 1,000 patient-years among people on dialysis was 1.5 times lower among blacks. It indicates that CKD is more frequent among black people but they survive dialysis more often than their white counterparts of the same age;

– regardless of all above mentioned determinants, raising awareness and literacy among doctors working in primary healthcare is the major task in fighting CKD; early detection and timely treatment promotes less frequent transitions of the disease from its 3 and 4 stages into stage 5, a terminal one.

Funding. The research was not granted any sponsor support.

Conflict of interests. The authors declare there is no any conflict of interests.

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Received: 23.10.2019
Accepted: 13.06.2020
Published: 30.06.2020

UDC 616-08-035
DOI: 10.21668/health.risk/2020.2.19.eng

Read online

RESISTANCE OF *HELICOBACTER PYLORI* TO ANTIBACTERIAL MEDICATIONS AS A RISK FACTOR OF INFECTION DEVELOPMENT

M.V. Neumoina, K.M. Perfilova, N.V. Neumoina, I.V. Shutova, T.A. Troshina, T.V. Shmakova, T.L. Denisenko

Academician I.N. Blokhina Nizhny Novgorod Scientific Research Institute of Epidemiology and Microbiology, 71 Malaya Yamskaya Str., Nizhny Novgorod, 603950, Russian Federation

The authors have analyzed research works, both by domestic and foreign researchers that dwell on frequency of H.pylori being resistant to antibacterial medications, the reasons for its occurrence, methods applied to determine it and ways to overcome it. Over the last 15 years there has been a growth in frequency of detecting H.pylori that was resistant to basic antibiotics used to eradicate the pathogen. The authors have established geographical diversity in resistance related to antibiotics intake by population. Bacteriological technique is the most valid for determining H.pylori sensitivity; however, it is rather difficult to apply it due to complicated procedures for the microorganism cultivation. Therefore, molecular-genetic techniques are widely used. H.pylori resistance to Clarithromycin has great practical significance as this antibiotic is able not only to produce antibacterial effects but also to destroy biofilms. Helicobacter that was resistant to Clarithromycin was the least frequently detected in northern European countries (1–3 %); it was the most frequently detected in Southern Europe, Asia, and South America (30–40 %). Research performed in several Russian regions revealed significant variations in frequency of detecting H.pylori resistant to Clarithromycin (5–40 %) and a growth in dynamics of this detection (from 5 to 15 %). Frequency of detecting helicobacter resistance to another widely used medication, Metronidazole, is also different in different geographic regions; it amounts to 17 % in Europe, 24 % in Russia, and 92 % in Africa. H.pylori still has low resistance to Amoxicillin and another reserve medication, Rifabutin.

The article also dwells on probable ways to overcome non-sensitivity of the pathogen to antibiotics and the necessity to develop procedures for treating H.pylori infection based on the results of examining the pathogen sensitivity with standardized techniques performed in different regions. Efficient H.pylori eradication reduces inflammation in the gastric mucosa, prevents ulcer formation and atrophy and reducers risks of stomach cancer.

***Key words**: Helicobacter pylori, eradication, resistance to antibiotics, Clarithromycin, Metronidazole, Amoxicillin, Levofloxacin, Tetracycline.*

Over the last decades *Helicobacter pylori* has been one of the most widely examined reasons for destructive gastric pathology [1, 2]. Treating patients infected with *H. pylori* with relevant eradication therapy is viewed as an efficient way to prevent stomach and duodenum ulcer and certain malignant neoplasms in the stomach [3, 4]. Therapy aimed

Margarita V. Neumoina – Candidate of Medical Sciences, Head of the Clinic for Infectious Diseases Treatment (e-mail: tak1510@yandex.ru; tel.: +7 (831)433-36-70; ORCID: http://orcid.org/0000-0003-0153-3573).

Kseniya M. Perfilova – Candidate of Medical Sciences, Deputy to the Chief Physician of the Clinic for Infectious Diseases Treatment (e-mail: kperfilova@yandex.ru; tel.: +7 (831) 433-74-66; ORCID: http://orcid.org/0000-0001-6395-9014).

Natal'ya V. Neumoina – Candidate of Medical Sciences, Chief Physician of the Clinic for Infectious Diseases Treatment (e-mail: tak1510@yandex.ru; tel.: +7 (831) 433-83-36; ORCID: http://orcid.org/0000-0002-1394-3484).

Irina V. Shutova – Candidate of Medical Sciences, Head of the department at the Clinic for Infectious Diseases Treatment (e-mail: tak1510@yandex.ru; tel.: +7 (831) 433-74-66; ORCID: http://orcid.org/0000-0002-7073-9113).

Tat'yana A. Troshina – Head of the department at the Clinic for Infectious Diseases Treatment (e-mail: tak1510@yandex.ru; tel.: +7 (831) 433-01-68; ORCID: http://orcid.org/0000-0002-3724-4258)

Tat'yana V. Shmakova – Candidate of Medical Sciences, Physician dealing with clinical laboratory diagnostics at the Clinic for Infectious Diseases Treatment (e-mail: tak1510@yandex.ru; tel.: +7 (831) 433-36-70; ORCID: https://orcid.org/0000-0002-6689-1411).

Tat'yana L. Denisenko – Bacteriologist at the Clinic for Infectious Diseases Treatment (e-mail: tak1510@yandex.ru; tel.: +7 (831) 433-36-70; ORCID: https://orcid.org/0000-0002-7928-7141).

at eradicating the pathogen usually includes the following antibacterial medications: Amoxicillin, Metronidazole, Clarithromycin, Tetracycline, Rifabutin, and Levofloxacin; their efficiency depends on a microorganism's sensitivity to them [5]. Eradication therapy has become less efficient in many countries all over the world due to a growth in number of *H. pylori* strains that are resistant to antibiotics; it is a most significant factor that determines infection persistence in patients with gastroduodenal pathology with variable morphological and clinical pictures of the disease. Bismuth preparations and proton pump inhibitors are basic medications applied to treat the infection as they create conditions that are favorable for effects produced by antibiotics [6, 7]. It is especially important to examine *H. pylori* resistance to Clarithromycin and Metronidazole as these two medications are most frequently used to eliminate the microorganism. *H. pylori* resistance to other antibiotics that are also used quite often, namely Amoxicillin and Tetracycline, remains quite weak [8, 9]. Clarithromycin produces direct anti-bacterial effects and is able to destroy matrices of biofilms that include the microorganism, promote its resistance to therapy with antibiotics, and protect the pathogen from a macro-organism's immune response. A growing prevalence of strains that are resistant to Clarithromycin is the leading cause for eradication therapy becoming less efficient [10, 11]. According to the 4th and 5th Maastricht agreements, it is possible to apply Clarithromycin to treat helicobacter infection only provided that the microorganism's resistance to this antibiotic is lower than 15–20 %. In all cases when resistance exceeds this level, it is not recommended to apply standard three-component first-line eradication therapy (Amoxicillin, Clarithromycin, and proton pump inhibitor) [12, 13].

Our research goal was to analyze literature sources published both in Russia and abroad that focused on *H. pylori* resistance to antibacterial preparations applied for eradication; to estimate significance of this resistance for antibacterial therapy efficiency; and to determine probable ways how to overcome *H. pylori* resistance in clinical practice.

Data and methods. We analyzed research works published by both domestic and foreign experts over the last 15 years. Literature sources were searched for in domestic (eLibrary, CyberLeninka.ru) and international (PubMed, CochraneLibrary) databases in Russian and English. A free access to the full text of a work was our priority.

Results and discussion. *H. pylori* has two types of resistance to antibiotics, natural (genetic) and acquired one [14]. Antibacterial preparations that *H. pylori* is naturally resistant to are applied in creating transport and selective media; they are Vancomycin, sulfonamides, nalidix acid, Trimethoprim, and Polymyxin [9, 15]. Acquired *H. pylori* resistance to antibiotics can be primary and secondary [9]. Primary *H. pylori* resistance to antibacterial preparations is viewed as an adaptive response by the microorganism to adverse environmental conditions occurring due to antibacterial preparations intake aimed at treating certain communicable diseases excluding helicobacter infection. Secondary *H. pylori* resistance to antibacterial preparations occurs after unsuccessful eradication therapy. Acquired resistance to antibiotics mostly occurs due to uncontrolled application of antibiotics and inadequate anti-helicobacter therapy [16, 17].

Helicobacter also tends to have phenotypic (reversible, non-genetic) resistance to antibiotics that occurs when a patient is treated with anti-helicobacter therapy and some bacteria are metabolically inactive (they are in cocci state). This resistance to antibiotics becomes apparent via eradication therapy being inefficient but true persistent resistance to antibacterial preparations

doesn't develop and it allows their successful application as a repeated course via prolonging treatment with anti-helicobacter therapy [18].

Up-to-date and standardized procedures are usually applied to determine *H. pylori* resistance to antibiotics; they are serial cultivations (in agar or broth, micro-cultivations); diffusion ones (disc diffusion test and E-test); variable molecular techniques. A serial cultivation involves inhibiting *H. pylori* on nutritional agar that contains an antibiotic in specific concentrations [19, 20]. Serial cultivations and E-test (determining minimal inhibiting concentration (MIC) with gradient bands) are used to estimate a minimal quantity of an antibiotic that is necessary to inhibit an infectious agent. Some researchers also applied molecular techniques, namely various polymerase chain reaction (PCR) modifications [1, 21].

According to systemic reviews published by foreign researchers prevalence of *H. pylori* strains that are resistant to antibacterial medications has been growing all over the world over the last decades. Studies performed worldwide from 2006 to 2009 allowed revealing the following parameters of the microorganism's resistance: 17.2 % to Clarithromycin; 26.7 %, Metronidazole; 11.2 %, Amoxicillin; 5.9 %, Tetracycline; 16.2 %, Levofloxacin; 1.4 %, Rifabutin; 9.6 % poly-resistance [22]. Variability of these parameters depended on geographical locations and frequency of medications intake by a population [23].

A large multi-center observational study was performed in 2008–2009 in Europe. As per its results high *H. pylori* resistance to several antibiotics was revealed; thus, it was 34.9 % to Metronidazole; a bit lower to Clarithromycin (17.5 %) and Levofloxacin (14.1 %); at the same time resistance to Tetracycline and Amoxicillin amounted to approximately 1 % [11].

An issue related to a possibility to efficiently apply Clarithromycin is of vital importance for practical healthcare. In 2004 a research group supervised by F. Megraud analyzed 20 research works published in Europe that focused on efficiency of conventional triple therapy applied to treat 2,751 patients. In case *H. pylori* strains were sensitive to Clarithromycin, eradication was successful in 88 % cases; but when the strains were resistance to the medication, it was successful in 18 % cases only [24].

Recently a mechanism of acquired *H. pylori* resistance to macrolides has been described. It involves nucleotides replacements in sections where antibiotics are bound with a big sub-unit of bacterial ribosome (structural changes in V domain of 23S-ribosomal RNA under effects produced by erythromycin-resistance methylase enzyme in 2142 and 2143 positions) [25]. This nucleotides replacement leads to weaker antibiotics binding with their target and occurrence of a microorganism's resistance to Clarithromycin. There can be point mutations that cause loss of sensitivity to this medication in previously sensitive strains [26]. And here cross-resistance to all macrolides occurs.

In case there are strains with A2142G replacement MIC for helicobacter increases up to 32–256 mg/L; accordingly, efficiency of three-component eradications goes down to 57.1 %. In case there is mutation in A2143G MIC increases up to 4–128 mg/L, and pathogen eradication efficiency goes down to 30.7 % [27]. Accordingly, research on phenotypic and/or genotypic *H. pylori* resistance is extremely important for predicting anti-helicobacter therapy efficiency and selecting preparations for eradication.

Apart from above mentioned chromosome mutations, activity of efflux pumps belonging to RND-family is also extremely important for occurrence of the microorganism's resistance to Clarithromycin [27, 28]. Efflux pumps are protein complexes that allow a bacterium to rapidly remove alien substances, including medications, from

a cell thus preventing any possibility for an antibiotic binding with a microorganism's ribosome.

Frequency of primary *H. pylori* resistance to Clarithromycin is different in different countries [29]. There was a study performed in Chile; it revealed a growth in frequency of detected *H. pylori* strains that were not sensitive to Clarithromycin over a 10-year period. The study involved serial cultivations and polymerase chain reaction that allowed revealing mutation in V domain of 23 pRNA: A2142C and C2147G. Over 2005–2007 in that country registered *H. pylori* resistance to Clarithromycin amounted to approximately 20 %. From 2015 to 2017 this bacterium's resistance to Clarithromycin grew up to 29.2 % [30]. These results obtained in Chile indicate that triple eradication first-line therapy is hardly efficient in the country.

Similar *H. pylori* resistance to Clarithromycin was registered in several Italian regions where it amounted to 21–24.1 % [31]. Researchers detected both single mutations in *H. pylori* strains and double ones, A2143G and C2195T. Similar results were obtained by Korean scientists. Having examined patients with helicobacter infection who had not been previously treated with eradication therapy, they revealed *H. pylori* in clinical isolates with a combination of mutations A2143G and T2182C [32].

On the contrary, in Northern European countries *H. pylori* resistance to Clarithromycin was rather weak. Most frequent resistance to macrolides was detected in the Netherlands (11 %) and Finland (2 %) via diffusion procedures applied to determine sensitivity [33, 34]. These results are probably due to antibacterial preparations being consumed in low doses by people living in these countries.

A later analysis, performed in 2009–2012, also confirmed there were regional differences in *H. pylori* resistance to Clarithromycin. Thus, in the Northern Ireland resistance amounted to 3 %; the highest resistance was detected in Japan (38.8 %) and China (37.2 %) [35, 36]. In Uzbekistan detected *H. pylori* resistance to Clarithromycin didn't exceed acceptable 20 % as it amounted to 13.3 % [37]. These differences can result from an ambiguous approach to applying macrolide antibiotics in these countries as well as due to more frequent use of these antibiotics to treat patients with extragastric, communicable, and respiratory diseases in Japan and China.

There were large-scale multi-centered studies performed in 18 European countries in 1998–2018 on *H. pylori* strains obtained from 1,232 patients; they revealed that there was a 2-time increase in frequency of microorganisms resistant to the most popular antibiotics applied for eradication. It was true for Clarithromycin also as resistance to it grew from 9.9 % in 1998 to 21.6 % in 2018 [38]. The greatest quantity of resistant bacteria was detected in Southern Europe, in particular Southern Italy (39.9 %), Croatia (34.6 %), and Greece (30 %). This high resistance in these countries is most likely due to frequent intake of antibacterial medications to treat respiratory diseases and flu [39, 40].

Clinical recommendations issued by the Russian Gastroenterological Association contain results obtained via several studies on *H. pylori* resistance to Clarithromycin in different regions in Russia; according to them, resistance doesn't exceed 15 % [41].

According to the 4th and 5th Maastricht recommendations, resistance to Clarithromycin is a determining factor for poorer efficiency of eradication therapy applied to treat *H. pylori*-associated gastroduodenal pathology. We analyzed results obtained in studies performed in Russia and revealed a growth in the microorganism's resistance to Clarithromycin with its maximum levels reached in central megacities. In the middle 1990-ties in Moscow there were no detected *H. pylori* strains that were resistant to

Clarithromycin[1]. But already in 1999 *H. pylori* resistance to Clarithromycin amounted to 17.1 % among adult population in Moscow. In 2005 the parameter was a bit higher – 19.3 % and it went down to 14.5 % by 2012 [42].

When interpreting resistance parameters, it is necessary to take into account a procedure that was applied to determine sensitivity. *H. pylori* resistance to Clarithromycin amounted to 40 % among patients suffering from ulcer in Saint Petersburg and the figure was obtained via molecular procedures for determining sensitivity [43]. Probably, the figure combined both primary and secondary *H. pylori* resistance to Clarithromycin. Another study also performed in Saint Petersburg involved disk diffusion test and as a result obtained primary *H. pylori* resistance to Clarithromycin was lower and amounted to 7.7 % [19].

H. pylori resistance to Clarithromycin was also low in Smolensk region over a period from 2009 to 2017. Antimicrobial resistance of *H. pylori* isolates was estimated in the region via serial cultivations. Resistance amounted to 5.3 % in 2009–2010 and it grew insignificantly in a period from 2015 to 2017, to 6.3 % [44]. Similar results were obtained in cities located in Volga region. In 2012 in Nizhniy Novgorod region primary *H. pylori* resistance to Clarithromycin amounted to 7.3 % as per data obtained via PCR; it grew up to 15.1 % in 2016 [45]. In Kazan researchers applied PCR procedure combined with restriction analysis to reveal A2142G, A2143G, and T2717C mutations in 23S gene of *H. pylori* pRNA that could lead to the microorganism's resistance to Clarithromycin. As per data published in 2012, they detected 12.9 % resistant clinical isolates [46]. In Novosibirsk primary *H. pylori* resistance to Clarithromycin determined via PCR was also low and amounted to 6 % [47]. Results obtained via studies performed in Russian cities indicate that patients with *H. pylori*-associated gastroduodenal pathology can be empirically prescribed first-line eradication therapy if it hasn't been used previously. Unfortunately there have been no studies on *H. pylori* sensitivity to antibiotics in most regions in Russia.

Frequency of detecting *H. pylori* resistance to another widely used preparation, Metronidazole, also has some geographical differences. In those countries where Metronidazole is actively applied to treat parasitic and urogenital diseases resistant *H. pylori* strains are detected much more frequently. In African countries the bacterium resistance reached 92.4 %; it was two times lower in America where in amounted to 44.1 %; 37.1 % in Asia, and it was significantly lower in Europe being equal to 17.0 % [16, 48, 49]. A basic reason for resistance to Metronidazole is inability of this antibacterial medication to transform into its active form. It is most likely due to mutations in genes that code oxygen-insensitive nitroreductase and flavin reductase.

Studies performed in Russia over a 10-year period allowed revealing a considerable growth in resistance to Metronidazole, from 3.8 % in 2009–2010 to 23.8 % in 2015–2017 [44]. There are also data on absence of any significant *H. pylori* resistance to Metronidazole and on rare resistance to bothmedications, Clarithromycin and Metronidazole [41].

Recently, experts and practical specialists have been paying their attention to Fluoroquinolones [11]. *H. pylori* resistance to Fluoroquinolones results from changes in nucleotide sequences in gyr A gene. Wide

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use of such preparations to treat various somatic and communicable diseases made for an increase in resistant strains quantity. Thus, in Smolensk region *H. pylori* resistance to Levofloxacin increased from 8.3 % in 2009–2010 to 24.5 % in 2015–2017 [44]. Should resistance reach such levels, Levofloxacin can't be recommended to replace Clarithromycin.

Rifabutin is rarely used in eradication schemes, only in cases when the first and second line therapy hasn't been successful. *H. pylori* resistance to Rifabutin is quite low and amounts to 1.4 %, and a mechanism of resistance formation is related to point mutations in rpo B gene that codes β – subunit in bacterial RNA-polymerase [50].

An issue related to occurrence and growth in number of poly-resistant *H. pylori* strains is the most pressing. Greater prevalence of such *H. pylori* strains may well be a reason for eradication therapy not being efficient and it requires searching for more optimal therapeutic schemes applied to treat an infection caused by *H. pylori* [15, 36]. To overcome primary *H. pylori* resistance to antibiotics, it is advisable to apply antibacterial therapy combined with double doses of proton pump inhibitors; to prolong therapy up to two weeks; to add bismuth preparations; to include probiotics into therapeutic schemes in order to increase eradication efficiency, reduce risks of side-effects, and the infection relapse.

Conclusion. *H. pylori*-associated pathology is a communicable infection regardless of its symptoms or stage. *H. pylori* eradication should be prescribed to all infected people in order to eliminate inflammation in stomach mucosa, prevent further progression of the disease until it turns into ulcer and atrophy, and reduce stomach cancer risks. Resistance to antibacterial preparations considerably reduces efficiency of therapy schemes, especially those that include macrolides. The World Health Organization ranks *H. pylori* that is resistant to Clarithromycin among bacteria that are the most hazardous for human health. Recommendations on treating patients with helicobacter-associated diseases proposed by Russian and world consensuses are based on awareness about regional *H. pylori* resistance to antibacterial medications. Judging on data given by various researchers, it seems necessary to standardize procedures for examining *H. pylori* resistance to most common antibacterial medications in Russia. Use of results obtained via standardized studies will allow working out regional recommendations for practical healthcare on how to select the most optimal and personified therapy schemes aimed at treating this infection.

As issue related to *H. pylori* resistance to antibacterial medications requires searching for new eradication strategies in order to prevent ulcer and oncologic gastric pathology and, consequently, to achieve higher life quality for patients suffering from *H. pylori*-associated gastroduodenal pathology.

Funding. The research was not granted any sponsor support.

Conflict of interests. The authors declare there is no any conflict of interests.

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Received: 05.05.2020
Accepted: 09.06.2020
Published: 30.06.2020

UDC 316.334: 614.253
DOI: 10.21668/health.risk/2020.2.20.eng

Read online

OCCUPATIONAL HEALTH RISKS FOR DOCTORS IN CONTEMPORARY PUBLIC HEALTHCARE SYSTEMS (REVIEW)

I.L. Krom, M.V. Erugina, M.G. Eremina, E.P. Kovalev, E.M. Dolgova, G.N. Bochkareva, E.A. Grigor'eva

Saratov State Medical University named after V.I. Razumovsky, 112 Bol'shaya Kazach'ya Str., Saratov, 410012, Russian Federation

Doctors' health is seen as a sign that a public healthcare system is efficient. Authors of the present work aimed to review occupational health risks for doctors in contemporary public healthcare systems; to do that, they analyzed publications taken from both domestic and foreign databases. Multiple research works indicate that doctors' health and their efficiency are closely connected with peculiarities of their working conditions. Literature contains convincing evidence that unfavorable working conditions exert their influence on doctors' health; induce occupational diseases, occupational stress and burnout. Specific attention paid to occupational burnout is due to its high prevalence as well as impacts exerted by it on individual health and occupational efficiency of doctors.

The authors note that researchers' interest to occupational stress occurs due to its negative effects on doctors' health and occupational efficiency and clinical safety as well. Some research works dwell on clinical context of occupational stress that includes strict requirements to work and adverse conditions that stimulate burnout and can result in a threat to a patient's safety. In researchers' opinion, specific development of occupational stress syndromes is predetermined by essence and peculiarities of occupational activities performed by doctors with different specialties. Prevalence of occupational burnout among doctors is associated with dysfunctional practices adopted in national public healthcare systems, conditions for medical aid provision, medical specialty, age and gender characteristics, and a stage in career development.

It is noted here that doctors' health is discussed in modern Russian research works not only within the context of unfavorable working conditions. An overall crisis and dysfunctional practices adopted in contemporary Russian public healthcare system have determined status inflation and marginalization of doctors' occupational group; it influences their individual health directly via financial deprivation and relative deprivation such as stress related to social comparison. In the authors' opinion, this stress ultimately results in occupational one.

Key words: *health risks for doctors, risk factors, doctors' efficiency, occupational stress, unfavorable working conditions, burnout, status inflation, financial deprivation.*

Irina L. Krom – Doctor of Medical Sciences, Professor at the Department for Public Health and Healthcare (including courses in science of law and history of medicine) (e-mail: irina.crom@yandex.ru; tel.: +7 (917) 209-48-02; ORCID: https://orcid.org/0000-0003-1355-5163).

Marina V. Erugina – Doctor of Medical Sciences, Head of the Department for Public Health and Healthcare (including courses in science of law and history of medicine) (e-mail: lab48@yandex.ru; tel.: +7 (902) 040-35-75; ORCID: https://orcid.org/0000-0003-4253-5313).

Mariya G. Eremina – Candidate of Medical Sciences, a candidate for doctor degree at the Department for Public Health and Healthcare (including courses in science of law and history of medicine) (e-mail: 913693@mail.ru; tel.: +7 (927) 223-10-53; ORCID: https://orcid.org/0000-0001-9752-1352).

Evgenii P. Kovalev – post-graduate student at the Department for Public Health and Healthcare (including courses in science of law and history of medicine) (e-mail: kovalevevgeni2005@yandex.ru; tel.: +7 (937) 225-25-64; ORCID: https://orcid.org/0000-0002-7725-3036).

Elena M. Dolgova – Candidate of Medical Sciences, Associate Professor at the Candidate of Medical Sciences (e-mail: emdolgova@list.ru; tel.: +7 (905) 382-53-62; ORCID: https://orcid.org/0000-0002-0135-1254).

Galina N. Bochkareva – Senior lecturer at the Candidate of Medical Sciences (e-mail: bofrida@rambler.ru; tel.: +7 (927) 108-10-47; ORCID: https://orcid.org/0000-0003-1990-7182).

Ekaterina A. Grigor'eva – post-graduate student at the Department for Public Health and Healthcare (e-mail: vrach-katerina@mail.ru; tel.: +7 (937) 972-75-42; ORCID: https://orcid.org/0000-0002-8623-729X).

Doctors' health is viewed as an integral part of their professional competence and as a parameter that shows efficiency of any public healthcare system [1, 2].

We analyzed publications from both domestic and foreign scientific, referential and full-text databases with our goal being to review health risk factors for doctors as a specific occupational group within public healthcare systems.

Multiple research works indicate that doctors' health and efficiency are closely connected with peculiarities of their working conditions. Literature sources give a lot of convincing evidence on impacts exerted by unfavorable occupational environment on doctors' health [3, 4].

Long working periods under great loads, time deficiency, extreme cognitive loads, and mental strain result in occupational stress which, in its turn, leads to individual's health deterioration [5–7]. According to P. Msaouel et al. [8] and A.A. Loerbroks et al. [9] prevalence of occupational stress among medical workers varies from 20 to 80 %. Prevalence equal to 57 % was detected among doctors in Germany and Japan [9, 10] and 81 % was detected for a mixed sampling that was made up of medical workers from various sections in a public healthcare system [11]. Authentic conclusions on occupational stress prevalence within national public healthcare systems are absent; it may be due to these systems as well as respondents' occupational profiles being different in different countries. There are also methodological differences that make it impossible to compare results obtained via examinations performed in different countries [11].

Researchers' interest in issues related to occupational stress comes from its obvious negative effects on doctors' health, their proficiency, and clinical safety [12, 13]. A lot of research works dwell on clinical context of occupational stress that includes high requirements fixed for working tasks and adverse working conditions that make for burnout and threats to patients' safety. In researchers' opinion, specific development of occupational stress syndromes is determined by peculiar conditions in which doctors with various specialties actualize their occupational activities [14]. J. Siegrist et al. [15] view occupational stress as an imbalance between great efforts (great strain) and low compensations (for example, low salaries, no career prospects, no respect and no clinical safety); they also note that occupational stress potentially has grave negative outcomes.

Over decades research works devoted to occupational stress have been expanding and their contents have been transforming from focusing on some specific cases to determining the phenomenon as being «existential and common for those who have occupations determined as «helper» ones» [16].

Research works describe in detail what negative outcomes may result from occupational stress. Occupational stress may be considered an occupational burnout syndrome or it can have «various masked or somatic forms» [17]. Burnout becomes obvious via overwhelming exhaustion, depersonalization or cynicism towards colleagues, patients, and work as well as a feeling that one is losing his or her professional efficiency [18]. The research performed by W. Wurm et al. [19] revealed that burnout and deep depression coincided in their symptoms and deficiency of a three-dimensional concept of burnout. As R.T. Lee et al. [12] believe, special attention paid to burnout in multiple research works is due to its prevalence and influence on doctors' health and professional competence.

There are several reasons for burnout; some of them are personal traits, great occupational stress, and peculiarities related to management of a medical organization; however, psychosocial occupational stress was identified as the prevailing predictor of mental strain in doctors [12, 15, 20, 21].

Prevalence of burnout among doctors is related to dysfunctional practices accepted in national public healthcare systems, conditions for rendering medical aid, medical specialty, age and gender characteristics, and a stage in career development [17, 22–29].

Estimates given to burnout in different research works are ranked depending on measuring (exhaustion, depersonalization, or occupational inefficiency) and degree of burnout. Taking into account growing prevalence of burnout and the problem reaching «epidemic» levels, we can state that burnout can have devastating consequences for doctors, their colleagues, patients, and a public healthcare system as a whole [30–32].

Doctor's health is being discussed in contemporary Russian research works not only within the context of occupational risks that are relevant to adverse occupational conditions and induce occupational diseases, occupational stress, and occupational burnout. Risks for doctors' health in contemporary Russia are caused by changes in their occupational activities and institutionally determined peculiarities related to doctors' occupational self-fulfillment over the last decades due to socioeconomic transformations involving, among other things, the public healthcare system in the country [33].

Healthcare is a specific activity and its peculiarities are related to the fact that any social transformations induce changes in a public healthcare system; these changes create a new level of stress for occupational groups [34]. Multiple Russian research works indicate that institutional changes happening at the moment exert their influence on doctors' occupational activities, their contents and specificity.

An occupation as an attribute of healthcare as a social institute is a «key indicator of a status» [22]. There are research works where a medical occupation is proven to traditionally occupy the highest rank places in any occupational hierarchy [35, 36].

Over the last decades doctors' occupational activities have been becoming more and more complicated due to «multiple functions that doctors have to perform and intensified occupational loads»[1]. Social requirements to doctors are becoming higher, their activities are being regulated stricter, and their responsibilities are only growing [37].

Contemporary period in public healthcare institutionalization in Russia can be characterized only as a crisis [38]. A.V. Reshetnikov [22] sees a crisis in public healthcare in Russia as a social institution in 90ties last century and 10ties this century as its inverse development and characterizes the contemporary public healthcare institution as «paradoxical» with a lot of «antinomies», one of them being a contradiction between declared significance of a medical occupation and actual decline in prestige attributed to it. According to A.V. Reshetnikov, socially determined transformations that the public healthcare institution is undergoing now lead to changes in a status and role of contemporary public healthcare system in Russia and violate stability of social and occupational groups. I.P. Popova [39] characterizes dynamics of occupational groups in healthcare and states that there are changes in «social and occupational status and trends in social mobility».

R.G. Gromova [40] notes that social mobility in post-Soviet Russia in early 1990ties had some specific features and one of them was prevailing descending social mobility caused by declining social positions of certain social groups. Groups with descending social mobility «are on the periphery in any social development and are the most prone to marginalization» [41]. A crisis and dysfunctional practices that are intrinsic to contemporary public healthcare institution in Russia have predetermined inflation in social position and marginalization of doctors' occupational group [42].

Socioeconomic position is viewed as an obligatory predictor of a person's health [43]. A phenomenon that describes dependence between health and socioeconomic position is known as social gradient [44]. Research results indicate that there is a persistent correlation between one's socioeconomic position and health [45, 46]. Low socioeconomic

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position influences a person's health at an individual level directly via financial deprivations and indirectly via stresses caused by social comparison [47]. Besides, differences in health determined by socioeconomic position also occur due to unequal access to recourses that are significant for health preservation [48].

N.N. Sedova [49] gives a definition to «a specific social position of a doctor» and notes that doctors in Russia «are not satisfied with changes in their social position that occur in their occupational group. They are not satisfied either with their salaries or their working conditions». A.V. Reschetnikov, when considering a salary as a criterion of a doctor's social position, indicates that growing loads doctors have to face are not in line with a growth in their salaries [22, 50].

In contemporary Russia doctors are the least socially protected occupational group. Research conducted by I.L. Krom et al. [51] revealed that most doctors in the region estimated their living standard as low, and only 1.4 % respondents stated they didn't face any financial deprivations.

Both foreign and domestic experience indicates that risks related to labor potential are most significant ones in public healthcare. Doctors' health as a predictor of growing availability and quality of medical aid predetermines success (or failure) in overcoming a crisis that contemporary public healthcare in Russia has to face. In relation to that it seems truly vital to perform research on issues and regularities related to development of labor potential in the public healthcare system and to develop mechanisms aimed at preserving its labor resources.

Funding. The research was not granted any sponsor support.

Conflict of interests. The authors declare there is no any conflict of interests.

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Received: 05.12.2019
Accepted: 03.06.2020
Published: 30.06.2020