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PREVENTIVE HEALTHCARE: TOPICAL ISSUES OF HEALTH RISK ANALYSIS

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Research article

OPTIMIZATION OF REGULATORY ACTIONS BASED ON A DIFFERENTIATED APPROACH TO MANAGING AMBIENT AIR QUALITY AND HEALTH RISKS

N.V. Zaitseva[1,2], S.V. Kleyn[1,2], D.A. Kiryanov[1], A.M. Andrishunas[1], V.M. Chigvintsev[1], S.Yu. Balashov[1]

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The study focuses on substantiating the most optimal regulatory actions aimed to minimize health risks caused by airborne exposures within Rospotrebnadzor activities including the Clean Air Federal project and the ongoing experiment on setting quotas for emissions. The aim of this study was to comparatively assess effectiveness of regulatory actions as regards specific subjects (exemplified by heat-power engineering objects) with or without use of differentiated approaches to managing ambient air quality and health risks.

We analyzed a database on priority sources of ambient air pollution in an analyzed area; performed a hygienic assessment of ambient air quality relying on computed data and also estimated contributions made by specific chemicals and objects to the total pollution; calculated population health risks; implemented an algorithm for substantiating optimal regulatory actions aimed to mitigate health risks under airborne exposures; comparatively analyzed activities stipulated by the Complex plan and suggested optimal regulatory actions identified by solving the optimization task. We conducted a reconnaissance stage-by-stage assessment of effectiveness of air protection activities over 2019–2023 relying on hygienic indicators and risk levels.

As a result, we established that implementation of air protection activities and a reduction in total emissions of more than 20 pollutants by heat-power engineering objects would not ensure significant improvement of environmental conditions in the analyzed area considering their share contributions. Safe standards would still be violated in residential areas with levels of chemicals reaching 6.25 single MPL and 7.0 average annual MPL. An optimal sufficient result, considering this share contribution, would be a reduction in emissions from all heat-power engineering objects by 3.47 thousand tons of 10 specific chemicals. This is lower than a reduction planned within the Complex plan on total emission reduction (18.1 thousand tons). To ensure conformity with safe standards that stipulate chemical levels in ambient air and to achieve permissible risk levels, it is necessary to apply a differentiated approach to reductions in emissions (by 1.06 thousand tons overall), which targets specific chemicals, at other sources of ambient air pollution.

Use of a differentiated approach to selecting optimal regulatory actions as regards all sources of ambient air pollution considering their share contributions will make it possible to define priority environmental protection activities, adjust the Complex plans and ensure conformity with safe standards and permissible risk levels in all residential areas.

Keywords: *ambient air quality, Clean Air Federal project, Complex plan of air protection activities, pollutant emissions, experiment of setting quotas, optimization task, contributions, safe standards, health risk, effectiveness of activities.*

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Legislation on ambient air protection plays the key role in providing environmental safety and sanitary-epidemiological wellbeing. Several instruments are fixed in it to accomplish state regulation of negative effects on the human environment. Establishing safety standards and limits of pollutant emissions for industry, motor transport and other pollution sources is one of the most significant elements in the sphere. The RF President Order dated May 07, 2018 No. 204 On National Goals and Strategic Tasks of The Russian Federation Development for the Period up to 2024 and implementation of the Ecology National project and the Clean Air Federal project have established target levels, which are to be achieved by decreasing ambient air pollution [1, 2].

To perform more effective control and reduce emissions of harmful chemicals into ambient air, an experiment on setting quotas for industrial emissions started on January 01, 2020 in Russia; it is planned to have been completed by the end of 2026. The experiment is being accomplished in accordance with the Federal Law issued on July 26, 2019 No 195-FZ[1], which stipulates setting fixed quotas of emissions for industrial enterprises as well as mechanisms and instruments for control and adherence to established limitations. The aim of this experiment is to search for optimal solutions that facilitate reductions in pollutant emissions into ambient air based on aggregated calculations of dispersion and health risk assessment. This is an important step towards sustainable development and environmental protection [3–6].

Thus, at present an experiment is being accomplished in order to improve ambient air quality in cities participating in the first stage of the Clean Air Federal project (12 cities overall). Its aim is to reduce total chemical emissions into ambient air (radioactive substances excluded) by 20 % (tons/year) by 2024 against 2017[1] [7]. Modeling of pollutant dispersion and assessment of ambient air pollution in these 12 cities covers approximately 50 thousand industrial emission sources of various types and configurations, emissions from motor transport at more than 3.3 thousand sections of traffic networks and more than 1.6 thousand of autonomous heat supply sources [3, 8]. According to the RF Government Order issued on July 07, 2022 No. 1852-r[2], the number of cities participating in the experiment grew by 29 thereby extending the list of pilot territories. The aim of this experiment is to reduce amounts of hazardous pollutant emissions by almost two times by 2030 against 2020 [9].

In order to implement relevant activities within the Clean Air Federal project, Complex plans of activities on reducing emissions of priority pollutants into ambient air have been developed and approved by the RF Government for each territory included into the experiment. It is noteworthy that the Complex plans developed for the first twelve cities stipulate a reduction in total emissions for each territory for the whole set of chemicals.

This wide-scale experimental approbation takes place for the first time in our country. It allows testing methods for modeling ambient air pollution and using their results in making

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[1] O provedenii eksperimenta po kvotirovaniyu vybrosov zagryaznyayushchikh veshchestv i vnesenii izmenenii v otdel'nye zakonodatel'nye akty Rossiiskoi Federatsii v chasti snizheniya zagryazneniya atmosfernogo vozdukha: Federal'nyi zakon ot 26.07.2019 № 195-FZ [On accomplishing the experiment on setting quotas for emissions of pollutants and making alterations into specific legal acts of the Russian Federation regarding reduction of ambient air pollution: The Federal Law issued on July 26, 2019 No. 195-FZ]. *KonsultantPlus*. Available at: https://www.consultant.ru/document/cons_doc_LAW_329955/ (February 14, 2024) (in Russian).

[2] Ob utverzhdenii perechnya gorodskikh poselenii i gorodskikh okrugov s vysokim i ochen' vysokim zagryazneniem atmosfernogo vozdukha, dopolnitel'no otnosyashchikhsya k territoriyam eksperimenta po kvotirovaniyu vybrosov zagryaznyayushchikh veshchestv (za isklyucheniem radioaktivnykh veshchestv) v atmosfernyi vozdukh na osnove svodnykh raschetov zagryazneniya atmosfernogo vozdukha: Rasporyazhenie Pravitel'stva RF ot 7 iyulya 2022 g. № 1852-r [On Approval of the List of Urban Settlements and Districts with High and Extremely high Levels of Ambient Air Pollution, Which Are Added to the List of Territories Covered by the Experiment on Setting Quotas of Pollutant Emissions (Radioactive Substances Excluded) into Ambient Air Based on Aggregated Calculations of Ambient Air Pollution: the RF Government Order issued on July 07, 2022 No. 1852-r]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/351103411 (February 17, 2024) (in Russian).

specific targeted managerial decisions on development, control, and effectiveness of programs within the system for establishing safety standards, renewal of transport infrastructure and urban development in general. In future, these approaches and obtained results are planned to be used on other territories in the RF with high levels of ambient air pollution.

According to State Reports[3], the total emissions equaled 22,205.1 thousand tons in the Russian Federation in 2022. Of them, approximately 77 % were emitted by economic entities operating in various industries. The list of cities where the air pollution index (API) was above 14 (very high) included 40 cities with total population more than 10.4 million people. One third of the cities in the list are located in the eastern part of the country in the Siberia and Far East Federal Districts (SFD and FEFD respectively). Permissible chemical levels in ambient air are established to be violated considerably in these two Federal Districts (actual levels reaching up to 5 MPL): on average, violations accounted for 0.25 % air samples in the FEFD and 0.16 % for the SFD. Most common pollutants include benzo(a)pyrene, particulate matter $PM_{2.5}$ and PM_{10}, formaldehyde, particulate matter, carbon oxide, carbon (soot), hydrogen sulphide, ammonia, nitrogen oxides, sulfur dioxide, hydrogen fluoride, and various metals such as manganese, nickel and others. These chemicals occur in ambient air due to large metallurgical and chemical plants and heat-and-power engineering objects that operate quite actively in these areas. Some of them are city-forming enterprises or socially significant objects that are important for life support of local communities [10, 11].

Given that, development of optimal regulatory actions aimed to reduce ambient air pollution with priority chemicals should rely on a system for compliance with safety criteria including health risk levels, minimization of health harm and limitations of excessiveness and economic inexpedience of implemented activities [12–16]. To provide the sanitary-epidemiological service with practical science-based tools, a methodology MR 2.1.6.0320-23[4] was developed in 2023, which is eligible for selecting optimal regulatory actions aimed to minimized airborne health risks. This methodology does not replace the procedure for setting emission quotas; rather, it allows estimating whether suggested environmental protection activities are adequate in a given situation.

The aim of this study was to comparatively assess effectiveness of regulatory actions as regards specific subjects (exemplified by heat-power engineering objects) with or without use of differentiated approaches to managing ambient air quality and health risks.

Materials and methods. To achieve the stated aim, we compared activities outlined in the Complex plan[5] and regulatory actions established on the basis of differentiated approaches as a result of solving the optimization task on a pilot territory in accordance with the algorithm described in the Methodical guidelines 2.1.6.0320-23[4] [4].

According to the MR 2.1.6.0320-23, selecting optimal actions aimed to minimize airborne health risks involves identification of calculated

[3] O sostoyanii i ob okhrane okruzhayushchei sredy Rossiiskoi Federatsii v 2022 godu: Gosudarstvennyi doklad [On the state and protection of the environment in the Russian federation in 2022: the State Report]. Moscow, Ministry of Natural Resources and Environment of the Russian Federation; M.V. Lomonosov's Moscow State University, 2023, 686 p. (in Russian); O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2022 godu: Gosudarstvennyi doklad [On sanitary-epidemiological welfare of the population in the Russian Federation in 2022: the State Report]. Moscow, the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2023, 368 p. (in Russian).

[4] MR 2.1.6.0320-23. Poryadok opredeleniya perechnya prioritetnykh zagryaznyayushchikh veshchestv i perechnya kvotiruemykh ob"ektov s obosnovaniem optimal'nykh napravlenii reguliruyushchikh vozdeistvii po minimizatsii aerogennykh riskov zdorov'yu naseleniya [The procedure for identifying the list of priority pollutants and objects mandatory for setting emission quotas along with substantiating optimal regulatory actions aimed to minimize airborne health risks], 2023, 36 p. (in Russian).

[5] Kompleksnyi plan meropriyatii po snizheniyu vybrosov zagryaznyayushchikh veshchestv v atmosfernyi vozdukh v g. Krasnoyarske, utv. Zamestitelem Predsedatelya Pravitel'stva RF 19.04.2022 № 3968p-P11 [The Complex Plan of activities on reduction of pollutant emissions into ambient air in Krasnoyarsk, approved by the Deputy Head of the RF Government on April 19, 2022 No. 3968p-P11]. *Professional'noe izdatel'stvo LLC.* Available at: https://www.profiz.ru/upl/Красноярск%2C%20план.pdf (February 17, 2024) (in Russian).

reference points or points of local peaks in densely populated residential areas. Such points describe chemical hazards under acute and chronic exposure. Use of the optimization method makes it possible to identify specific economic entities and establish differentiated reductions in emissions of priority chemicals. This ensures compliance with safety standards including health risks levels on an analyzed territory. Optimization based on branch algorithms and algorithms of linear programming boundaries is aimed at finding optimal conditions with the use of a target function, which includes a minimal reduction in emissions in the whole residential area. The total minimal reduction in pollutant emissions at all objects under regulation (without considering economic characteristics of implemented activities) is assumed to lead to minimal technological changes and ensure compliance with safety standards and acceptable levels of health risks in residential areas due to implementation of relevant optimal regulatory actions.

Krasnoyarsk was chosen as a pilot territory for testing methodical approaches and implementing the algorithm for solving the optimization task. The city is included into the Clean Air Federal project; it is a large economic, industrial and energy-producing center where electric and heat energy is produced, transported and sold to end customers. Heat-and-power engineering is among leading industries on the analyzed territory and this gave grounds for more profound analysis of activities with their focus on heat-power engineering objects (HPEO) in this study.

Thus, in Krasnoyarsk, the total volume of pollutant emissions, both from stationary and mobile sources, is above 140.8 thousand tons per year. Of them, approximately 55 thousand tons are emitted by heat-power engineering objects that are parts of the unified centralized system. It consists of thermal power stations, coal-fueled and electrical boiler houses supplying heat for the city population. In addition to that, 40 residential blocks in the city are equipped with autonomous heat supply sources that supply heat to houses and some social objects and emit approximately 5.3 thousand tons per year.

The task was to assess effectiveness of investment programs and complex plans related to minimization of health risks and hazards caused by energy-producing enterprises for people living in Krasnoyarsk. To do that, we used initial data taken from the systematized database on stationary and mobile emission sources in Krasnoyarsk (the data were provided by the Ministry of Natural Resources and submitted to Rospotrebnadzor as an electronic report following the official enquiry). The database contained information about 6411 sources of 251 pollutants: 5977 emission sources (3597 regulated and 2422 unregulated) that belonged to 807 enterprises and organizations operating in the city, 171 autonomous heat supply sources (residential areas with private houses) and 263 sections of the city traffic network.

The data base on heat-power engineering objects included 302 enterprises that either produced and distributed energy or had heat supply sources at their facilities, such as major heat supply sources (thermal power stations (TPS) 1, 2 and 3) and 171 autonomous heat supply sources that emitted 55 chemicals. Figure 1 provides geographic location of heat-power engineering objects in Krasnoyarsk (a situation map).

In order to solve the optimization task, data arrays were prepared with levels of occurring calculated concentrations in residential areas and levels of occurring health risks. Dispersion of chemicals from an emission sources in ambient air was calculated using Ekolog-Gorod 4.6 Unified Program for Calculating Ambient Air Pollution. Health risks caused by chemical pollutants in ambient air emitted by both all sources and exclusively by heat-power engineering objects and autonomous heat supply sources were assessed in accordance with the Guide R 2.1.10.1920-04[6] by accomplishing all necessary steps in relevant sequence. Obtained results were visualized by using ArcView 3.2 and ArcGIS 9.3.1 software.

[6] R 2.1.10.1920-04. Human Health Risk Assessment from Environmental Chemicals. Moscow, the Federal Center for State Sanitary and Epidemiological Surveillance of RF Ministry of Health, 2004, 143 p. (in Russian).

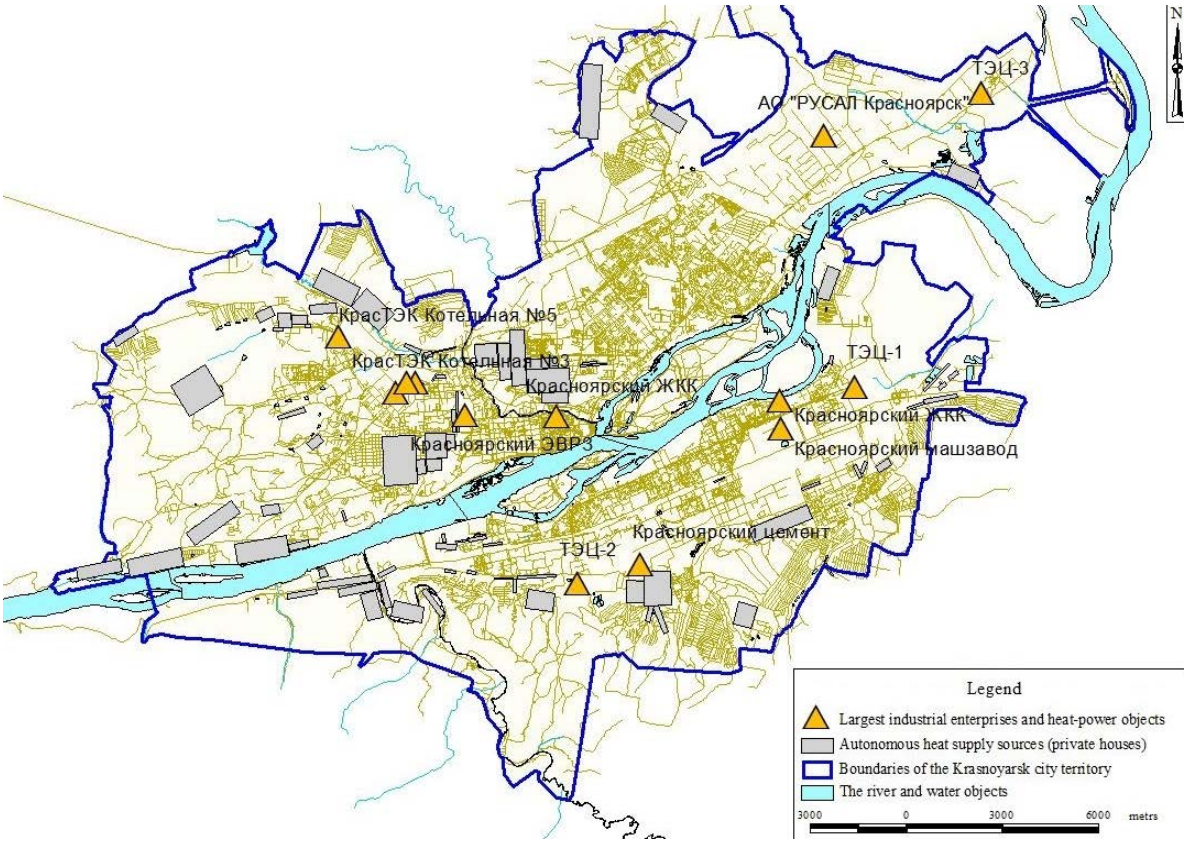

Figure 1. The map showing locations of heat-power engineering objects within the Krasnoyarsk city territory

We conducted a reconnaissance stage-by-stage assessment of effectiveness of air protection activities over 2019–2023 relying on current changes in ambient air quality at four monitoring posts of Rospotrebnadzor per 37 pollutants and occurring levels of health risks.

Results and discussion. Investigations and hygienic analysis of ambient air quality based on calculated dispersion of pollutants from all sources on the analyzed territory revealed that safety standards were violated in residential areas as per 17 chemicals: manganese and its compound (up to 1.03 single MPL, up to 11 average annual MPL), benzo(a)pyrene (up to 4.5 average annual MPL), nitrogen dioxide (up to 6.3 single MPL, up to 2 average annual MPL), carbon (soot) (up to 1.6 single MPL), carbon oxide (up to 3.9 single MPL), gaseous fluorides (up to 1.4 single MPL), chlorine (up to 1.6 single MPL, up to 2.7 average annual MPL), benzene (up to 2.1 single MPL), phenol (up to 2.1 single MPL), particulate matter (up to 3.2 single MPL), dust with 20 to 70 % SiO_2 (up to 5.2 single MPL), dust with SiO_2 below 20 % (up to 1.6 single MPL), abrasive dust (up to 2.0 single MPL), prop-2-en-1-al (up to 1.5 single MPL), sodium hydroxide (up to 1.1 single MPL), sulfur dioxide (up to 1.1 single MPL), butadiene and (up to 1.1 average annual MPL). It is worth noting that solely heat-power engineering objects cause violations of safe standards for ambient air quality in residential areas as per nitrogen dioxide (up to 3.04 single MPL), carbon (up to 1.52 single MPL), carbon oxide (up to 3.84 single MPL), particulate matter (up to 3.19 single MPL), inorganic dust: 70–20 % SiO_2 (up to 5.1 single MPL), inorganic dust: SiO_2 below 20 % (up to 1.1 single MPL).

Practically all people living in the city (89 %) are exposed to elevated ambient air pollution from all emission sources: 1064.6 thousand people are exposed to more than 1 single MPL and 351.9 thousand people to more than 1 average annual MPL.

Established calculated levels under acute inhalation exposure create elevated hazard

quotients per six chemicals: nitrogen dioxide, benzene, particulate matter, sodium hydroxide, buta-1,3-diene, and prop-2-en-1-al, up to 2.1–48.8 HQac. These risk levels result in higher likelihood of acute diseases of the respiratory organs, eyes, developmental disorders, diseases of the reproductive and immune systems and systemic effects, up to 4.1–49.8 HIac. Approximately 131.5 thousand people or 12.2 % of the city population live in areas with 'alerting' (hazard indexes are between 3 and 6) and 'high' (HI > 6) acute health risks.

Elevated hazard quotients are determined by six chemicals under chronic inhalation exposure: nitrogen dioxide, benzo(a)pyrene, manganese and its compounds, nickel oxide, buta-1,3-diene, and chlorine, up to 1.6–40.4 HQch. Effects of the foregoing chemicals create unacceptable risks for the respiratory system, central nervous and peripheral nervous system, reproductive, cardiovascular and immune systems, blood, and developmental processes, between 1.6 and 52.5 HIch (Figure 2). Overall, approximately 15.8 thousand people or 1.5 % of the city population live in areas with elevated health risks established as per aggregated calculations of pollutant dispersion.

Assessment of carcinogenic risks did not establish any elevated levels of the total individual carcinogenic health risk related to exposure to the analyzed chemicals in ambient air on the analyzed territory as per calculated data.

As can be seen in Figure 1, heat-power engineering objects (emission sources located at industrial enterprises, emissions from boiler houses and autonomous heat supply sources) are scattered near to or within residential areas in the city. Zones affected by them are determined by both even locations and low-height emission source able to create local ambient air pollution.

Contributions made by heat-power engineering objects to average annual ground concentrations were assessed for the whole city territory based on calculated data. This assessment revealed that contributions made by 55 analyzed chemicals varied between 1 and 99 % in different areas in the city; a significant contribution (more than 50 %) was made by chemicals, calculated levels of which were higher than the established safety standards (Table 1).

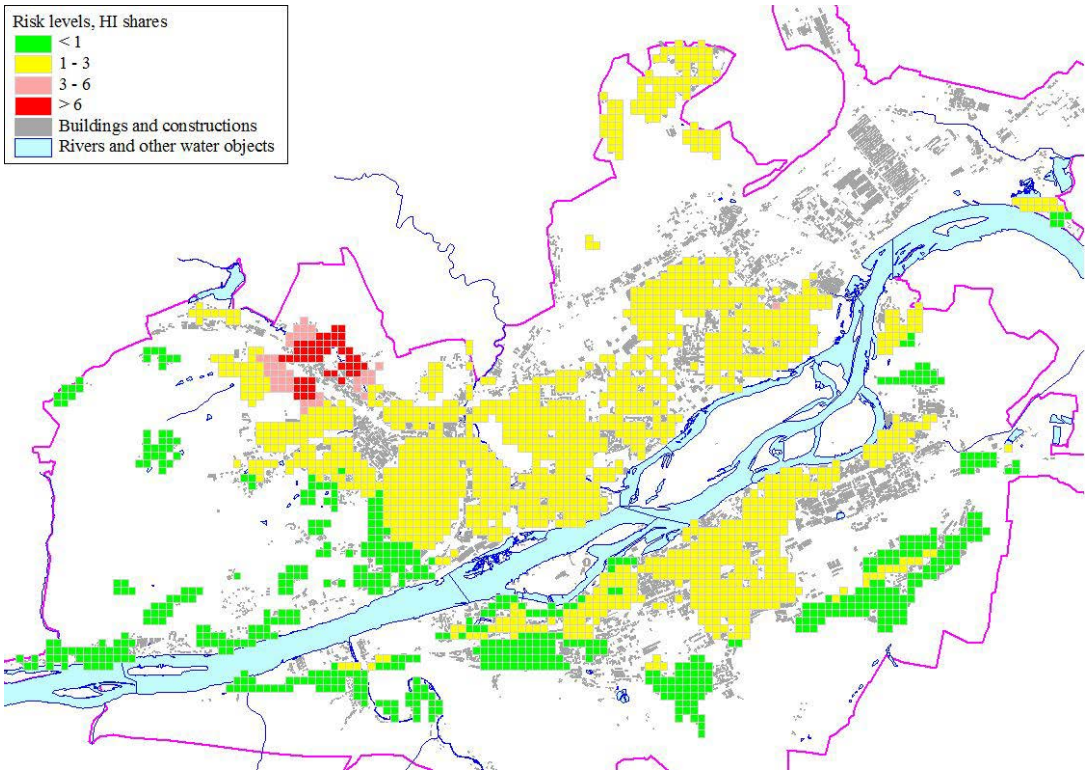

Figure 2. The map showing spatial distribution of non-carcinogenic Kchronic health risks for the respiratory organs based on calculated data, HIch percentages

Table 1

Data on contributions made by heat-power engineering objects (HPEO) to average annual ground concentrations in the city as a whole in residential areas: a fragment on some chemicals, calculated levels of which are higher than safety standards

Code	Chemical	Contributions of HPEO to the total gross emissions*	Contributions of HPEO to the average annual concentrations, %		
			Minimum	Medium	Maximum
301	Nitrogen dioxide (Nitrogen (IV) oxide)	69.3	4.17 %	22.77 %	66.41 %
328	Carbon (soot)	59.4	19.30 %	75.00 %	**92.70 %**
330	Sulfur dioxide (Sulfuric anhydride)	69.0	36.10 %	68.10 %	89.99 %
337	Carbon oxide	16.4	20.62 %	62.25 %	**93.04 %**
2902	Particulate matter	55.8	16.95 %	86.53 %	**99.59 %**
2908	Inorganic dust: 70–20 % SiO_2	89.3	39.09 %	87.84 %	**99.09 %**
2909	Inorganic dust: SiO_2 up to 20 %	7.9	2.35 %	25.54 %	87.50 %
2930	Abrasive dust (white corundum, monocrystalline alumina)	4.5	0.07 %	1.86 %	71.53 %

N o t e: * means total contributions made by only TPS-1, TPS-2, TPS-3, 35 boiler houses, and autonomous heat supply sources.

The total contribution made by heat-power engineering objects to health risks varied between 1 and 37 % for different target organs and systems.

A profound analysis of the Complex plan established that a goal was to reduce pollutant emissions from heat-power engineering objects by 42.6 thousand tons by 2024, or 22.3 % from the 2017 level. It should be achieved by implementing various technical, technological and organizational measures including TPS upgrading, decommissioning of coal-fueled boiler houses, moving people from dilapidated housing with stove heating, providing private houses with centralized heat supply or gas heating and some others. In particular, the Complex plan of air protection activities aimed at reducing emissions from heat-power engineering objects stipulates a reduction in emissions or a number of emission sources by Siberian Generating Company LLC, Krasnoyarskaya TPS-1, 35 municipal boiler houses and in dilapidated housing with stove heating.

In particular, Siberian Generating Company LLC plans to install an automated system for control of pollutant emissions into ambient air at its heat-power engineering objects, namely, thermal power stations in Krasnoyarsk. In addition to that, the company plans to add new generating capabilities to already existing ones at Krasnoyarskaya TPS-3 to balance heat loads after 35 ineffective coal-fueled boiler houses are decommissioned.

Ineffective coal-fueled boiler houses have been established to emit 52 pollutants typical for this economic activity. The Complex plan stipulates a reduction in total emissions from these 35 boiler houses by 7.7 % (10.8 thousand tons). Implementation of these measures is expected to reduce local single concentrations, which are higher than safe standards (more than 1.1 single MPL) in residential areas, for example, by 10 % per such pollutants as nitrogen dioxide and inorganic dust: 70–20 % SiO_2; still, their levels are going to remain at 1.1–4.4 single MPL. In particular, the implemented measures on emission reduction will result in a decrease in levels of inorganic dust: 70–20 % SiO_2 down to 1.0 single MPL and make it possible to remove 0.53 thousand people from as area with elevated pollution under acute inhalation exposure. Average annual concentrations will remain stable at the level of 1.1–7.0 average annual MPL.

Optimization approaches to selecting regulatory actions demonstrated that a reduction by 120.1 tons (or by 1.1 % of the total gross emissions from 35 coal-fueled boiler

houses in 2017) as per 7 chemicals would be optimal considering the contribution made by these boiler houses into the total ambient air pollution. The foregoing seven chemicals include particulate matter, chromium, manganese and its compounds, carbon (soot), inorganic dust: 70–20 % SiO_2, inorganic dust: SiO_2 up to 20 %, and sulfur dioxide. Currently, their total emissions equal 241.9 tons, between 9 and 100 % (Table 2).

Thus, specifically, parameterized activities have been developed for only 12 ineffective coal-fueled boiler houses for which the Complex plan stipulates a 6.3 % reduction in the total emission (8.8 thousand tons) per 19 chemicals (Table 2).

The Complex plan also stipulates moving people from dilapidated housing with stove heating. This will reduce the total emissions by 0.22 % (0.3 thousand tons) of the 2017 level.

According to the aggregated database on sources of pollutant emissions on the analyzed territory, autonomous heat supply sources emit seven pollutants: nitrogen dioxide, nitrogen (II) oxide, sulfur dioxide, carbon oxide, benzo(a)pyrene, particulate matter, and inorganic dust: 70–20 % SiO_2. Currently, their total emissions are above 5.3 thousand tons (8.7 % of the total gross emissions from all heat-power engineering objects ion the analyzed territory).

Implementation of air protection activities within the Complex plan will lead to a slight decrease (by 0.01–0.03 single MPL) in the highest single levels of chemicals, which are higher than safety standards. These concentrations will remain at the level of up to 1.1–6.25 single MPL. Average annual levels of chemicals, which are higher than safety standards (up to 1.1–6.98 average annual MPL), will remain practically the same.

When solving the optimization task and within the differentiated approach to selecting regulatory actions, we established that it was optimal to reduce emissions of six chemicals by autonomous heat supply sources given their contribution to the total ambient air pollution. These six chemicals include sulfur dioxide, nitrogen dioxide, benzo(a)pyrene, inorganic dust: 70–20 % SiO_2, carbon oxide, and particulate matter. Their total emissions currently equal 1.4 thousand tons per year. To ensure compliance with the sanitary-hygienic standards for chemical levels and to achieve acceptable health risk levels in the total residential areas, it is necessary to reduce emissions of these six chemicals by 1–100 %. The overall reduction, given the contribution made by autonomous heat supply source to ambient air pollution, should be equal to 658.6 tons, which is 2.1 times higher than the reduction stipulated by the Complex plan (Table 3). Table 4 provides a fragment of the detailed data on reductions in emissions of some specific chemicals by autonomous heat supply sources according to the Complex plan and optimal reductions in emissions of the said sources recommended considering the optimization criterion.

Table 2

Comparative assessment of planned complex air protection activities aimed at reducing emissions of specific chemicals into ambient air and differentiating optimized regulatory actions at 12 coal-fueled boiler houses (tons/year)

Chemical	Complex plan, tons/year	Optimized regulatory actions	
		tons/year	Reduction against 2017, %
Chromium	0.0001	0.0017	9
Nitrogen dioxide	878.453	–	–
Nitrogen (II) oxide	142.734	–	–
Carbon (soot)	859.055	–	–
Sulfur dioxide	1101.932	–	–
Carbon oxide	5018.029	–	–
Inorganic dust: 70–20 % SiO_2	788.427	119.68	50
and other chemicals	25.778	0.000068	100
Total:	8814.408	119.7	1.3

Table 3

Comparative assessment of planned complex air protection activities and differentiated optimized regulatory actions aimed at reducing total emissions of specific chemicals into ambient air concerning autonomous heat supply sources (tons/year)

Chemical	Complex plan, tons/year	Optimized regulatory actions, tons/year
Nitrogen dioxide	6.777	18.01
Nitrogen (II) oxide	1.172	-
Sulfur dioxide	3.576	0.173
Carbon oxide	256.250	228.39
Benzo(a)pyrene	0.000	0.000049
Particulate matter	32.739	55.618
Inorganic dust: 70–20 % SiO_2	10.095	356.398
Total:	310.609	658.608

Table 4

A fragment of the complete list of autonomous heat supply sources which are subject to planned air protection regulatory actions according to the Complex plan and recommended optimal reductions in emissions by them

No.	Emitted pollutants that are subject to optimization	Emission mass (tons/year)	A share of a chemical in total emissions, %	A reduction in total emissions according to the Complex plan, %	Reductions in emissions as per results of solving the optimization task concerning the analyzed chemicals, %
	Autonomous heat supply sources in Badalyk settlement				
1	0703 Benzo(a)pyrene	1.73E-05	1.8E-05	–	100
	Autonomous heat supply sources in Peschanka settlement				
1	2908 Inorganic dust: 70–20 % SiO_2	12.397499	13.2	–	11
	Autonomous heat supply sources in Torgashino settlement				
1	0301 Nitrogen dioxide (Nitrogen (IV) oxide)	10.545777	2.1	–	100
2	2908 Inorganic dust: 70–20 % SiO_2	71.905526	14.4		46
	Autonomous heat supply sources in Laletino settlement				
1	0301 Nitrogen dioxide (Nitrogen (IV) oxide)	9.80651	2.1	16.2	36
2	0337 Carbon oxide	339.490704	74.1		37
3	2902 Particulate matter	34.52616	7.5		43
4	2908 Inorganic dust: 70–20 % SiO_2	58.956965	12.9		73

Currently TPS-1 emits 36 chemical pollutants into ambient air and its total emissions are 16 thousand tons. The Complex plan of activities aimed at reducing pollutant emissions into ambient air stipulates a reduction in emission of all chemical by this TPS by 7.0 thousand tons (43.7 %).

The differentiated approach to selecting optimal regulatory actions demonstrated that it was optimal to reduce emissions of only one chemical by TPS-1, given its contribution to ambient air pollution. This chemical is inorganic dust: 70–20 % SiO_2 with its contribution currently being 5.9 thousand tons (35 %) in the total emissions by TPS-1. To ensure compliance with the sanitary-hygienic standards for chemical levels and to achieve acceptable health risk levels in the total residential area (at 678 points involved in setting emission quotas), it is necessary to reduce emissions of inorganic dust: 70–20 % SiO_2 by 46 %, or 2.7 thousand tons, of the total emissions form this TPS.

Therefore, the Complex plan stipulates the total reduction in emissions form heat-power engineering objects by 18.1 thousand

tons per more than 20 chemicals[7] (particulate matter, nitrogen dioxide, nitrogen (II) oxide, carbon (soot), sulfur dioxide, chromium, inorganic dust: 70–20 % SiO_2, inorganic dust: SiO_2 up to 20 % and others) (Table 5).

Table 5

Comparative assessment of planned complex air protection activities aimed at reducing pollutant emissions into ambient air and differentiated optimized regulatory actions at heat-power engineering objects (tons/year)

Action	Complex plan, tons/year	Optimization task, tons/year
35 boiler houses	10.8 thousand	0.12 thousand
Autonomous heat supply sources	0.3 thousand	0.65 thousand
TPS-1	7.0 thousand	2.69 thousand
Total:	18.1 thousand	3.47 thousand

The results obtained by solving the optimization task clearly indicate that it is optimal to reduce emissions from heat-power engineering objects per 10 chemicals only (carbon, nitrogen dioxide, benzo(a)pyrene, particulate matter, chromium, sulfur dioxide, carbon oxide, manganese, inorganic dust: 70–20 % SiO_2, SiO_2 up to 20 %) between 1 and 100 %. The total reduction will equal 3.474 thousand tons a year, which is 5.2 times lower than stipulated by the Complex plan; still it will ensure compliance with the existing safety standards and achieving acceptable levels of health risks.

Implementation of air protection activities and reductions in the total emissions from heat-power engineering objects stipulated in the Complex plan will not significantly improve living conditions on the analyzed territory given the estimated contributions made by them to ambient air pollution. On the contrary, recommended differentiated optimal reductions in emissions estimated as per the results of solving the optimization task will ensure the relevant positive changes.

Moreover, additional evidence has been provided to support the above conclusions, namely, the results obtained by predictive health risk assessment. Implementation of air protection activities stipulated by the Complex plan is expected to bring about a slight positive trend, which is a 1.1–1.2 times decline in risks of diseases of the nervous, hematopoietic, cardiovascular, reproductive, immune, and respiratory systems. Carcinogenic risks mostly occurring due to exposure to formaldehyde will remain stably high (reaching $3.28 \cdot 10^{-4}$). Acute and chronic risks for target organs and systems, including the respiratory, cardiovascular and immune systems, eyes, blood, and developmental processes, will be equal to 6.5–25.5 HIac and 11.9–22.6 HIch. Implementation of activates within the Complex plan will make it possible to move approximately 50 thousand people from zones with unacceptable acute health risks and 120 thousand people from zones with unacceptable chronic health risks into ones with minimal (target) health risks [8].

To ensure compliance with the safety standards for chemical levels in ambient air (1 single MPL, 1 average annual MPL) and to achieve acceptable levels of health risks (1 HQ, 3 HI, $CR \leq 1 \cdot 10^{-4}$, $CR_T \leq 1 \cdot 10^{-4}$) on the analyzed territory, it is necessary to achieve differentiated reductions in emissions not only from heat-power engineering objects but also from other emission sources (economic entities and motor transport) by 1.06 thousand tons overall, including nitrogen dioxide, by 0.941 thousand tons (between 6 and 100 % at different sources); carbon, by 0.00128 thousand tons (between 19 and 100 %); sulfur dioxide, by 0.0021 tons (100 %); benzo(a)pyrene, by 0.87 tons (78–100 %); particulate matter, by 0.262 tons (24–47 %); carbon oxide, by 0.156 tons (100 %); inorganic dust: 70–20 % SiO_2, by 42.93 tons (7–100 %); inorganic dust: SiO_2 up to 20 %, by 0.61 tons (14–100 %); manganese, by 0.65 tons (86–93 %).

Reconnaissance assessment was performed to estimate effectiveness of air protection activities relying on current changes in ambient air quality per all chemicals at four monitoring posts of Rospotrebnadzor over

[7] The number of chemicals has been identified only for 12 boiler houses and autonomous heat supply sources, for which parameterized data on planned measures have been provided.

2019–2023. It demonstrated a decrease in the highest single concentrations of five analyzed chemicals: formaldehyde, gaseous fluorides, ammonia, carbon oxide, ethyl benzene (the decrease rate varied between 63.9–1.79 %) down to 0.46–2.75 single maximum MPL. Still, a certain growth in single concentrations was detected for seven chemicals: nitrogen dioxide, nitrogen (II) oxide, particulate matter, PM_{10}, $PM_{2.5}$, hydroxybenzene, dimethyl benzene by 1.8–8.5 times up to 1.87–5.71 single MPL. A decrease was also established in average annual levels of two chemicals, formaldehyde and benzene (the decline rate varied between 94.1–54.9 %) down to 0.21–0.64 average annual MPL and a certain growth was established for five chemicals: nitrogen dioxide, benzo(a)pyrene, particulate matter, $PM_{2.5}$, and PM_{10} (the growth rate is 1.2–5.1 times) up to 1.1–2.36 annual average MPL.

The established trends as changes in exposure manifested themselves in levels of created health risks. Over 2019–2023, a decline was established in individual carcinogenic risk levels caused by exposure to airborne benzene (by 89.8 %) down to $1.42 \cdot 10^{-5}$, hazard quotients under short-term (acute) inhalation exposure to formaldehyde and benzene (by 49.8–79.5 %) down to 1.2 HQac; a certain growth was established for PM_{10}, $PM_{2.5}$ and particulate matter in general (by 60.5–42.4 %) up to 11.3 HQac. Over the analyzed 5-year period, there was a decline in hazard quotients of non-carcinogenic effects under chronic inhalation exposure to benzene (by 89.8 %) down to 1.41 HQch and a certain ascending trend for hazard quotients associated with nitrogen dioxide, benzo (a)pyrene, particulate matter, $PM_{2.5}$ and PM_{10} by 2.1–6.6 times up to 2.76 HQch.

At present, many research articles report rather ambiguous results of the ongoing experiment. Thus, implementation of the Complex plan on the pilot territories has demonstrated that, according to social-hygienic monitoring data, ambient air quality still does not comply with the mandatory sanitary-hygienic requirements in some cities [17–20]. Practical experience indicates that many tools for state regulation of ambient air pollution that are fixed in the legislation have a theoretically high potential but are hardly efficient in practice. This is due to high expenditure on environmental protection, low motivation of economic entities to reduce negative effects on ambient air, errors and miscalculations in planning, making and implementing decisions significant for environmental protection [21–24].

A study by A.V. Komarova and E.A. Maklakova [7] has demonstrated that quotas set for pollutant emissions do not consider suggestions made by enterprises or technological and economic expedience of reducing emissions at sources with preset quotas. Moreover, several important factors are neglected such as uneven and non-simultaneous work of different equipment, changes in work regimes and different stages in metallurgical production processes (non-stationary emissions).

Up-to-date scientific research should involve changes in approaches to regulation of ambient air pollution. Therefore, it is advisable to concentrate efforts on reducing emissions of priority pollutants and health risk factors considering their contributions to the overall pollution instead of reducing the total emission volumes by 22 %. Priority pollutants are chemicals that can potentially produce the most harmful effects on the environment and human health. Such an approach allows concentrating on the most hazardous chemicals and achieving the maximum possible results in raising ambient air quality [4, 13, 14, 23].

Uncertainties of the present study include possible inaccuracy and changeability of parameters of pollution sources; impossibility to consider simultaneous work of all these sources; inaccuracies in completeness of the systemic assessment of spatial-differentiated calculated exposure and health risks; gaps in the scientific theory of prediction based on cause-effect relations (model uncertainties).

Conclusions. A differentiated approach to selecting optimal regulatory actions involves identification of priority chemicals and objects for setting emission quotas considering their contributions to total ambient air pollution. It turned out to be relevant and precise in mini-

mization of airborne health risks and provision of sanitary-epidemiological safety in all residential areas in the analyzed city. Approbation of the methodical approach fixed in the Methodical Guidelines MR 2.1.6.0320-23 with heat-power engineering objects used as an example demonstrates that it is eligible for ambient air quality management under local or total ambient air pollution created by emission sources, which are heterogeneous in their intensity and structure, located in close proximity to residential areas.

Our study results show that implementation of air protection measures and reductions by 18.1 thousand tons in the total emissions of more than 20 chemicals by heat-power engineering objects in accordance with the Complex Plan and considering their contributions to total ambient air pollution (between 1 and 99 % in different areas per different chemicals; contributions to health risks reach 37 %) will not significantly improve the living conditions for people residing in the analyzed areas. This is due to persisting violations of safety standards since peak chemical levels will remain 6.25 single MPL and 7.0 average annual MPL. In contrast to that, desirable improvement can be achieved by suggested optimal regulatory actions based on the differentiated approach to managing ambient air quality and health risks.

A differentiated reduction by 3.47 thousand tons in emissions from all heat-power engineering objects is optimal and sufficient considering contributions made by emission sources and specific chemicals to total ambient air pollution. This is 5.2 times lower than reductions stipulated by the Complex Plan for reductions in emissions. It is 2.69 thousand tons lower (16.8 % of the 2017 emissions) at the TPS-1; by 0.12 thousand tons at all ineffective coal-fueled boiler houses (1.1 %); by 0.65 thousand tons at autonomous heat supply sources (12.3 %). The following ten chemicals should be considered priority ones and mandatory for reduction at heat-power engineering objects in the analyzed city: nitrogen dioxide, carbon, sulfur dioxide, benzo(a)pyrene, particulate matter, carbon oxide, chromium, inorganic dust: 70–20 % SiO_2, up to 20 % SiO_2, and manganese. Reductions in their levels vary between 1 and 100 % and are determined individually for each object. To ensure compliance with the safety standards for chemical levels in ambient air and to achieve acceptable levels of health risks on the analyzed territory, it is necessary to achieve object-specific differentiated reductions in emissions not only from heat-power engineering objects but also from other emission sources (economic entities and motor transport) by 1.06 thousand tons overall. Implementation of the suggested optimal regulatory actions at heat-power engineering objects in the analyzed city considering their contributions will ensure compliance with safety standards and acceptable health risk levels in all residential areas and at all points used for setting quotas of emissions.

Use of a differentiated approach to selecting optimal regulatory actions as regards all sources of ambient air pollution will make it possible for decision-makers to define priority environmental protection activities, adjust the Complex plans on ambient air quality improvement, update regional urban development plans, and motivate the business community to implement effective measures aimed to reduce emissions of chemicals, which are priority ones as per health risk criteria. This will also support systemic interdepartmental interactions in order to provide sanitary-epidemiological wellbeing and environmental safety,

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Research article

SCIENTIFIC SUBSTANTIATION OF AVERAGE ANNUAL MAXIMUM PERMISSIBLE LEVEL OF VANADIUM PENTOXIDE IN AMBIENT AIR AS PER PERMISSIBLE HEALTH RISK

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Relevance of this study is determined by the sanitary-epidemiological legislation of the Russian Federation with stipulated requirements to create hygiene standards for environmental factors ensuring their safety for people. These hygienic standards should guarantee absence of impermissible lifetime health risks.

Divanadium pentoxide is a chemical that should be mandatorily regulated in ambient air under long-term exposure due to its wide prevalence and high toxicity.

An average annual MPL for divanadium pentoxide was established by using systemic analysis of research literature and regulatory documents. According to selection results, three key epidemiological studies were taken for further analysis. They provided evidence of adverse effects produced by divanadium pentoxide on human health (the respiratory organs in particular) under chronic inhalation exposure.

When analyzing a study design, we paid special attention to description of observation groups, values of exposure and nature of its effects, adverse health outcomes caused by exposure to divanadium pentoxide as well as to a type and a value of a point of departure. We calculated a value of the total (complex) uncertainty factor in order to establish an average annual maximum permissible level of the analyzed chemical.

As a result, we suggest a scientifically substantiated (among other things, as per permissible health risk levels) average annual maximum permissible level for divanadium pentoxide, which equals 0.0001 mg/m^3. This level is safe for human health under lifetime exposure. It is noteworthy that this level corresponds to 'low uncertainty', which indicates its high safety for human health.

Keywords: *average annual MPL, divanadium pentoxide, ambient air, risk indicators, scientific substantiation, hygiene standard, environmental factors, uncertainty factor.*

Legal grounds for establishing safe levels of chemicals in ambient air are fixed by the RF Federal Law issued on March 30, 1990 No. 52-FZ On Sanitary-Epidemiological Wellbeing of the Population. It stipulates general principles and fundamentals of the state policy in the sphere of providing sanitary-epidemiological wellbeing of the population, in particular, sanitary-epidemiological requirements to ambient air[1]. According to the 52-FZ, maximum permissible levels in ambient air serve as indicators describing safety for human life and health and are determined in conformity with the valid sanitary rules and

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norms (SanPiN 1.2.3685-21 Hygienic Standards and Requirements to Providing Safety and (or) Harmlessness of Environmental Factors for People[2]). Development of sanitary rules involves establishing requirements to prevent harmful environmental factors from affecting human health. This includes identifying those conditions, which give grounds for calculating and assessing health risks[1]. This implies that a safe standard describes an environmental factor as regards its lifetime safety for humans[1] as absence of any impermissible health risks. Given that, it is advisable to substantiate average annual maximum permissible levels (MPLav.an.) relying on a permissible health risk as a key criterion.

Relevance of examining divanadium pentoxide is determined by volumes of the chemical emitted into ambient air by industries. According to Rosprirodnadzor data (the Form 2-TP), approximately 150 tons of divanadium pentoxide are annually emitted into ambient air[3]. Over 2011–2018, an average volume of divanadium pentoxide emitted into ambient air equaled 328 tons[4].

Industry is a universally recognized major source of ambient air pollution (56 % of all pollution types); metallurgy accounts for 23 % in overall industrial pollution. Divanadium pentoxide is mostly emitted into ambient air by ferrous metallurgy (95 %). Divanadium pentoxide is most often used as a dopant to make wearproof, heatproof and corrosion-proof alloys (primarily, some specific steels). As of 2019, Russia took the 5th place in the world as a steel producer with the total steel output being 71.6 million tons per year.

At present, more than 1.5 thousand ferrous metallurgic productions operate in the Russian Federation. Seventy percent of them are city-forming enterprises and this means that people who live in such monotowns are exposed to airborne divanadium pentoxide. The largest ferrous metallurgy plants are located in the Urals (31.1 %), Siberian (18.5 %), Central (17.6 %) and Volga (14.5 %) Federal Districts.

An average working period of a metallurgy plant in Russia is established to exceed 140 years (exemplified by 30 largest ones). Still, metallurgic production continues to develop and this is the reason for a long-term exposure to divanadium pentoxide, likely, a lifetime one.

Relevance of regulating levels of divanadium pentoxide arises due to its high toxicity, which is determined by several adverse effects occurring under inhalation exposure. Divanadium pentoxide is considered to primarily affect the respiratory organs [1–10]. However, hazard identification performed in some studies established adverse effects produced by divanadium pentoxide on other organs and systems, for example, eyes[5] [11–15], skin [11], and the immune system as dysfunction of its humoral and cellular components [6, 16, 17]. According to the Federal Register of Potentially Hazardous Chemicals and Biological Agents, negative health outcomes can also occur in the central nervous system, cardiovascular system, gastrointestinal tract, liver, kidneys, adrenals, spleen, teeth, and bone tissue;

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[2] Ob utverzhdenii sanitarnykh pravil i norm SanPiN 1.2.3685-21 «Gigienicheskie normativy i trebovaniya k obespecheniyu bezopasnosti i (ili) bezvrednosti dlya cheloveka faktorov sredy obitaniya»: Postanovlenie glavnogo gosudarstvennogo sanitarnogo vracha Rossiiskoi Federatsii ot 28.01.2021 № 2 (s izmeneniyami na 30 dekabrya 2022 goda) [On Approval of the sanitary rules and norms SanPiN 1.2.3685-21 Hygienic Standards and Requirements to Providing Safety and (or) Harmlessness of Environmental Factors for People: the Order by the RF Chief Sanitary Inspector dated January 28, 2021 No. 2 (last edited on December 30, 2022)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573500115 (November 30, 2023) (in Russian).

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changes in peripheral blood and metabolic disorders are also possible[6].

The foregoing determined **the aim of this study,** which was to substantiate the maximum permissible level of divanadium pentoxide in ambient air as per permissible health risks under long-term exposure.

Materials and methods. Literature sources were selected by systemic analysis with emphasis on those investigating occurrence of negative health outcomes under chronic inhalation exposure to divanadium pentoxide. Our research covered more than 100 foreign and Russian works including articles, reports and reviews as well as regulatory and substantiating documents.

Several criteria were used to include materials into further analysis: a full text of an article available in open access; an article containing quantitative indicators that describe an analyzed dependence – response model; available data on a level of exposure to divanadium pentoxide and detailed description of a study design.

Next, we selected key studies most relevant for establishing an average annual maximum permissible level (MPLav.an.) of divanadium pentoxide.

Methodical approaches applied in this work to identify a study that could provide a solid ground for substantiating MPLav.an. as well as an algorithm for substantiating it have been described in detail in research literature[7].

Uncertainty of an average annual MPL was established by estimating indicators that were critical and considered any interspecies and / or intraspecies extrapolation; exposure mode applied in a study (manageable or real world conditions, acute / subchronic / chronic exposure); choice on a point of departure and initial data volume.

The ultimate uncertainty was identified based on three most significant indicators in accordance with semi-quantitative criteria provided in Table 1.

Table 1

Criteria to describe correspondence of safe standard uncertainty

Criterion	Uncertainty
Below 300	Low uncertainty
Between 301 and 600	Medium uncertainty
Between 601 and 1000	High uncertainty

Results and discussion. According to selection results, three key epidemiological studies were taken for further analysis:

– an epidemiological study by G.B. Irsigler et al. with its focus on effects produced by divanadium pentoxide under subchronic inhalation exposure (South Africa) [8];

– an epidemiological study by M. Kiviluoto on effects of divanadium pentoxide under chronic inhalation exposure produced on workers employed at divanadium pentoxide production in Finland [18–20];

– an epidemiological study by C.E. Lewis on effects produced by divanadium pentoxide on workers at vanadium productions in the USA under subchronic inhalation exposure [3].

Analysis of a level able to cause a negative health outcome allowed establishing a point of departure for MPLav.an. substantiation. The lowest exposure that causes an adverse effect (LOAEL) was taken as this point of departure in all analyzed studies.

Critical points and corresponding values of modifying factors were established relying on analysis of a study design. Detailed description of study designs is provided in Table 2.

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Table 2

Description of key study designs used to establish average annual MPL of divanadium pentoxide

Parameter	G.B. Irsigler, et al. (1999)	M. Kiviluoto (1979–1981)	C.E. Lewis (1959)
Study	Epidemiological	Epidemiological	Epidemiological
Study type	Case – control	Case – control	Case – control
Case	12 workers employed at vanadium production (South Africa)	63 workers employed at divanadium pentoxide production, average work records equal to 11 years (Finland)	24 workers employed at vanadium production (USA)
Sensitivity of a case group	Workers	Workers	Workers
Control	12 workers employed at vanadium production but not exposed to divanadium pentoxide	22 mine operators not exposed to divanadium pentoxide	45 workers not exposed to divanadium pentoxide, comparable as per age and socioeconomic status
Exposure type	Inhalation	Inhalation	Inhalation
Characteristics of exposure	Subchronic exposure (6 months)	Chronic exposure (260 air samples taken in the breathing zone between 1970 and 1976)	Subchronic exposure (6 months)
Exposure level, mg/m^3	Between 0.15 and 1.53	Between 0.018 and 0.89	Between 0.097 and 0.243 (Colorado) Between 0.018 and 0.925 (Ohio)
Negative outcomes	Bronchial hyperreaction	Elevated levels of neutrophils and plasmatic cells in nasal duct mucosa	Cough, mucus, irritated eye, throat and nose mucosa, nose bleeding, hoarseness
Critical organ / system corresponding to negative health outcomes	Respiratory organs	Respiratory organs	Respiratory organs
Point of departure	LOAEL = 0.015 mg/m^3	LOAEL = 0.018 mg/m^3	LOAEL = 0.018 mg/m^3

All analyzed studies were case – control ones and were performed on workers employed at divanadium pentoxide production. This makes it possible to reduce levels of uncertainty and modifying factors as much as possible considering interspecies variations but simultaneously to increase a level of a factor responsible for intraspecies variations.

In all analyzed studies, LOAEL for respiratory dysfunction is taken as the point of departure. This fact confirms findings of most studies focusing on effects produced by divanadium pentoxide on human health and provides solid evidence that it is the respiratory system that first reacts to them and is a target one in this respect.

At the same time, certain differences were established in profound examination of a level, which brought about negative changes. Thus, for example, M. Kiviluoto reports preclinical laboratory disorders in his study such as authentic quantitative changes in cellular components in tissues, which indicates earlier signs of negative effects produced by divanadium on the body. But effects described by G.B. Irsigler et al. and C.E. Lewis manifested themselves as non-specific clinical symptoms such as cough, mucus, etc. Identification of negative outcomes at a lower organizational level was a priority factor in selecting a key study as regards this parameter.

Analysis of exposure load revealed that divanadium pentoxide affected the body by inhalation in all key studies. However, inhalation exposure was subchronic in the studies by G.B. Irsigler et al. and C.E. Lewis and lasted

6 months and only M. Kiviluoto described chronic exposure (between 1970 and 1976); average working records in the branch equaled 11 years and air samples (260 samples were taken overall, 64 in 1970–1975 and 196 in 1976) were taken in the breathing zone. In this case, a key study for establishing an average annual MPL is the one describing longer exposure.

Exposures identified for workers in all three studies were given as ranges of concentrations. All three studies report that any level within those ranges can have negative effects on human health. Bearing in mind that the analyzed studies were epidemiological and, consequently, an exposure mode was not manageable as regards a dose per one person, it seems impossible to establish an exact concentration that caused negative health outcomes. This is an uncertainty of this study.

However, researchers took a minimal level reported in their studies as LOAEL. The lowest LOAEL of divanadium pentoxide in the breathing zone was detected in the study by G.B. Irsigler et al., 0.015 mg/m^3. In two other studies (M. Kiviluoto and C.E. Lewis), the lowest exposure was fixed at the same level, 0.018 mg/m^3.

Control groups were comparable with cases in all there analyzed studies.

We identified values of modifying factors for each critical point relying on the results obtained by analyzing design of the key studies. Table 3 provides semi-quantitative assessment of modifying factors for each study.

Depending on a study, several modifying factors are the most significant for establishing a safe level of divanadium pentoxide. They consider sensitivity of a group under exposure, an exposure mode as regards real world conditions, a type of a point of departure and exposure duration.

The interspecies extrapolation factor and the factor that considers an initial data volume were minimal in all studies and equaled one.

We used the total (complex) uncertainty factor in our calculations, which equaled 180 in all studies (since it is advisable to use not more than three modifying factors). Given that, we established values recommended for use as an average annual MPL of divanadium pentoxide, which are 0.0008 mg/m^3 and 0.0001 mg/m^3. The latter value of 0.0001 mg/m^3 was established relying on findings of two studies (M. Kiviluoto and C.E. Lewis).

Since the safe standardization principle states that a limiting indicator should be used, we recommend using a value of 0.0001 mg/m^3 as an average annual MPL of divanadium pentoxide.

Results obtained by calculating total uncertainty revealed that the established safe level corresponded to ‘low uncertainty’, which means its high safety for human health.

Table 3

Modifying factors for critical research points*

Modifying factor	G.B. Irsigler et al., 1999	M. Kiviluoto, 1979–1981	C.E. Lewis, 1959
Interspecies extrapolation factor	1	1	1
Intraspecies extrapolation factor	**10**	**10**	**10**
Factor of extrapolation from manageable exposure to real world conditions	3	**3**	3
Factor that considers a type of a point of departure	**6**	**6**	**6**
Factor that considers a volume of initial data	1	1	1
Extrapolation of exposure duration	**3**	1	**3**
Total (complex) uncertainty factor	**180**	**180**	**180**

Note: * indicators that were considered in calculating the total (complex) uncertainty factor are given in bold.

At present, there is evidence, that a level of divanadium pentoxide that equals 0.0001 mg/m^3 is safe for humans. For example, minimum risk levels (MRLs) for vanadium compounds were established at the same level by the Agency for Toxic Substances and Disease Registry (ATSDR) of the US State Department of Health and Human Services. Substantiation materials report that identification of these levels was based on a toxicological study performed on F344 rats [16]. It established several negative health outcomes such as dysfunctions of some respiratory organs (lung tissues, the larynx and nasal cavity) under chronic exposure to 0.05 mg/m^3 of divanadium pentoxide. When establishing MRL, ATSDR experts used calculation methods and software for mathematic modeling. They established MRL of divanadium pentoxide to equal 0.0001 mg/m^3 based on a level equivalent for humans ($BMCL_{HEC}$) calculated with use of modifying factors, which amounted to 10 and 3 in their quantitative equivalent.

The key study for establishing a safe standard was the one by M. Kiviluoto, although the same results were obtained relying on two independent studies in our research on substantiating an average annual MPL for divanadium pentoxide. This is easily explained by the fact that negative health outcomes in the respiratory system were identified at the cellular level in the study by M. Kiviluoto, which is lower than in the study by C.E. Lewis. In addition to that, the volume of initial data was also larger, more air samples were analyzed and the case group included more people.

The substantiated average annual MPL of divanadium pentoxide is equal to its reference concentration (RfC) under chronic inhalation exposure[8]. This allows us to conclude that the average annual MPL equal to 0.0001 mg/m^3 corresponds to permissible risk for human health.

Conclusion. Therefore, the findings reported in the epidemiological study by M. Kiviluoto were used as substantiation of the average annual maximum permissible level of divanadium pentoxide. LOAEL equal to 0.018 mg/m^3 of divanadium pentoxide was taken as the point of departure since this dose was able to cause negative health outcomes in the respiratory organs. The total modifying factor equal to 180 was used in calculating a safe standard for the chemical.

The established average annual maximum permissible level in ambient air equals 0.0001 mg/m^3. This level has been substantiated relying on permissible levels of health risks and therefore it ensures lifetime safety for human health.

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Research article

IDENTIFICATION OF HAZARDS FOR HUMAN HEALTH UNDER CHEMICAL POLLUTION IN AIR INSIDE IN-PATIENT HOSPITALS

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Use of various physical and chemical research techniques, including chromato-mass-spectrometry, made it possible to identify and quantify more than 40 organic compounds in air inside healthcare organizations, including saturated, unsaturated, cyclic, and aromatic hydrocarbons; terpenes, alcohols, aldehydes, esters, ketones, halogen-containing compounds, and organic acids. Levels of ethanol, dichloromethane, carbon tetrachloride, ethyl acetate, propyl acetate, acetone, terpene hydrocarbons, and acetic acid made the main contribution to the total content of all identified compounds. Most detected substances were present in concentrations not exceeding hygienic standards, except for chloroform and iodoform, the levels of which were up to 2 times higher than average daily MPL in intensive care wards and a bronchoscopy room. Organic acids and chlorinated organic compounds were found in elevated concentrations compared with insides of non-medical public buildings. Among the wide list of identified substances, hygienic standards have not been established for more than 70 % of compounds and it is not possible to give a hygienic assessment of hazards or safety of their presence in air inside healthcare facilities. Despite that, the information obtained in this study is extremely useful for accomplishing an important stage in health risk analysis, which is identification of hazards for health of patients and healthcare workers posed by chemical air pollution inside healthcare organizations when using the risk analysis methodology.

In this study, we assessed effects produced by operations of UV recirculator irradiators for air disinfection on its chemical composition inside healthcare institutions. The assessment showed that when such devices worked in the presence of patients and staff, there was an increase in the amount of pollutants in air and their total concentration grew from two to more than four times.

When analyzing risks for health of staff and patients, hazard identification within risk-based control of chemical air pollution in the hospital environment should include monitoring of formaldehyde, styrene, ammonia, ethanol, isopropanol, chloroform, dichloroethane, acetic acid along with identification of a wide range of volatile organic compounds; it should also cover ammonia as one of the priority pollutants occurring in the environment from human excretory products.

Keywords: *chemical pollution, air, in-patient hospitals, internal sources of chemical pollution, physical and chemical research, chromato-mass spectrometric identification, hazard identification, priority chemicals for monitoring, closed-type UV irradiators, risk analysis.*

Air pollution is a major ecological threat for human health. The RF President Order dated March 11, 2019 No. 97 On the Basics of the RF State Policy in the Sphere of Providing Chemical and Biological Safety for the Period up to 2025 and beyond[1] stipulates several priority trends of the state policy in the sphere of providing chemical and biological safety. They include monitoring of chemical risks, development of legal regulations, implementation of activities aimed to prevent and minimize chemical risks, stronger protection of the country population and environment from adverse effects produced by hazardous chemical factors, as well as assessment of effectiveness and chemical safety of 'air cleaning and disin-

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fecting' components of implemented environment protection activities.

Complex analysis of chemical pollution in the environment, identification of new chemical hazards and prediction of their possible outcomes are among priority tasks of the state policy in the sphere of chemical safety concerning monitoring of chemical pollution in the environment. Another important task is to assess effectiveness and chemical safety of technologies applied in air conditioning, disinfection and cleaning of the environment.

Chemical cleanness of air inside in-patient hospitals is an important factor in providing the best conditions for patients' fastest recovery and recreation as well as protecting health of medical personnel [1, 2].

It is a well-known fact that patients and healthcare workers are exposed to a whole set of physical and chemical factors inside modern in-patient hospitals. Such factors include radiation, electromagnetic radiation of various frequencies, noise, ion and ozone exposures, UV-radiation, and chemical pollution of indoor air.

Better provision of healthcare organizations with technical equipment, implementation of up-to-date medical equipment and devices, use of effective disinfectants and disinfecting technologies, new furniture, new medications and new treatment methods are the reason for physical and chemical factors creating a specific indoor environment in in-patient hospitals alongside biological contamination. This specific environment can affect patients' treatment and recovery [3–7]. Our studies have revealed that in-patients hospitals are places with elevated health risks caused by exposure to adverse factors intrinsic for indoor environment in them [8]. This creates higher sanitary-epidemiological and hygienic requirements to indoor air quality, on the one hand, for patients' recovery and, on the other hand, for providing safe workplace settings for healthcare workers.

Given that, further development of methods applied to assess a sanitary-hygienic situation is a most significant guarantee of more qualitative healthcare. This includes chemical and analytical monitoring of chemical pollution in air inside healthcare organizations and chemical safety of technologies applied to clean and disinfect it.

In this study, our aim was to assess chemical pollution of air inside healthcare organizations performing different functions. The assessment involved identifying and quantifying the maximum full range of volatile organic compounds and establishing priority pollutants with the highest hygienic significance. This was necessary for accomplishing the hazard identification stage within risk-based control of the indoor environment inside in-patient hospitals.

Materials and methods. We chose three in-patients hospitals as our research objects. They were a multi-profile municipal clinical hospital, a maternity hospital and an in-patient hospital of a scientific research institute specializing in treating inflammatory bowel disease. We identified and quantified chemical pollution in air inside surgery wards, patient wards, treatment and dressing rooms, laboratory and diagnostic rooms, a physiotherapy department, staff rooms, corridors, buffets, and nutrition units. Overall, we examined 96 premises with various functional purposes. Also, the attention focus was on such research objects as supply-exhaust ventilation systems and split systems installed in the examined premises.

Snap samples were taken in the examined premises in different seasons. Sampling was made in a usual operation environment for these premises considering typical microclimatic parameters and ventilation work modes in accordance with the construction design with closed windows and doors. No further measures were taken to make the examined premises more airtight. Air samples were taken in an average breathing zone at a height between 1 and 1.5 meters from the floor. At least three air samples were taken in each premise.

Some experimental investigations were accomplished in laboratories equipped with three different kinds of closed-type UV recirculator irradiators (different makes). It was

done to assess influence exerted by new disinfection technologies on chemical pollution in air inside healthcare organizations. It is allowed to use UV-devices in such premises for a long time even when people are present in them. All three different makes of UV recirculator irradiators were equipped with ozone-free bactericidal lamps.

We identified chemicals that polluted air inside in-patient hospitals by chromatography-mass spectrometry and photocolorimetry. Chromatography-mass spectrometry made it possible to identify and quantify practically the entire range of volatile organic compounds present in indoor air in the examined in-patient hospitals with sensitivity equal to or even below the existing hygiene standards. Chromatographic-mass spectrometric investigations were accomplished on a gas chromatograph mass spectrometer Focus DSQ (USA) in conformity with the relevant methodical documents[2].

Levels of formaldehyde and nitrogen oxides were identified in air by using colorimetric methods. Ozone levels were identified with an ozone gas analyzer 3.02P-R; oxygen, gas analyzer PKG-4; carbon dioxide, gas analyzer Optogaz 500.4S. Levels of mercury vapors were identified in indoor air with a mercury analyzer, model RA-915M.

Levels of identified chemicals were compared with average annual, average daily and single maximum permissible levels (MPL) established for ambient air in residential areas; in case such MPLs were absent, the established levels were compared with tentative safe exposure levels (TSEL)[3].

Results and discussion. Indoor air quality is known to depend, to a great extent, on ambient air quality as regards its chemical structure. All buildings, including those used by healthcare organizations, have constant air exchange with the external environment and therefore are unable to protect people from ambient air pollution even in premises with installed air conditioning [9]. Chemical pollution tends to be even higher inside premises than in ambient air, as regards quantity of identified chemicals and their identified levels as well.

Chromatography-mass spectrometry made it possible to obtain the most comprehensive picture of chemical pollution in air inside in-patient hospitals with volatile organic compounds (VOCs). In particular, we managed to identify their total concentration, which, in case no hygiene standards are provided for a particular chemical, can be an eligible indicator describing chemical pollution in air inside premises.

Table 1 provides VOC levels in air inside some work and staff rooms with different functional purposes in the examined in-patients hospitals. Table 2 provides data on VOC levels in patient wards with different numbers of beds in them.

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[3] SanPiN 1.2.3685-21 Gigienicheskie normativy i trebovaniya k obespecheniyu bezopasnosti i (ili) bezvrednosti dlya cheloveka faktorov sredy obitaniya, utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha Rossiiskoi Federatsii ot 28 yanvarya 2021 goda № 2 [Hygienic standards and requirements to providing safety and (or) harmlessness of environmental factors for people, approved by the Order of the RF Chief Sanitary Inspector on January 28, 2021 No. 2]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573500115 (December 11, 2023) (in Russian).

Table 1

Volatile organic compounds identified in air inside premises of in-patient hospitals with different functional purposes

No.	Chemical	Concentration, mg/m^3				
		Intensive care ward	Bronchoscopy ward	Gastroscopy ward	Doctor's office	Treatment room
Saturated hydrocarbons						
1	Pentane	< 0.001	< 0.001	< 0.001	0.004	0.007
2	Hexane	0.190	0.080	0.030	0.050	0.060
3	Isooctane	0.006	0.230	< 0.001	0.004	0.001
4	Heptacosane	< 0.001	< 0.001	0.020	< 0.001	< 0.001
Cyclic hydrocarbons						
5	Cyclohexane	0.009	0.003	0.002	0.005	0.001
Unsaturated hydrocarbons						
6	Acetylene	0.060	0.040	0.010	0.010	0.020
7	Isoprene	0.003	0.002	< 0.001	0.005	0.004
Aromatic hydrocarbons						
8	Benzene	0.004	0.001	< 0.001	0.002	0.002
9	Toluene	0.170	0.140	0.050	0.070	0.060
10	Styrene	0.001	0.001	< 0.001	< 0.001	0.002
Terpenes						
11	α-Pinene	0.004	0.003	0.001	0.003	0.002
12	Limonene	0.002	0.001	0.003	0.004	0.001
Oxygen-containing compounds, including						
alcohols						
13	Methanol	0.007	0.003	0.006	0.002	0.001
14	Ethanol	0.110	0.120	0.010	0.010	0.060
15	Isooctadecanol	< 0.001	< 0.001	0.005	< 0.001	< 0.001
organic acids						
16	Acetic	0.002	0.004	< 0.001	0.001	0.001
17	Dodecanoic	0.050	0.070	0.030	0.004	0.002
18	Tetradecanoic	0.040	0.050	0.020	0.001	0.002
19	Pentadecanoic	0.040	0.040	0.010	0.003	0.004
20	Palmitic	0.050	0.070	0.010	0.006	0.005
21	Hexadecenoic	0.020	0.030	0.010	0.001	0.001
22	Oleic	0.030	0.050	0.009	0.002	0.002
mixed and simple ethers						
23	Ethyl acetate	0.020	0.010	0.030	0.010	0.010
24	Dibutyl phthalate	0.090	0.040	0.06	0.005	0.008
25	Dihexyl phthalate	0.004	0.050	0.008	0.001	0.003
26	Monooctyl phthalate	0.009	0.010	0.007	< 0.001	0.030
27	Dioctyl phthalate	0.002	0.003	0.001	0.001	0.004
28	Docotyl adipate	0.040	0.030	0.05	0.008	0.030
29	Diethyl ether	0.060	0.050	0.030	0.010	0.010
aldehydes and ketones						
30	Acetone	0.007	< 0.001	0.003	< 0.001	< 0.001
31	Benzaldehyde	0.010	0.003	0.002	0.006	0.008
32	Formaldehyde	0.001	0.008	0.006	0.010	0.003
33	2 6-butylhydroquinone	0.010	0.005	0.060	0.005	0.004
34	Divinylbenzophenon	0.001	0.001	< 0.001	< 0.001	0.003
terpene ketones						
35	Camphor	0.050	0.030	0.040	0.020	0.020
Sulfur-containing organic compounds						
36	Ethyl mercaptan	0.001	< 0.001	< 0.001	0.001	0.001
37	Dibutyl sulfide	0.001	< 0.001	0.002	< 0.001	0.001

End of the Table 1

No.	Chemical	Concentration, mg/m^3				
		Intensive care ward	Bronchoscopy ward	Gastroscopy ward	Doctor's office	Treatment room
Halogenated organic compounds						
38	Chloroform	0.060	0.050	0.060	0.010	0.020
39	Tetrachloromethane	0.140	0.150	0.090	0.030	0.040
40	Dichloroethane	0.001	0.002	< 0.001	0.005	0.003
41	Hexachloroethane	0.008	0.006	0.005	0.001	0.002
42	Bromomethane	0.001	0.002	0.001	< 0.001	< 0.001
43	Iodoform	0.050	0.030	0.040	0.020	0.020
Total organic compound concentration		1.364	1.418	0.721	0.330	0.458

Table 2

Volatile organic compounds identified in air inside patient wards of in-patient hospitals

No.	Chemical	Concentration, mg/m^3			
		5-bed ward	4-bed ward	2-bed ward	1-bed ward
Saturated hydrocarbons					
1	Hexane and its isomers	0.070	0.050	0.080	0.040
2	Isooctane	0.020	0.010	0.020	0.010
3	Decane	0.003	0.005	0.006	0.010
4	Tetradecane	0.005	0.003	0.008	0.002
5	Hexadecane	0.002	0.001	0.002	0.001
Cyclic hydrocarbons					
6	Cyclohexane	0.007	0.004	0.005	0.006
7	Methyl cyclohexane	< 0.001	0.001	0.002	0.001
Unsaturated hydrocarbons					
8	Isoprene	0.002	0.001	0.001	0.003
Aromatic hydrocarbons					
9	Toluene	0.030	0.020	0.010	0.040
10	o-Xylene	0.002	0.003	0.001	0.001
11	p-Xylene	0.003	0.004	0.006	0.005
Terpenes					
12	α-Pinene	0.040	0.010	0.030	0.020
13	β-Pinene	0.050	0.060	0.090	0.040
14	Limonene	0.010	0.020	0.050	0.060
15	Carene	0.030	0.060	0.030	0.070
Alcohols					
16	Methanol	0.001	< 0.001	0.001	0.002
17	Ethanol	0.060	0.040	0.050	0.080
18	Isopropanol	0.009	0.004	0.003	0.010
19	Isopentanol	0.001	0.001	< 0.001	0.002
Organic acids					
20	Acetic	0.030	0.050	0.070	0.020
21	Propionic	0.008	0.003	0.002	0.006
22	Pentanoic	0.001	0.001	< 0.001	< 0.001
23	Hexanoic	0.001	< 0.001	< 0.001	0.002
Simple and mixed ethers					
24	Methyl acetate	< 0.001	0.004	0.002	< 0.001
25	Ethyl acetate	0.090	0.050	0.030	0.060
26	Propyl acetate	0.001	0.001	0.002	0.002
27	Ethyl propionate	< 0.001	0.001	< 0.001	< 0.001
28	Dibutyl phthalate	0.003	0.002	0.001	0.001

End of the Table 2

No.	Chemical	Concentration, mg/m^3			
		5-bed ward	4-bed ward	2-bed ward	1-bed ward
29	Dioctyl phthalate	0.001	< 0.001	< 0.001	0.001
30	Dioxane	0.003	0.002	0.001	0.002
31	Methyl methacrylate	0.001	0.001	< 0.001	0.001
Aldehydes and ketones					
32	Acetone	0.020	0.030	0.030	0.010
33	Methyl isobutyl ketone	0.001	0.002	0.001	0.003
34	Nonanal	0.001	< 0.001	0.002	< 0.001
35	Formaldehyde	0.004	0.006	0.008	0.003
36	Acetyl acetone	< 0.001	< 0.001	< 0.001	0.001
Terpene ketones					
37	Camphor	0.040	0.020	0.030	0.020
Halogenated organic compounds					
38	Dichloromethane	0.002	0.003	0.002	0.001
39	Chloroform	0.010	0.020	0.010	0.030
40	Tetrachloromethane	0.001	0.008	0.009	0.010
41	Dichloroethane	0.001	0.001	0.001	0.001
42	Tetrachloroethylene	0.003	0.002	0.004	0.003
43	Chlorobenzene	< 0.001	< 0.001	0.002	< 0.001
Total organic compound concentration		0.587	0.434	0.602	0.580

Obviously, the chromatographic-mass spectrometric investigations, which aimed to identify and quantify a wide range of chemical in environmental objects, established more than 40 volatile organic compounds in air inside in-patient hospitals with different functional purposes. These chemicals belonged to different groups including saturated, unsaturated, cyclic, and aromatic hydrocarbons; terpenes; alcohols; aldehydes; ethers; ketones; halogenated organic compounds; organic acids. Chemical air pollution inside premises with different functional purposes has different quantitative and qualitative structure and depends on presence or absence of internal pollution sources, in particular, use of technical or chemical cleaners, disinfectants or air conditioning as well as use of different technical devices for diagnostics or maintaining patients' vital activities.

Levels of ethanol, dichloromethane, tetrachloromethane, ethyl acetate, propyl acetate, acetone, terpene hydrocarbons, and acetic acids were shown to make the major contribution to the total concentrations of all identified organic compounds.

It is noteworthy that most identified chemicals were detected in concentrations not exceeding the existing hygiene standards. Chloroform and iodoform were the only exceptions with their levels being almost 2 times higher than the existing standards in the intensive care ward and the bronchoscopy ward.

At the same time, our attention was drawn to chemicals occurring in air in concentrations higher than their usual levels inside non-medical public buildings. Such chemicals include organic acids and chlorinated organic compounds. The highest chemical levels were established in air inside the intensive care ward and the bronchoscopy ward.

In addition to that, higher levels of ethanol, acetone, acetic acid and terpenes (α-pinene, β-pinene, limonene, and carene) were established in air inside patient wards. It is worth noting that we did not identify any significant differences in levels of chemical pollution in air between wards with different number of beds since their square and volume per one patient conformed to the existing regulations.

It is rather alerting that among the wide list of identified substances, hygienic standards have not been established for more than 70 % of compounds and therefore it is not possible to give a hygienic assessment of hazards or

safety of their presence in air inside healthcare facilities. In an effort to achieve that, as well as to perform comparative monitoring of chemical pollution in air inside wards with different functional purposes, we calculated the total volatile organic compound concentration covering all chemicals identified in air inside the examined premises.

Despite the fact that a total volatile organic compound concentration in air cannot fully describe health hazards posed by chemical contamination, it is still used quite often in present studies by many researchers both for comparative assessment and for assessment of total chemical pollution in indoor air [10–13]. It should also be noted that any information about identification of a wide range of organic compounds in air inside in-patient hospitals can be extremely useful at the hazard identification stage within analysis of health risks for healthcare workers and patients caused by chemical pollution in air inside in-patient hospitals.

In some countries, suggestions have been made to develop some regulations as regards a total volatile organic compound concentration in air inside premises not used for any production [14–17]. Thus, in Germany and Great Britain, a total volatile organic compound concentration in indoor air below 0.3 mg/m³ is considered safe in case hygiene standards are not violated for any of identified chemicals. This value is 0.5 mg/m³ in China; 0.4 mg/m³ in Japan; between 0.2 and 0.6 mg/m³ in Finland [18].

The total volatile organic compound concentrations established in air inside premises in in-patient hospitals with different functional purposes and patient wards (Tables 1 and 2) clearly show it is rather inadvisable to use this indicator to assess either health hazards or safety. At the same time, the said indicator can be effectively used to make comparative assessments of chemical pollution in air when it comes down to premises with the same functional purpose or to assess effectiveness and safety of cleaning, disinfecting or air- conditioning technologies applied inside a given premise.

Table 3 provides ranges of total volatile organic compound concentrations and levels of pother chemicals in air inside all examined premises in in-patient hospitals.

Obviously, the highest total volatile organic compound concentrations were established in air inside patient wards; the lowest ones, in surgery wards, treatment and dressing rooms.

Levels of mercury vapors were below the established safety standards in all examined premises and the chemical was identified only in trace quantities.

Levels of carbon dioxide and oxygen directly depended on a number of people in a room and time they spent inside it as well as on ventilation system functioning.

Monitoring of ozone levels in air inside in-patient hospitals revealed its levels to be 0.005–0.03 mg/m³ in summer, which is either equal or below its average daily maximum

Table 3

Ranges of identified chemical concentrations in indoor air inside in-patient hospitals

Indicator, concentration		Research objects				
		Patient wards	Surgery wards, treatment and dressing rooms	Diagnostic rooms and laboratories	Physio-therapeutic wards	Auxiliary rooms (nutrition units and corridors)
Total volatile organic compound concentration, mg/m³		0.43–1.67	0.27–0.46	0.36–1.42	0.35 – 0.88	0.38–1.45
Mercury vapors, mg/m³		< 0.00005	< 0.00003	< 0.00003	< 0.00004	< 0.00005
Ozone, mg/m³	summer	0.0–0.03	0.001–0.01	0.0–0.005	0.01–0.03	0.0–0.03
	winter	< 0.005	< 0.005	< 0.005	< 0.005	< 0.005
Carbon dioxide, pmm		400–1600	400–610	600–1200	500–800	450–710
Oxygen, %		20.6–20.8	20.8–21.4	19.0–20.1	20.0–20.9	20.8–21.0

permissible level in ambient air in residential areas (0.03 mg/m^3). In autumn and winter, when windows are usually closed, ozone was not identified in indoor air in in-patient hospitals.

Therefore, we established that air inside modern healthcare facilities tends to have a multi-component chemical structure, which is formed mostly depending on presence of internal pollution sources and their capacity. It is noteworthy that not only construction and finishing materials or human excretory products create chemical pollution in indoor air in healthcare organizations. A considerable contribution to it is also made by disinfectants, medications, and medical devices applied both to treat patients and to maintain proper quality of indoor air.

Thus, at present UV recirculator irradiators are widely used to disinfect air in healthcare facilities. However, when they work for a long time in premises where people are present, complaints are often made as regards some alien unpleasant smells [19–21].

Effects produced by UV recirculator irradiators manufactured by different companies and applied to disinfect air inside healthcare organizations were examined in an experiment with a chamber. Table 4 provides the results of these investigations including a wide range of identified chemicals and their levels in air inside the experimental chamber prior to and after treatment with UV irradiators.

Table 4

Chemical structure of air inside the chamber prior to after 3-hour treatment with different UV recirculator irradiators

No.	Chemical	RfC, mg/m^3	MPL*, mg/m^3	Concentration, mg/m^3			
				Background	No. 1	No. 2	No. 3
1	Ethanol	n/id	5.0	0.15	0.22	0.25	0.12
2	Acetone	31.0	0.35**	0.10	0.13	0.16	0.14
3	Isopropanol	0.2	0.6**	0.015	0.015	0.016	0.015
4	Pentane	1.0	25.0	0.01	0.01	0.01	0.011
5	Ethyl acetate	0.07	0.1	0.04	0.05	0.04	0.06
6	Benzene	0.005	0.1	0.010	0.020	0.015	0.010
7	Toluene	0.4	0.6	0.03	0.04	0.07	0.13
8	Hexanal	n/id	0.02**	0.015	0.020	0.020	0.060
9	Butyl acetate	n/id	0.1	0.012	0.012	0.012	0.010
10	Ethylbenzene	1.0	0.02	0.013	0.013	0.015	0.020
11	m,p-Xylenes	0.1	0.2	0.035	0.040	0.090	0.170
12	o-Xylene	0.1	0.2	0.032	0.045	0.060	0.120
13	Nonane	0.02	n/id	0.02	0.04	0.90	0.18
14	a-Pinene	n/id	0.3**	0.06	0.10	0.10	0.11
15	Methylpropyl cyclohexane	n/id	n/id	< 0.001	0.07	0.09	0.15
16	Decane	n/id	n/id	0.06	0.25	0.40	0.60
17	Undecane isomers	n/id	n/id	0.02	0.12	0.16	0.20
18	Methylbutyl cyclohexane	n/id	n/id	< 0.001	0.120	0.140	0.160
19	Undecane	n/id	n/id	0.07	0.40	0.30	0.65
20	Dodecane isomers	n/id	n/id	0.012	0.060	0.040	0.040
21	Pentyl cyclohexane	n/id	n/id	< 0.001	0.05	0.03	0.03
22	Dodecane	n/id	n/id	0.08	0.01	0.09	0.12
23	Styrene	1.0	0.002	< 0.001	< 0.001	0.002	< 0.001
24	Nitrogen oxide	0.06	0.06	0.015	0.017	0.020	0.015
25	Nitrogen dioxide	0.04	0.04	0.020	0.025	0.029	0.020
26	Carbon oxide	3.0	3.0	1.0	1.0	1.0	1.0
Total organic compound concentration				0.784	1.835	3.010	3.206

N o t e: RfC is maximum acceptable concentration below which no adverse health effects should result from long (chronic) exposure in most sensitive individuals; * means average daily maximum permissible level (MPL$_{av.d.}$) of pollutants in ambient air in residential areas (Sanitary Rules and Norms SanPiN 1.2.3685-21); ** means single maximum permissible level MPL$_s$ of pollutants in ambient air in residential areas (Sanitary Rules and Norms SanPiN 1.2.3685-21).

Obviously, work of each examined device resulted in occurrence of methylpropyl-, methylbutyl- and pentyl cyclohexanes, saturated acyclic hydrocarbons, in air in the examined premises. All these chemicals have not been identified in background air. By now, safety standards have been established only for one chemical in this group, namely cyclohexane. Its single maximum permissible level ($MPL_{s.}$) is 1.4 mg/m³ in air in residential areas. The chemical is of hazard class IV. It is noteworthy that saturated acyclic hydrocarbons can be found in oil and gases and are widely used as solvents in fuels.

In addition to that, work of UV irradiators creates higher levels of nonane (between 2 and 45 times), decane (up to 10 times), undecane (up to 10 times, xylenes (up to 4 times), toluene (more than 4 times), benzene (up to 2 times), hexanal (up to 4 times) and some other hydrocarbons in indoor air. We established that work of the device No. 2 created elevated styrene levels and the working irradiator No. 3 emitted toluene, xylenes and hexanal into indoor air. Work of UV irradiators was established to lead to a greater quantity of pollutants in indoor air as well as a growth in their total concentrations, which went up by between 2 and 4 and even more times. In particular, they grew by 2.3 times due to work of the device No 1; device No. 2, by 3.8 times; and device No. 3, by 4.1 times.

At the same time, tests aiming to identify levels of nitrogen oxides and ozone did not establish their emissions in indoor air due to work of all analyzed devices. After 3-hour use of the analyzed devices, levels of nitrogen oxides and ozone in indoor air were not higher than average daily MPL and did not differ from background concentrations.

Therefore, our study revealed higher levels of saturated and acyclic hydrocarbons (nonane, decane, undecame, and cyclohexanes) in indoor air due to work of UV recirculator irradiators of all three examined makes. Analysis of the study results makes it possible to assume that these identified chemicals occur in indoor air due to emission from materials, which device cases and some spare parts are made of; or, they occur in indoor air due to transformation of some pollutants under effects of UV radiation [22]. However, further chemical and analytical investigations are required to prove these assumptions.

Air inside healthcare facilities contains multiple chemicals and some of them are likely to transform under influence of working devices and technologies applied in healthcare organizations. Given that, we can make a statement that assessment of health risks posed by effects of chemical pollution on patients' health should involve monitoring that covers the entire range of chemicals coming from various pollution sources.

However, in contrast to microbiological monitoring, control of physical and chemical factors that affect patients and healthcare workers in in-patients hospitals is often accomplished with insufficient methodical support. This is due to absence of relevant regulatory and methodical documents aimed to provide methodical support for complex hygienic assessment of the indoor environment inside healthcare facilities considering the entire range of affecting factors.

In addition to that, another significant issue has not been resolved yet. It concerns absence of adequate hygienic assessments of hazards posed by multi-component chemical pollution in indoor air since there are no established hygiene / safety standards for more than a half of identified chemicals. Use of a total volatile organic compound concentration is eligible only for comparative assessments of chemical levels in premises with the same functional purposes. The ultimate goal is to perform adequate assessment of hazards or safety of air inside in-patient hospitals considering possible pollution created by internal sources (human excretory products, use of various technical means for air cleaning and disinfection, etc.). To achieve it, it is advisable to use the following algorithm of a chemical and analytical investigation: identification of a most comprehensive range of pollutants; selection of priority pollutants for monitoring; use of the risk analysis metho-

dology[4] [23–25]. The latter is especially important since health risk analysis is known to allow predicting and minimizing a growth in incidence among healthcare workers under occupational long-term exposure to chemicals in low doses, which can often be below MPLs[4] [24, 25].

We created a list of the chemicals with the greatest hygienic significance relying on our study results and considering the following criteria: a) frequency of occurrence in air inside in-patient hospitals; b) identified levels; c) likelihood of a chemical simultaneously coming from several sources. This list is relevant for analyzing health risks for healthcare workers and patients as well as for conducting chemical and analytical control of quality and safety of air inside healthcare facilities. It includes the following chemicals: formaldehyde, styrene, ethanol, isopropanol, chloroform, dichloroethane, acetic acid, as well as ammonia as one of the priority pollutants occurring in air from human excretory products [8, 9, 22]. The list covers chemicals from different chemical groups typical for major sources of chemical pollution in air inside healthcare facilities. Table 5 provides chemical groups, hazard classes and major pollution sources for each chemical selected for monitoring.

Air inside healthcare facilities contains multiple chemicals and some of them are likely to transform under influence of physical and chemical factors used in air cleaning, disinfection or air conditioning. Given that, assessment of health risks posed by effects of chemical pollution on patients' health should involve monitoring of possible changes in quality of the indoor environment under impacts of applied technologies and use of the risk analysis methodology.

Conclusions. We identified and quantified between 25 and 43 chemicals in air inside in-patient hospitals. They belonged to different chemical groups including saturated, unsaturated, cyclic, and aromatic hydrocarbons; terpenes, alcohols, aldehydes, esters, ketones, halogen-containing compounds, and organic acids. Quantitative and qualitative structures of air inside premises with different fictional purposes are different and depend on presence or absence of internal pollution sources, in particular, technical devices for air cleaning, disinfection or conditioning as well as use of various technical diagnostic devices.

Major contributions to the total chemical concentrations in air inside in-patient hospitals were made by ethanol, dichloromethane, tetrachloromethane, ethyl acetate, propyl acetate, acetone, terpenes, acetic acid, and dichloroethane.

Table 5

The list of priority chemical for monitoring and analysis of health risks for healthcare workers and patients in air inside in-patient hospitals

Chemical	Group	Hazard class	Major pollution sources
Formaldehyde	Aldehydes	2	Furniture, construction and finishing materials, disinfectants
Styrene	Aromatic hydrocarbons	2	Construction and finishing materials, cases of household appliances and medical devices
Ethanol	Alcohols	4	Treatment, disinfection including that off medical devices
Isopropanol	Alcohols	3	Household chemicals, room cleaning and disinfection, lacquers, paints
Chloroform	Chlorinated organic compounds	2	Disinfectants
Dichloroethane	Chlorinated organic compounds	2	Disinfectants
Acetic acid	Organic acids	3	Excretory products
Ammonia	Nitrogen-containing compounds	4	Excretory products, construction materials

[4] Dubel E.V. Gigienicheskaya otsenka faktorov riska zdorov'yu meditsinskikh rabotnikov krupnogo mnogoprofil'nogo statsionara [Hygienic assessment of risk factors for healthcare workers employed at a large multi-profile in-patient hospital]: Abstract of the thesis … for Candidate of Medical Sciences. Arkhangelsk, 2016, 25 p. (in Russian).

Organic acids and chlorinated organic compounds were found in elevated concentrations compared with insides of non-medical public buildings. The highest chemical levels in air inside in-patient hospitals were identified in patient wards and diagnostic rooms.

We have established in this study that chemical pollution in air inside healthcare facilities is multicomponent and hygiene or safety standards are not fixed for more than a half of the identified chemicals. Given that, we can conclude that hygienic assessment of hazards posed by chemical pollution in air inside healthcare facilities should rely on using the health risk assessment methodology, which makes it possible to assess hazards of exposure to chemicals both for healthcare workers and for oversensitive patients.

When accomplishing the first stage in assessing health risks for staff and patients as well as within risk-based control of chemical pollution in air inside in-patient hospitals, it is advisable to conduct monitoring of the established priority chemicals, in particular, formaldehyde, styrene, ethanol, isopropanol, chloroform, dichloroethane, and acetic acid as well as ammonia as one of the priority pollutants occurring in the environment from human excretory products.

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Research article

ASSESSMENT OF PUBLIC HEALTH RISKS CAUSED BY PHTHALATES MIGRATING FROM POLYMER MATERIAL TO BOTTLED WATER

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At present, consumption of packaged drinking water is growing worldwide. In this regard, ensuring packaged drinking water safety, which directly depends on the composition and quality of used polymer materials, is becoming especially relevant. Bottles made of polymer materials, i.e. polyethylene terephthalate and polycarbonate, is the most common packaging for drinking water.

The aim of this study was to assess population health risks caused by exposure to phthalates migrating from polymer bottles into drinking water.

The study was carried out according to the requirements of the Customs Union Technical Regulation… on packaging and Instruction... on sanitary-chemical study of goods. Bottles and model media were analyzed using gas chromatography with mass-spectrometric detection. Risk assessment was performed according to the current guidelines.

The study findings allow to report the following phthalate levels in bottle samples: di(2-ethylhexyl)phthalate (DEHP), 1.7–4.2 mg/kg; di-n-butyl phthalate (DnBP), <2.4–31.3 mg/kg; diisobutyl phthalate (DiBP), 2.2–10.2 mg/kg. Phthalate migration into model media occurred from all analyzed samples: DEHP and DiBP migrated from Polyethylene terephthalate in quantities equal to 8.6–71.0 µg/l and from < 2.6 to 19.2 µg/l respectively; DEHP, DnBP, and DiBP migrated from polycarbonate, 31.5–43.5 µg/l, 4.8–6.2 µg/l, and 17.0–54.0 µg/l, respectively.

The identified phthalate levels are safe according to the performed assessment of health risks associated with chronic intake of harmful substances with drinking water. The values of the estrogenicity equivalent calculated for the analyzed phthalates in model samples of bottled water were seen at a minimum level in Russian Federation as compared to other countries.

The results of this study can be used in safety assessment of polymer bottles for drinking water.

Keywords: *packaged drinking water, bottled water, model medium, phthalate migration, di(2-ethylhexyl) phthalate (DEHP), di-n-Butylphtalate (DnBP), diisobutylphthalate (DiBP), safety, health risk assessment.*

Packaged (bottled) water production has been growing steadily worldwide and the output reached $6.6 \cdot 10^{10}$ liters in 2020 [1]. People tend to think that bottled water is tastier than tapped one, more tolerable and safer as well [2]. However, some studies accomplished in several countries have reported organic compounds in bottled water; among such compounds, phthalates are given more and more attention due to their potential hazardous effects on human health [3–5]

Exposure to phthalates can cause some adverse health outcomes including endocrine disruptions, diseases of the nervous, cardiovascular, and reproductive systems [6, 7]. Di(2-ethylhexyl)phthalate (DEHP), di-n-butyl phthalate (DnBP), diisobutyl phthalate (DiBP), and benzyl butyl phthalate (BBP) are

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included into the SVHC list (Substances of Very High Concern) of the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), a European Union regulation. Certain limitations are imposed on their production and use considering their cumulative effects and co-exposure to all four phthalates [8, 9].

According to A. Pradhan et al. and V.R. Kay et al., DEHP and other phthalates produced negative effects on male and female reproductive systems in animal experiments and also on development of estrogen-sensitive tissues [10, 11]. Perinatal exposure to phthalates had certain adverse effects on animal offspring including stillbirth, increased prenatal fetus death rate, and congenital malformations including reproductive ones [12]. Phthalates are known to modulate gene expression, cell maturation, and apoptosis in mammal tissues due to their genomic, non-genomic and epigenetic mechanisms of action [13].

A study accomplished on a group of children with detected premature breast development revealed significantly high levels of phthalates and their metabolites in blood serum samples. The study results indicate a potential association between plasticizers with known estrogenic and anti-androgenic activity (dimethyl, diethyl, dibutyl and di-(2-ethylhexyl) phthalates) and the cause of premature breast development in a female population [14].

Upon oral exposure, phthalates are initially metabolized in the saliva and gastrointestinal tract into monoester metabolites. Importantly, toxicological effects of phthalates are caused by these monoester metabolites, not the original parent compounds. Several previous studies have detected phthalates in different human matrices, including urine, blood, breast milk, semen, ovarian follicular fluid, and saliva. In addition to that, phthalate metabolites have been found in maternal and cord blood, placenta tissues, and amniotic fluid [15].

Studies accomplished in the USA and Germany have identified a tentative daily exposure to phthalates within the following ranges: DEHP, between ~ 3 and 30 μg/kg/day; DnBP, between 0.84 and 5.22 μg/kg/day; and DiBP, between 0.12 and 1.4 μg/kg/day [16, 17].

Considering toxic effects of phthalates as well as population exposure to them, we can state it is necessary to assess their levels in bottled water as a source of their intake into the body.

Bottles made of polymer materials, i.e. polyethylene terephthalate (PET) and polycarbonate are the most common packages for drinking water [18].

These materials contain plasticizing additives, which are usually DEHP, DiBP, and DnBP. As a rule, phthalates do not form any strong bonds within a polymer and are easily released from ready-made goods [19].

Initial water, production processes and package materials can be potential sources of phthalates in bottled water [2]. However, a study identified significantly high levels of phthalates in materials plastic bottles were made of. Identified di-ethyl-hexyl phthalate levels were within 393–1499 mg/kg; levels of diethyl phthalate and dimethyl phthalates were 3.1 and 14.8 mg/kg respectively [20]. This indicates that package is the most likely source of phthalates in drinking water.

Some studies focused in identifying DEHP in bottled water; as a result, in 2012 13.9 % of 379 brands were established to fail to conform to the WHO recommendations (8 μg/l). Generalized results of studies accomplished all over the world have established frequency of five target phthalates in more than three hundred samples of bottled water from 21 countries, which is 67.6 % for dibutyl phthalate (DBP), 61.7 % for DEHP, 47.1 % for diethyl phthalate (DEP), 36.9 % for BBP, and 30.1 % for dimethyl phthalate (DMP). Maximum levels of these phthalates are 222.0; 94.1; 34.2; 109.0 and 61.3 μg/l respectively [21–23].

Therefore, the composition and quality of package polymer materials have direct influence on food safety. To protect population health, a relevant task is to study quality and safety of polymer packages that contact various food products, drinking water included.

The EU Commission Regulation on plastic materials and articles intended to come into contact with food[1] stipulates special standards for DEHP, BBP, and DBP, which regulate introduction of these components into food.

In the Russian Federation, requirements to safety of package drinking water[2] and package[3] do not cover these chemicals in the stipulated lists of sanitary-hygienic indicators.

The aim of this study was to assess population health risks caused by exposure to phthalates migrating from polymer package into drinking water.

Several tasks needed to be accomplished to reach it:

♦ Hazard identification. It was necessary to identify residual quantities of phthalates (DEHP, DnBP, and DiBP) in two package materials and determine levels of their migration for polyethylene terephthalate (PET) and polycarbonate (PC) produced in the RF by six manufacturers in conformity with the CU TR 005/2011[3];

♦ Assessment of health risks (carcinogenic and non-carcinogenic ones) for people who consume bottled drinking water every day;

♦ Assessment of potential estrogenic effects of phthalates due to bottled drinking water consumption based on toxicological examinations.

Materials and methods. To identify hazards, laboratory tests were planned and accomplished relaying on the requirements of the Customs Union Technical Regulations[3] and the Instruction on sanitary-chemical study of articles made of polymers and other synthetic materials[4].

Nine samples of polymer bottles for drinking water made of PETP and PC were examined within this study; they were all produced in the Russian Federation by six different manufacturers. Of them, seven were PETP bottles of 0.6, 6 and 19 liters in volume; the remaining two were PC bottles of 19 liters in volume. The samples were taken at production facilities and were new products ready to be filled with water. Twenty-seven samples of polymers (3 for each sample bottle) were prepared to laboratory tests.

Phthalate migration was estimated by simulating a contact between a medium (drinking water) and polymer materials. Polymer samples (4 × 5 cm, square of 40 cm^2) were submerged into the model medium (distilled water, pH = 7) and put into a thermostat for 30 days under 20 °C. Isotopic labeled analogues or analyte isomers were employed as internal standards: DBP-D4 to measure DBP and DiBP; DEHP-D4 to measure DEHP. They had been added to the model medium prior to the beginning of the experiment. Upon test completion, phthalates were extracted from the model medium by liquid-liquid extraction in hexane (5 cm^3). Analyte extracts were analyzed by gas chromatography-mass spectrome-

[1] Commission Regulation (EU) No 10/2011 of 14 January 2011 on plastic materials and articles intended to come into contact with food. *Official Journal of the European Union*. Available at: https://www.ctec.lv/userfiles/files/regulations%2010-2011-EU.pdf (July 13, 2023).

[2] TR EAES 044/2017. O bezopasnosti upakovannoi pit'evoi vody, vklyuchaya prirodnuyu mineral'nuyu vodu: Tekhnicheskii reglament Evraziiskogo ekonomicheskogo soyuza (s izmeneniyami na 5 oktyabrya 2021 goda), prinyat Resheniem Soveta Evraziiskoi ekonomicheskoi komissii ot 23 iyunya 2017 goda № 45 [EAEU TR 044/2017. On safety of packaged drinking water including natural mineral water: Technical Regulations of the Eurasian Economic Union (with alterations of October 5, 2021), approved by the decision of the Eurasian Economic Commission Council on June 23, 2017 No. 45]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/456090353 (July 13, 2023) (in Russian).

[3] TR TS 005/2011. O bezopasnosti upakovki: Tekhnicheskii reglament Tamozhennogo soyuza (s izmeneniyami na 18 oktyabrya 2016 goda), utv. Resheniem Komissii Tamozhennogo soyuza ot 16 avgusta 2011 goda № 769 [CU TR 005/2011. On safety of package: Customs Union Technical Regulations (with alterations of October 18, 2016), approved by the decision of the Customs Union Commission on August 16, 2011 No. 769]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/902299529 (July 13, 2023) (in Russian).

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try (GC-MS)[5] [23, 24]. Limit of quantification equaled 0.0040; 0.0026; 0.0026 mg/dm^3 for DEHP, DnBP, and DiBP respectively. Experiment data were statistically analyzed using Microsoft Excel 2010.

To quantify phthalates in a polymer, fragments were cut out of package samples, then ground and homogenized. The analyzed samples were put into retorts; internal standards and extracting agent (methanol) were added. Analytes were extracted by using an US-field under heating. Extracts were analyzed by GC-MS in selected ion registration mode. The LOQ equaled 0.56; 1.5; 1.5 mg/kg for DEHP, DnBP, and DiBP respectively[5].

Since levels of the quantified chemicals were statistically significantly not distributed normally, medians and interquartile range (25–75 percentiles) were used to describe the results and maximum and minimum values were calculated as well. Minimum and maximum values and median were calculated for to PC bottles (4 samples).

Calculation methods. Average daily intake of phthalates with drinking water was calculated for humans in conformity with the valid Guide Human Health Risk Assessment from Environmental Chemicals[6]. Variables in the formula are set in conformity with the recommended standard values of exposure factors stipulated in the Guide. Water consumption by children younger than 18 years was identified relying on the Methodical Guidelines on Physiological Needs of various population groups[7] which stipulates 1.5–1.6 liters for boys and 1.4–1.5 liters for girls (aged 14–17 years).

Average daily intake was calculated for children younger than 6 years (body mass is 15 kg, water consumption is 1 l/day), for children aged between 6 and 18 years (body mass is 42 kg, water consumption is 1.5 l/day) and for adults (body mass is 70 kg, water consumption is 2 l/day). Exposure frequency was 350 days/year.

To comparatively analyze estrogenic potential, the estrogenicity equivalent (*EEQ*) was calculated and the results were compared with those provided in other studies [9]:

$$EEQ = \Sigma EP_i \cdot C,$$

where *EP* is an estrogenic potential of a specific phthalate identified in vitro; *C* is a level of a specific phthalate.

Estrogenic activity of 17b-estradiol (E2) is established to equal 1 [22]. In case a compound has stronger estrogenic activity than (E2), its *EP* value is above 1; in case its estrogenic activity is weaker, below 1.

Results and discussion. Residual phthalate quantities were identified in all samples of polymer package. Phthalate levels were within a wide range: DEHP, 1.7–4.2 mg/kg; DnBP, < 2.4–31.3 mg/kg; DiBP, 2.2–10.2 mg/kg. It is worth noting that DnBP was identified only in three samples out of nine. The experiment results are provided in Tables 1 and 2. Based on the experiment data, phthalate levels (medians) were distributed as follows from high to low in PET package: DiBP > DEHP > DnBP; in PC package: DEHO > DiBP > DnBP.

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[5] Zaritskaya E.V., Eremin G.B., Markova O.L., Ganichev P.A., Myasnikov I.O. Rezul'taty laboratornykh issledovanii soderzhaniya di(2-etilgeksil)ftalata, di(n-butil)ftalata, di(izobutil)ftalata i bisfenola A v tare iz polietilentereftalata i polikarbonata i ikh migratsii v model'nye sredy pri razlichnykh usloviyakh khraneniya butilirovannoi vody [The results of laboratory tests on quantification of di(2-ethylhexyl)phthalate, di(n-butyl)phthalate, di(isobutyl)phthalate and bisphenol A in package made of polyethylene terephthalate (PETP) and polycarbonate (PC) and their migration into model media under different conditions of bottled water storage]: database, the Certificate of Database Registration: 2020622808 dated December 24, 2020, application No. 2020622554 dated December 08, 2020 (in Russian).

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Table 1

Phthalate levels in package material (PET) and model medium (distilled water)

Indicator	Research object, level	*Min*	*Max*	*Me*	Q_{25}–Q_{75}
DEHP CAS 117-81-7	Package, mg/kg	1.7	2.8	2.4	2.2–2.5
	Water, μg/l	8.6	71.0	14.5	13.0–18.8
DnBP CAS 84-74-2	Package, mg/kg	< 2.4	31.3	1.2	3.5–10.2
	Water, μg/l	< 2.6	< 2.6	< 2.6	–
DiBP CAS 84-69-5	Package, mg/kg	3.5	10.2	5.6	3.4–6.4
	Water, μg/l	< 2.6	19.2	9.3	5.6–11.0

Table 2

Phthalate levels in package material (PC) and model medium (distilled water)

Indicator	Research object, level	*Min*	*Max*	*Me*
DEHP CAS 117-81-7	Package, mg/kg	3.4	4.2	3.8
	Water, μg/l	31.5	43.5	37.5
DnBP CAS 84-74-2	Package, mg/kg	< 2.4	2.4	1.8
	Water, μg/l	4.8	6.2	4.8
DiBP CAS 84-69-5	Package, mg/kg	2.2	4.6	3.4
	Water, μg/l	17.0	54.0	18.0

Phthalates were detected in all water extracts that contacted PET. DEHP levels were within 8.6–71.0 μg/l range; DiBP, between < 2.6 and 19.2 μg/l. DnBP was not identified.

Three phthalates were identified in analyzed samples of model media that contacted PC. However, maximum levels were detected for DEHP and DiBP, respectively 31.5–43.5 μg/l; 17.0–54.0 μg/l. DnBP levels were within 4.8–6.2 μg/l range.

Migration of two phthalates, namely DEHP and DiBP, occurs from both analyzed polymer materials judging by these experimental results; it is worth noting that phthalate migration was much faster from PC than PET as evidenced by estimated total contents of phthalates.

Phthalate occurrence in a material and in water medium means it is quite possible for polymer package components to migrate from polymer package into drinking water. Therefore, it is necessary to assess potential effects on health of people who consume packaged drinking water.

Health risks were assessed based on the obtained experimental data. We calculated daily intake, chronic carcinogenic and non-carcinogenic risks caused by consuming dirking water in package made of PET and PC. The results are provided in Tables 3 and 4.

Levels of non-carcinogenic risks caused by consuming drinking water from bottles made of PET and PC are ranked as permissible for all age groups; the highest HQ values were identified for children younger than 6 years. Levels of carcinogenic risk fall within the second risk range, which means risk is permissible. Such levels do not require any activities aimed at risk mitigation and are only subject to permanent control. The highest risk levels were identified for consumption of drinking water in PC package.

Similar studies were accomplished in China with their aim to identify phthalates in packaged drinking water and to assess health risks. The highest levels were typical for such phthalates as DEHP, DnBP, and DiBP. Their levels were identified within a range from the limit of detection to 0.041 mg/l (DEHP), 0.016 mg/l (DiBP), and 0.0049 mg/l (DnBP). Assessed health risks were ranked as permissible considering their mean values [25].

The estrogenicity equivalent was calculated in order to compare likely estrogenic effects caused by consuming packaged drinking water (Table 5).

Table 3

Health risk assessment for consumption of bottled drinking water packaged in PET

CAS	Phtha-late	*C*	*RfD*	*SFo*	*I* younger than 6 years	*I* aged 6–18 years	*I* adults	*HQ* younger than 6 years	*HQ* aged 6–18 years	*HQ* adults	*CR*
117-81-7	DEHP	0.0145	0.02	0.014	9.27E-04	4.97E-04	3.97E-04	4.63E-02	2.48E-02	1.99E-02	5.56E-06
84-74-2	DnBP	0.0013	0.1	-	8.31E-05	4.45E-05	3.56E-05	8.31E-04	4.45E-04	3.56E-04	-
84-69-5	DiBP	0.0093	-	-	5.95E-04	3.18E-04	2.55E-04	-	-	-	-

Table 4

Health risk assessment for consumption of bottled drinking water packaged in PC

CAS	Phtha-late	*C*	*RfD*	*SFo*	*I* younger than 6 years	*I* aged 6–18 years	*I* adults	*HQ* younger than 6 years	*HQ* aged 6–18 years	*HQ* adults	*CR*
117-81-7	DEHP	0.0375	0.02	0.014	2.40E-03	1.28E-03	1.03E-03	1.20E-01	6.42E-02	5.14E-02	3.36E-05
84-74-2	DnBP	0.00475	0.1	-	3.04E-04	1.63E-04	1.30E-04	3.04E-03	1.63E-03	1.30E-03	
84-69-5	DiBP	0.018	-	-	1.15E-03	6.16E-04	4.93E-04	-	-	-	

Table 5

The estrogenicity equivalent calculation

Country	Phthalates	Rank among countries	Average level (µg/l)	Estrogenic potential	Estrogenicity equivalent
Thailand	DEHP	2	61.1	3.00E-07	0.018
	DBP		31.8	4.10E-05	1.304
	Total phthalates				1.322
Saudi Arabia	DEHP	4	6.2	3.00E-07	0.002
	DBP		3.1	4.10E-05	0.127
	Total phthalates				0.129
Mexico	DEHP	1	-	3.00E-07	-
	DBP		45.1	4.10E-05	1.849
	Total phthalates				1.849
Pakistan	DEHP	3	3.8	3.00E-07	0.001
	DBP		17.8	4.10E-05	0.730
	Total phthalates				0.731
Russian Federation (PETP)	DEHP	6	14.5	3.00E-07	4.35E-06
	DBP		1.3	4.10E-05	5.33E-05
	Total phthalates				5.77E-05
Russian Federation (PC)	DEHP	5	37.5	3.00E-07	1.13E-05
	DBP		4.8	4.10E-05	1.95E-04
	Total phthalates				2.06E-04

The lowest possible ranks of the estrogenicity equivalent in packaged drinking water (5 and 6) were calculated for the Russian Federation among all countries where similar studies were accomplished. Nevertheless, some authors report levels of phthalates in packaged drinking water that can still have adverse estrogenic effects. This calls for further systemic studies of bottled water safety related to phthalates.

Attention should also be paid to the fact that the data in our experiments were obtained for 30-day exposure under 20 °C; quality of most packaged drinking water is guaranteed for a period up to 24 months and this may require additional long-term experiments on phthalates migration.

Conclusions. The results of hazard identification allowed estimating levels of target phthalates in a limited sample of two polymer materials and their migration into drinking water.

The study established that daily intake of drinking water packaged in up-to-date polymer bottles did not created impermissible health risks due to exposure to phthalates. The highest HQ values were obtained for children younger by 6 years due to exposure to DEHP migrating from PET samples where they equaled 4.63E-02 and for PC samples where they equaled 1.20E-01. Both values corresponded to permissible risk levels. Identified carcinogenic risks reached their maximum permissible levels ($1 \cdot 10^{-4}$–$1 \cdot 10^{-6}$): they equaled 5.56E-06 for PET samples and 3.36E-05 for PC samples.

The results of this study can be used in estimating safety of new polymer packages for drinking water.

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Research article

CLUSTER APPROACH TO THE STUDY OF POPULATION HEALTH RISKS POSED BY CONTAMINATION OF FOOD PRODUCTS WITH HEAVY METALS

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Food products are a source of energy and essential substances but also of anthropogenic contaminants such as heavy metals. The aim of the study was to assess population health risks posed by contamination of food products with heavy metals, taking into account peculiarities of food preferences. An epidemiological study of actual nutrition of adult population of Samara region was conducted, the sample size was 1,856 people.

At the first stage, using factor analysis, respondents' adherence to a certain model of food preferences was established; at the second stage, 5 homogeneous groups (clusters) of people with similar types of nutrition were formed using cluster analysis. The first cluster included individuals with maximum commitment to a high level of consumption of all studied foods; the second cluster was characterized by commitment to consumption of high-calorie foods such as baked goods, confectionery, sausages, potatoes, eggs, and cheese. Individuals from the cluster 3 showed a distinct preference for consumption of vegetables, fruit and dairy products. Individuals from the cluster 4 had no special preferences for any of the studied foods. The fifth cluster included people who had maximum preference for meat and meat products, smoked meats, pickles and salted fish. The content of cadmium, mercury, lead, and arsenic in food products was assessed via atomic absorption and photometric methods. The study relied on using social and hygienic monitoring data from the Samara Regional Rospotrebnadzor (Federal Service for Surveillance on Consumer Rights and Human Wellbeing) collection. Risk assessment of carcinogenic and non-carcinogenic effects was carried out in each of the five formed clusters taking into account modern methodological approaches.

It was found that in all food clusters, the hazard coefficients for intake of contaminants in median concentrations and in the 90th percentile did not exceed permissible levels. In all clusters, the endocrine system was most at risk (HI = 1.68 ÷ 1.25). For all clusters, carcinogenic risk (for median concentrations) was created by arsenic both at the individual and the population level. The risk was the highest for people whose diets were characterized by high levels of consumption of high-calorie products. Cluster approach makes it possible to identify the most vulnerable groups of population in terms of risk burden for making managerial decisions and carrying out preventive measures.

Keywords: *contamination, heavy metals, cluster analysis, public health risks, actual nutrition, food preferences, carcinogenic risk, non-carcinogenic risk.*

Nutrition has a significant impact on human health. Nutritional factor can have both positive and negative effects on the body, as, on the one hand, food is a source of essential substances, but on the other hand, foreign components such as xenobiotics found in food products can negatively affect humans. Since each individual has certain food preferences, expressed quantitatively and qualitatively in consumption of various foods, the amount of foreign components consumed with food will differ for various groups. Heavy metals are recognized as one of the most dangerous xenobiotics for humans. Contamination of food with heavy metals is a global problem for human health [1], since they are non-biodegradable pollutants that tend to accumulate and can be transferred to soil [2]. Heavy metals are found in all ecosystems; while their natural concentrations vary depending on local geology, human economic activity leads to the accumulation of heavy metals in significant concentrations in the environment [3]. A number of heavy metals, including nickel, iron, magnesium, copper and zinc, in food products in low concentrations are vital for the most important human biological functions, in particular, for metabolic processes (cytochro-

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me and enzyme functions) [4, 5]. Other elements, including lead, cadmium, mercury, arsenic and aluminum, have a toxic effect on the body even in low concentrations, while having no significant biological value for humans, and are classified as insignificant for metabolic and biological functions [6–8].

Adverse effect of heavy metals is due to acute or chronic toxic effect on the main metabolic processes. Accumulation of heavy metals in organs and systems interferes with antioxidant protection thereby increasing risks of oxidative stress [9]. Exposure to heavy metals creates elevated risks of developing malignant neoplasms, reproductive disorders, diseases of the cardiovascular, endocrine and nervous systems [10].

According to WHO, as of 1 June, 2020, arsenic, cadmium, lead and mercury are among the 10 chemicals causing serious public health concern [11]. Although these elements are known to be toxic, their diverse technological, medical and agricultural applications still pose a huge threat to human health.

National studies assessing the risk posed by food contamination mainly use data provided by the Federal State Statistics Service on the average annual per capita consumption of the main food groups [12–14]. On the one hand, this approach simplifies risk assessment procedures and does not require special epidemiological studies of the population's nutrition. On the other hand, in this case we obtain averaged risk indicators without taking into account peculiarities of food preferences in different population groups. Nevertheless, there are studies in literature concerning risk assessment based on actual nutrition data obtained via methods of 24-hour (daily) diet reproduction and frequency assessment of a diet. They provide a more accurate risk assessment, which is necessary for managerial decisions and preventive measures [15]. In addition, calculation of exposure to contaminants in accordance with current recommendations in the Russian Federation is based on the standard body weight of 70 kg; similarly, average body weight in a surveyed group is applied in international research. In particular, based on the latest statistical data provided by the National Health Commission of the People's Republic of China in 2020, the average body weight for adult men and women was 69.6 and 59 kg respectively and this value was taken into account when calculating non-carcinogenic and carcinogenic risks. Meanwhile, using individual body weight values in calculations makes it possible to increase the accuracy of determining the level of risk [16].

Therefore, at present, it is relevant to solve a hygienic problem of assessing risks for population health posed by food contamination with heavy metals, taking into account use of epidemiological methods based on an individual assessment of diet structure. This will ultimately allow obtaining the most accurate risk assessment and making management decisions to reduce the level of risk in various population groups while taking into account individual food preferences.

The goal of the study is to assess population health risk posed by contamination of food products with heavy metals, based on a cluster analysis of actual nutrition.

Materials and methods. The object of this study is adult working age population permanently residing on the territory of the Samara region (n = 1856 people), including employees of regional enterprises of fuel and energy production, automotive industry, food production, healthcare, education, agriculture and office workers. To analyze actual nutrition, questionnaires were compiled based on frequency assessment of diets, taking into account consumption of various food groups and portion sizes over the past month. Photos of food were used for clarity.

At the first stage of assessment of actual nutrition, adherence to a certain model of food preference was established by using factor analysis; nutrition models included foods with a factor value of over 0.3. At the second stage, people with similar food preferences were combined into clusters (allocation of homogeneous groups using McKean k-means clustering, Ward's dendrogram method, Euclidean distance, and variance analysis). Average values of adherence to nutrition models ($M \pm SD$) were

obtained during the analysis of dendrograms (Ward method, clustering, and Euclidean distance). Based on variance analysis of the formed food clusters, highly significant differences in average adherence ($p < 0.001$) were obtained for each nutrition model. Negative values of adherence indicated a low level of food consumption in a particular diet model; positive values indicated a high level of food consumption. Formation of a specific cluster was based on the highest values of adherence to food consumption (nutrition models) with a factor value of over 0.3. Based on obtained data, diets with homogeneous food preferences were systematized using Nutri-prof custom software package (version 2.9). This made it possible to assess consumption of the main food groups in each of the five nutrition clusters [17]. Next, carcinogenic and non-carcinogenic risks associated with the intake of heavy metals with food were assessed for each of the five food clusters. Contamination of food products with heavy metals consumed by the population was assessed based on cadmium, mercury, lead, and arsenic levels. Food products were represented by the following groups: bread and bread products, vegetable oil and other fats, milk and dairy products, meat and meat products, eggs, fish and fish products, sugar and confectionery, fruit and berries, vegetables and gourds, potatoes. The analysis involved using social and hygienic monitoring data provided by the Samara Regional Rospotrebnadzor Office; overall, we analyzed 82,354 results of sample testing collected over 12 years. When calculating exposure, median values of contaminant concentration were taken into account; the 90th percentile was used for maximum values taking into account average body weight value calculated in each particular cluster based on the body weight data provided by the respondents. Risks of carcinogenic and non-carcinogenic effect were assessed in accordance with MU 2.3.7.2519-09 'Determining exposure and risk assessment of the effect of chemical contaminants in food products on the population'[1] and R 2.1.10.1920-04 'Human Health Risk Assessment from Environmental Chemicals'[2]. Non-carcinogenic risk (HQ) of exposure to a contaminant was calculated, taking into account exposure and the reference (safe) level of exposure, as well as the total hazard index (HI) for combined exposure to contaminants with unidirectional effect. Average daily doses of a contaminant over a lifetime and the slope factor were taken into account to calculate individual and population carcinogenic risks. Statistical analysis was carried out using SPSS 25 software.

Results and discussion. During the assessment of actual nutrition of the population, patterns were found indicating a similar nature of food preferences among surveyed individuals. At the first stage of statistical data processing, 5 nutrition models were formed by factor analysis taking into account food preferences for various foods with a factor over 0.3. Nutrition model No. 1 was characterized by a variety of products of plant and animal origin and did not have a clear focus. Nutrition model No. 2 was characterized by excessive consumption of high-calorie foods (baked goods, pasta, potatoes, confectionery, oil and butter, sausages, and cheese). Nutrition model No. 3 was characterized by high factor in terms of preference for food products of plant origin (vegetables, fruit, and nuts). The bases of nutrition model No. 4 were dairy products, fish and eggs. Nutrition model No. 5 was characterized by a meat-salt focus due to significant consumption of meat products, including sausages, smoked meats, salted fish, and pickled vegetables. Since each person adhered to the obtained nutrition model to a certain extent, a cluster method was used at the second stage, which allowed to form homogeneous groups of individuals (selection of

[1] MU 2.3.7.2519-09. Opredelenie ekspozitsii i otsenka riska vozdeistviya khimicheskikh kontaminantov pishchevykh produktov na naselenie [Determining exposure and risk assessment of the effect of chemical contaminants in food products on the population]: methodological guidelines. Moscow, Federal Center for Hygiene and Epidemiology of Rospotrebnadzor, 2010, 27 p. (in Russian).

[2] R 2.1.10.1920-04. Human Health Risk Assessment from Environmental Chemicals. Moscow, Federal Center for State Sanitary and Epidemiological Surveillance of the Ministry of Health of the Russian Federation, 2004, 143 p. (in Russian).

homogeneous groups was carried out by the McKean *k*-means method); then, a preliminary analysis of dendrograms was carried out and average values of adherence to nutrition models ($M \pm SD$) were obtained. Based on the variance analysis of the formed food clusters, highly significant differences in average adherence ($p < 0.001$) were obtained for each nutrition model.

The same maximum adherence to all five nutrition models with a high level of consumption of all studied foods was noted for individuals in the first cluster. Individuals in the second cluster were characterized by high commitment to consumption of high-calorie products such as baked goods, potatoes, confectionery, sausages, eggs, and cheese (model No. 2). For individuals from the cluster 3, there was a distinct preference for vegetables and fruit, as well as dairy products (models No. 3 and 4). Individuals from the cluster 4, unlike those from the cluster 1, adhered to all dietary patterns, but with a low level of consumption for all studied foods. The fifth cluster was made up of people with maximum preferences for the consumption of meat and meat products, smoked meats, pickled foods, and salted fish (model No. 5).

Using custom software package 'Nutriprof' (version 2.9), data on consumption of the main food groups were obtained for each food cluster (Table 2).

For subsequent assessment of exposure and the hazard coefficient, we used data on the content of heavy metals in the main groups of food products median concentration (*Me*) and the 90th percentile concentration (Table 3).

Exposure and hazard index values with various intake methods for median values (*Me*) of contaminant concentration and the 90th percentile were calculated for all four analyzed heavy metals in each group of people with similar food preferences (Table 4).

Table 1

Parameters of individuals' adherence to certain nutrition models ($M \pm SD$)

Model of nutrition	Cluster 1	Cluster 2	Cluster 3	Cluster 4	Cluster 5	*P*
No. 1	1.43 ± 1.73	-0.18 ± 1.21	0.86 ± 1.54	-0.28 ± 0.51	0.28 ± 1.21	<0.001
No. 2	2.19 ± 1.57	1.54 ± 0.73	-0.78 ± 0.81	-0.37 ± 0.42	-0.19 ± 0.86	<0.001
No. 3	1.72 ± 1.55	-0.08 ± 1.23	1.69 ± 1.48	-0.27 ± 0.44	-0.23 ± 0.79	<0.001
No. 4	1.62 ± 1.88	-0.25 ± 1.23	0.67 ± 1.53	-0.17 ± 0.52	0.25 ± 1.27	<0.001
No. 5	1.58 ± 2.83	-0.21 ± 0.79	-0.59 ± 0.77	-0.24 ± 0.39	1.54 ± 0.76	<0.001

Table 2

Median values of consumption of the main food groups depending on a cluster (g/day)

Food group	Cluster				
	1	2	3	4	5
Bread and bread products	243.3	253.2	173.4	137.3	231.8
Vegetable oil and other fats	47.7	50.1	34.5	28.8	51.0
Milk and dairy products	130.4	133.4	140.0	129.3	132.1
Meat and meat products	143.6	152.3	80.5	77.0	170.7
Eggs	22.7	19.7	17.5	19.7	26.0
Fish and fish products	17.5	18.9	14.2	18.6	23.8
Sugar and confectionery	50.4	63.3	39.7	43.0	42.2
Fruit and berries	114.0	105.8	149.9	126.8	101.9
Vegetables and gourds	151.0	144.9	186.8	138.1	141.6
Potatoes	76.2	85.5	92.3	72.9	81.6

Table 3

Heavy metals content (mg/kg) for food groups

Food group	Cadmium		Mercury		Lead		Arsenic	
	Me	90	*Me*	90	*Me*	90	*Me*	90
Bread and bread products	0.011	0.0258	0.0033	0.0112	0.0474	0.158	0.006	0.0087
Vegetable oil and other fats	0.0087	0.0232	0.0034	0.00776	0.0223	0.0737	0.0040	0.0068
Milk and dairy products	0.0134	0.0155	0.0017	0.0031	0.0362	0.0655	0.0074	0.0084
Meat and meat products	0.0073	0.0264	0.0052	0.01277	0.0441	0.111	0.0041	0.0048
Eggs	0.0037	0.0042	0.0034	0.00461	0.0248	0.056	0.008	0.0094
Fish and fish products	0.0122	0.0364	0.0162	0.04733	0.0749	0.2552	0.005	0.0092
Sugar and confectionery	0.0124	0.0262	0.0041	0.01769	0.0312	0.1047	0.0061	0.0069
Fruits and berries	0.0112	0.0114	0.0023	0.00561	0.0256	0.0712	0.005	0.0092
Vegetables and gourds	0.0056	0.0158	0.0022	0.00913	0.0361	0.133	0.002	0.0077
Potatoes	0.0055	0.0073	0.0018	0.0088	0.0605	0.1273	0.006	0.0081

Table 4

Exposure values (mg/kg) and hazard coefficients, taking into account food preferences and various methods of contaminant intake

Food group	Cluster									
	1		2		3		4		5	
	Exp *Me*	Exp 90	Exp *Me*	Exp 90	Exp *Me*	Exp 90	Exp *Me*	Exp 90	Exp *Me*	Exp 90
Cadmium										
Bread and bread products	3.08E-05	7.21E-05	3.20E-05	7.51E-05	2.20E-05	5.15E-05	1.74E-05	4.07E-05	2.93E-05	6.87E-05
Vegetable oil and other fats	4.77E-06	1.27E-05	5.01E-06	1.34E-05	3.45E-06	9.21E-06	2.90E-06	7.74E-06	5.07E-06	1.35E-05
Milk and dairy products	2.01E-05	2.32E-05	2.06E-05	2.38E-05	2.16E-05	2.49E-05	1.99E-05	2.30E-05	2.03E-05	2.35E-05
Meat and meat products	1.20E-05	4.36E-05	1.27E-05	4.61E-05	6.76E-06	2.44E-05	6.76E-06	2.44E-05	1.43E-05	5.18E-05
Eggs	9.67E-07	1.10E-06	8.39E-07	9.52E-07	7.46E-07	8.46E-07	8.39E-07	9.52E-07	1.11E-06	1.26E-06
Fish and fish products	2.46E-06	7.34E-06	2.65E-06	7.91E-06	2.00E-06	5.96E-06	2.61E-06	7.79E-06	3.34E-06	9.97E-06
Sugar and confectionery	7.19E-06	1.52E-05	9.02E-06	1.91E-05	5.70E-06	1.20E-05	6.13E-06	1.30E-05	6.01E-06	1.27E-05
Fruit and berries	1.47E-05	1.49E-05	1.36E-05	1.39E-05	1.93E-05	1.96E-05	1.63E-05	1.66E-05	1.31E-05	1.34E-05
Vegetables and gourds	9.72E-06	2.74E-05	9.33E-06	2.63E-05	1.20E-05	3.39E-05	8.89E-06	2.51E-05	9.12E-06	2.57E-05
Potatoes	4.81E-06	6.39E-06	5.40E-06	7.17E-06	5.84E-06	7.75E-06	4.61E-06	6.11E-06	5.16E-06	6.85E-06
HQ	0.22	0.45	0.22	0.46	0.19	0.38	0.17	0.33	0.21	0.45
Mercury										
Bread and bread products	1.04E-05	3.54E-05	1.08E-05	3.68E-05	7.44E-06	2.53E-05	5.88E-06	2.00E-05	9.93E-06	3.37E-05
Vegetable oil and other fats	2.10E-06	4.80E-06	2.21E-06	5.05E-06	1.52E-06	3.48E-06	1.28E-06	2.93E-06	2.24E-06	5.11E-06
Milk and dairy products	2.88E-06	5.25E-06	2.95E-06	5.37E-06	3.09E-06	5.64E-06	2.86E-06	5.21E-06	2.92E-06	5.32E-06
Meat and meat products	9.70E-06	2.38E-05	1.03E-05	2.52E-05	5.44E-06	1.34E-05	5.44E-06	1.34E-05	1.15E-05	2.83E-05

End of the Table 4

Food group	Cluster									
	1		2		3		4		5	
	Exp *Me*	Exp 90	Exp *Me*	Exp 90	Exp *Me*	Exp 90	Exp *Me*	Exp 90	Exp *Me*	Exp 90
Eggs	1.00E-06	1.36E-06	8.71E-07	1.18E-06	7.74E-07	1.05E-06	8.71E-07	1.18E-06	1.15E-06	1.56E-06
Fish and fish products	3.69E-06	1.08E-05	3.98E-06	1.16E-05	3.00E-06	8.76E-06	3.92E-06	1.15E-05	5.01E-06	1.47E-05
Sugar and confectionery	2.68E-06	1.16E-05	3.37E-06	1.45E-05	2.13E-06	9.19E-06	2.29E-06	9.88E-06	2.25E-06	9.69E-06
Fruit and berries	3.40E-06	8.30E-06	3.16E-06	7.70E-06	4.48E-06	1.09E-05	3.79E-06	9.24E-06	3.04E-06	7.43E-06
Vegetables and gourds	4.31E-06	1.79E-05	4.14E-06	1.72E-05	5.34E-06	2.22E-05	3.95E-06	1.64E-05	4.05E-06	1.68E-05
Potatoes	1.78E-06	8.70E-06	2.00E-06	9.77E-06	2.16E-06	1.06E-05	1.70E-06	8.33E-06	1.91E-06	9.33E-06
HQ	0.14	0.42	0.14	0.44	0.11	0.36	0.1	0.32	0.14	0.44
Lead										
Bread and bread products	1.04E-05	3.54E-05	1.08E-05	3.68E-05	7.44E-06	2.53E-05	5.88E-06	2.00E-05	9.93E-06	3.37E-05
Vegetable oil and other fats	2.10E-06	4.80E-06	2.21E-06	5.05E-06	1.52E-06	3.48E-06	1.28E-06	2.93E-06	2.24E-06	5.11E-06
Milk and dairy products	2.88E-06	5.25E-06	2.95E-06	5.37E-06	3.09E-06	5.64E-06	2.86E-06	5.21E-06	2.92E-06	5.32E-06
Meat and meat products	9.70E-06	2.38E-05	1.03E-05	2.52E-05	5.44E-06	1.34E-05	5.44E-06	1.34E-05	1.15E-05	2.83E-05
Eggs	1.00E-06	1.36E-06	8.71E-07	1.18E-06	7.74E-07	1.05E-06	8.71E-07	1.18E-06	1.15E-06	1.56E-06
Fish and fish products	3.69E-06	1.08E-05	3.98E-06	1.16E-05	3.00E-06	8.76E-06	3.92E-06	1.15E-05	5.01E-06	1.47E-05
Sugar and confectionery	2.68E-06	1.16E-05	3.37E-06	1.45E-05	2.13E-06	9.19E-06	2.29E-06	9.88E-06	2.25E-06	9.69E-06
Fruit and berries	3.40E-06	8.30E-06	3.16E-06	7.70E-06	4.48E-06	1.09E-05	3.79E-06	9.24E-06	3.04E-06	7.43E-06
Vegetables and gourds	4.31E-06	1.79E-05	4.14E-06	1.72E-05	5.34E-06	2.22E-05	3.95E-06	1.64E-05	4.05E-06	1.68E-05
Potatoes	1.78E-06	8.70E-06	2.00E-06	9.77E-06	2.16E-06	1.06E-05	1.70E-06	8.33E-06	1.91E-06	9.33E-06
HQ	0.15	0.42	0.15	0.44	0.13	0.38	0.11	0.33	0.15	0.43
Arsenic										
Bread and bread products	1.90E-05	2.75E-05	1.97E-05	2.86E-05	1.35E-05	1.96E-05	1.07E-05	1.55E-05	1.81E-05	2.62E-05
Vegetable oil and other fats	2.48E-06	4.21E-06	2.60E-06	4.43E-06	1.79E-06	3.05E-06	1.51E-06	2.56E-06	2.63E-06	4.48E-06
Milk and dairy products	1.25E-05	1.42E-05	1.28E-05	1.46E-05	1.35E-05	1.53E-05	1.24E-05	1.41E-05	1.27E-05	1.44E-05
Meat and meat products	7.64E-06	8.20E-06	8.08E-06	8.67E-06	4.29E-06	4.60E-06	4.29E-06	4.60E-06	9.09E-06	9.75E-06
Eggs	2.36E-06	2.66E-06	2.05E-06	2.31E-06	1.82E-06	2.05E-06	2.05E-06	2.31E-06	2.70E-06	3.04E-06
Fish and fish products	1.14E-06	2.05E-06	1.23E-06	2.21E-06	9.25E-07	1.67E-06	1.21E-06	2.18E-06	1.55E-06	2.79E-06
Sugar and confectionery	4.19E-06	4.52E-06	5.26E-06	5.67E-06	3.32E-06	3.58E-06	3.58E-06	3.85E-06	3.51E-06	3.78E-06
Fruit and berries	7.40E-06	1.33E-05	6.87E-06	1.24E-05	9.73E-06	1.75E-05	8.24E-06	1.48E-05	6.62E-06	1.19E-05
Vegetables and gourds	3.92E-06	1.51E-05	3.76E-06	1.45E-05	4.85E-06	1.87E-05	3.59E-06	1.38E-05	3.68E-06	1.42E-05
Potatoes	5.93E-06	7.91E-06	6.66E-06	8.88E-06	7.19E-06	9.59E-06	5.68E-06	7.57E-06	6.36E-06	8.48E-06
HQ	0.22	0.33	0.23	0.34	0.2	0.32	0.18	0.27	0.22	0.33

It was found that the hazard coefficients for intake of contaminants in the median concentration and in the 90th percentile did not exceed the permissible level in all food clusters.

Based on the results of assessment of hazard coefficients, the greatest non–carcinogenic risk for various methods of contaminant intake is due to lead in the clusters 1, 2, 5 and cadmium in the clusters 1, 2 and 5. The greatest non–carcinogenic risk due to intake of mercury from food is characteristic of the clusters 1, 2 and 5; risks associated with intake of arsenic are highest for the 2nd cluster. V.M. Boev et al. found that HQ was at the permissible level for intake of individual contaminants, as well as HI for combined intake of lead, cadmium, arsenic and mercury with food in median concentrations and in the 90th percentile [18]. Research conducted by A.G. Setko et al. assessed non-carcinogenic risk and demonstrated that the level of risk was at an acceptable level (HQ ≤ 1) for main contaminants (nitrates, mercury, arsenic, cadmium) between 2007 and 2015 [19].

The study of contribution of specific food products groups that pose maximum risk according to the hazard index demonstrated that bread and bread products play a major role in formation of risks both when all the studied contaminants are in median concentrations and in the 90th percentile concentrations in the first and second nutrition clusters, with the greatest contribution made by intake of lead and cadmium in maximum concentrations with this type of food products (Table 5).

Contribution of milk and dairy products to formation of the cadmium hazard coefficient in median concentrations was noted at maximum values in the clusters 3 and 4 (21.7–23.1 %). The share of meat products in formation of the hazard coefficient, taking into account intake of mercury in median concentrations, ranges from 17 to 26.2 %; the largest contribution is typical for the clusters 1, 2 and 5. When considering contribution of sugar and confectionery products to formation of the hazard coefficient in the 90th percentile, maximum values of 10.8 % and 10.1 % were found in the 4th nutrition cluster due to intake of mercury. Plant-based diet of the cluster 3 indicates maximum contribution of vegetables and gourds to formation of the hazard coefficient for lead. The contribution of eggs, potatoes, fish and fish products on average does not exceed 10 % of non-carcinogenic risk for analyzed contaminants with various intake methods, which is also determined by the nature of individual consumption.

Analysis of literature on food contamination with heavy metals has shown that studies of risk are often based on data from the Federal State Statistics Service on average annual per capita consumption of the main groups of food products, which indicate regional peculiarities of risk formation. Thus, results of assessment of exposure to heavy metals in the Orenburg region on the basis of average per capita food consumption showed that milk and dairy products ranked first in terms of contributions to total exposure to lead, cadmium and arsenic; vegetables and gourds ranked second and third in terms of contributions to total exposure to lead, cadmium and arsenic; bread products, vegetables and gourds ranked first in terms of contributions to total mercury exposure, bread products ranked second, milk and dairy products ranked third [18]. Assessment of non–carcinogenic risks to health of the population of 16 districts of the Republic of Bashkortostan from contamination with lead, cadmium, chromium, nickel, copper, and zinc revealed 3 districts with high risk values (HI = 1.01–1.34) due to consumption of vegetable crops by the population of these districts [20]. In the Saratov region, bread and dairy products made the greatest contribution to formation of non-carcinogenic risks posed by food contaminated with heavy metals [21]. In our study, we used a methodological approach that takes into account peculiarities of food preferences in the surveyed population, which allowed us to more accurately assess the risk burden caused by contamination, identify the most vulnerable groups of the population in terms of high risks in order to take managerial decisions and organize preventive measures.

Table 5

Contribution of food products (%) to the formation of hazard coefficient in various food clusters, taking into account oral intake of contaminants

Food group	Cluster of nutrition	Cadmium		Mercury		Lead		Arsenic	
		Me	90	*Me*	90	*Me*	90	*Me*	90
Bread and bread products	1	28.6	32.2	24.8	27.7	28.8	33.3	28.6	27.2
	2	28.8	32.1	24.8	27.4	28.8	33.5	28.7	27.6
	3	22.1	27.1	21.0	22.9	22.5	26.3	22.3	20.3
	4	20.1	24.6	18.4	20.4	20.8	24.6	20.1	18.8
	5	27.4	30.2	22.6	25.6	26.9	31.5	27.0	26.5
Vegetable oil and other fats	1	4.4	5.7	5.0	3.8	2.7	3.0	3.7	4.2
	2	4.5	5.7	5.1	3.8	2.7	3.1	3.8	4.3
	3	3.5	4.8	4.3	3.2	2.1	2.4	3.0	3.2
	4	3.4	4.7	4.0	3.0	2.1	2.4	2.8	3.1
	5	4.7	5.9	5.1	3.9	2.8	3.2	3.9	4.5
Milk and dairy products	1	18.7	10.4	6.9	4.1	11.8	7.4	18.9	14.1
	2	18.5	10.2	6.7	4.0	11.6	7.3	18.6	14.1
	3	21.7	13.1	8.7	5.1	13.9	8.8	22.1	15.8
	4	23.1	13.9	8.9	5.3	15.0	9.6	23.4	17.1
	5	19.0	10.3	6.6	4.0	11.7	7.4	19.0	14.6
Meat and meat products	1	11.2	19.4	23.1	18.6	15.8	13.8	11.5	8.9
	2	11.5	19.7	23.4	18.7	16.1	14.1	11.7	9.1
	3	6.8	12.8	15.4	12.1	9.7	8.6	7.1	5.2
	4	7.8	14.8	17.0	13.6	11.4	10.1	8.1	6.1
	5	13.4	22.8	26.2	21.5	18.4	16.3	13.6	9.9
Eggs	1	0.9	0.5	2.4	1.1	1.4	1.1	3.6	2.7
	2	0.8	0.4	2.0	0.9	1.2	0.9	3.0	2.3
	3	0.8	0.4	2.2	1.0	1.2	0.9	3.0	2.2
	4	1.0	0.6	2.7	1.2	1.6	1.3	3.9	2.9
	5	1.0	0.6	2.6	1.2	1.6	1.3	4.0	3.1
Fish and fish products	1	2.3	3.3	8.8	8.4	3.3	3.9	1.7	2.1
	2	2.4	3.4	9.1	8.6	3.4	4.0	1.8	2.2
	3	2.0	3.1	8.5	7.9	2.9	3.5	1.5	1.8
	4	3.0	4.7	12.3	11.7	4.5	5.4	2.3	2.7
	5	3.1	4.4	11.4	11.1	4.4	5.2	2.3	2.8
Sugar and confectionery	1	6.7	6.8	6.4	9.1	3.9	4.6	6.0	4.5
	2	8.1	8.2	7.7	10.8	4.7	5.5	7.3	5.5
	3	5.7	6.3	6.0	8.3	3.4	4.0	5.2	3.7
	4	7.1	7.8	7.2	10.1	4.3	5.1	6.4	4.7
	5	5.6	5.6	5.1	7.3	3.2	3.8	5.2	3.8
Fruit and berries	1	13.7	6.7	8.1	6.5	7.3	7.0	11.2	13.5
	2	12.2	5.9	7.2	5.7	6.5	6.3	10.0	12.2
	3	19.4	10.3	12.7	9.9	10.5	10.2	16.0	18.5
	4	18.9	10.0	11.8	9,4	10.4	10.2	15.5	18.4
	5	12.3	5.9	6.9	5.6	6.4	6.2	9.9	12.0
Vegetables and gourds	1	9.0	12.2	10.3	14.0	13.6	17.4	5.9	14.9
	2	8.4	11.3	9.5	12.8	12.6	16.1	5.5	14.0
	3	12.1	17.8	15.1	20.1	18.5	23.9	8.0	19.3
	4	10.3	15.2	12.3	16.7	15.9	20.8	6.8	16.8
	5	8.5	11.3	9.2	12.7	12.5	16.2	5.5	14.3
Potatoes	1	4.5	2.9	4.2	6.8	11.5	8.4	8.9	7.9
	2	4.9	3.1	4.6	7.3	12.4	9.1	9.7	8.7
	3	5.9	4.1	6.1	9.6	15.3	11.3	11.8	10.0
	4	5.3	3.7	5.3	8.5	14.1	10.5	10.7	9.3
	5	4.8	3.0	4.3	7.1	12.1	8.9	9.5	8.6

Assessment of the hazard index for the combined effects of heavy metals on critical organs and systems was carried out in various clusters based on the pessimistic scenario of food contaminant consumption in the 90th percentile concentrations. Based on the obtained results, the highest total hazard index under simultaneous exposure to cadmium, mercury, lead and arsenic was noted in the second cluster for the endocrine system (HI = 1.68); the lowest risk level for this system was noted in the fourth cluster (HI = 1.25). Under combined exposure to mercury, arsenic and lead in maximum concentrations as regards the nervous system, the highest value of the total hazard index was also characteristic of the second cluster (HI = 1.22), and the minimum value was found in the fourth nutrition cluster (HI = 0.92). Risk of adverse effects on kidneys due to intake of cadmium and mercury was found to be acceptable. Risk levels were also found to be acceptable for effects of combined intake of mercury and lead on the reproductive system, intake of arsenic on the cardiovascular system, skin and gastrointestinal tract, and intake of lead on the hematopoietic system.

Assessment of hazard index for the combined effects of heavy metals on the body in similar studies, which did not consider peculiarities of food preferences in various population groups, found the highest risks for the endocrine system, central nervous system, and reproductive system [18]. Chemical contamination of food also has a negative impact on children as the most vulnerable category of the population with imperfect protection systems against xenobiotics. Correlation analysis between chemical contamination of food on young children and indicators of primary morbidity of children in the Russian Federation between 2012–2017 helped establish the relationship between contamination of food consumed by the analyzed heavy metals and primary incidence of endocrine pathology in both children of the first year of life and children from 0 to 14 years of various nosologies: obesity, insulin-dependent and insulin-independent diabetes mellitus [22, 23]. Analysis of these risks is necessary to predict development of adverse effects on a number of target organs under contaminant intake scenarios in different age groups [24–26].

Assessment of carcinogenic risk, taking into account intake of cadmium, arsenic and lead, demonstrated that when arsenic was ingested in median concentrations by the clusters 1, 2 and 5, the risk level corresponded to the third range (individual lifetime risk of more than $1 \cdot 10^{-4}$, but less than $1 \cdot 10^{-3}$), which is unacceptable, while the maximum level of carcinogenic risk was characteristic of the second cluster (Table 6). Carcinogenic risk caused by intake of cadmium and lead in median concentrations in all clusters was at the maximum permissible level.

Analysis of risk for the population of the Samara region from combined intake of the analyzed contaminants in the median concentration demonstrated that the largest number of new cases, 1.76 per 10,000 population, was found in the second cluster, due to intake of arsenic in the median concentration only, the number of new cases was also maximum in the second cluster, 1.03 per 10,000 population over 70 years.

Table 6

Level of carcinogenic risk in various nutrition clusters based on concentrations of heavy metals, taking into account various intake scenarios

Nutrition cluster	Arsenic		Cadmium		Lead	
	Me	90	*Me*	90	*Me*	90
1	1.01E-04	1.51E-04	4.61E-05	9.62E-05	2.43E-05	7.05E-05
2	1.03E-04	1.6E-04	4.77E-05	1.01E-04	2.53E-05	7.31E-05
3	9.11E-05	1.45E-04	4.26E-05	8.16E-05	2.21E-05	6.37E-05
4	7.93E-05	1.23E-04	3.69E-05	7.05E-05	1.89E-05	5.38E-05
5	1.01E-04	1.51E-04	4.59E-05	9.77E-05	2.48E-05	7.12E-05

When studying carcinogenic risks, taking into account intake of heavy metals in maximum concentrations (the 90th percentile), it was found that the level of this risk also corresponded to the third range (individual lifetime risk of more than $1 \cdot 10^{-4}$, but less than $1 \cdot 10^{-3}$), which is unacceptable, due to intake of arsenic in all clusters and intake of cadmium in the second cluster.

Due to combined intake of all three analyzed contaminants in maximum concentrations, the level of carcinogenic risk corresponded to the third range in all five clusters. The highest value of carcinogenic risk was noted in the second cluster.

Levels of risk for the population of the Samara region demonstrated that the second cluster had the highest probability of developing cancer equaling 1.6 new cases per 10,000 people over 70 years due to intake of arsenic in the 90th percentile concentration (pessimistic scenario); the maximum probability due to intake of cadmium was noted in the first cluster, 1.01 new cases per 10,000 people; the highest probability due to intake of lead was detected in the second cluster, 0.73 new cases per 10,000 people over 70 years. The highest number of new cases – 3.33 per 10,000 people, was also found in the second cluster due to combined intake of the analyzed contaminants in the 90th percentile concentrations.

Development of malignant neoplasms of the gastrointestinal tract due to intake of carcinogens with food has been confirmed by epidemiological studies conducted by various authors. Thus, cadmium, lead and arsenic are recognized as primary carcinogens for colon cancer; cadmium in food is recognized as primary carcinogen for cancer of recto-sigmoid junction and rectum [27, 28].

Thus, assessment of levels of population health risks posed by food contamination with heavy metals was conducted in this study. It involved clustering of the surveyed population based on the nature of food preferences, as well as taking into account the actual body weight in each cluster. This allows for the most accurate assessment of these risks and prediction of adverse effects in various population groups; the study results can be used for managerial decisions as well as for planning activities related to social and hygienic monitoring. In addition, the proposed cluster approach can be used to assess multithread effects of chemical compounds on various population groups.

Conclusions. In this study, five population groups with similar food preferences were formed based on the cluster analysis of actual nutrition and data on the nature of consumption of the main food groups were obtained for each cluster. In all clusters, the hazard coefficients for intake of contaminants in median concentrations and in the 90th percentile concentration did not exceed permissible level, while the greatest non-carcinogenic risk due to intake of lead, cadmium, and mercury was detected among people with a high level of consumption of all analyzed products (the first cluster). The highest carcinogenic risks were also identified for people whose diets were based on high consumption of high-calorie products such as bread, potatoes, confectionery, processed meat and dairy products (the second cluster) as well as among individuals whose diet was based on high consumption of meat products, processed meat and fish (the fifth cluster).

Formation of risk level, taking into account contributions of the main food groups, is influenced by the regional aspects of consumption of locally produced products and those imported from other regions. Under various intake scenarios in all food clusters, endocrine system is most at risk: the maximum level (HI = 1.68) was detected in the "high–calorie" second cluster; the minimum level (HI = 1.25), in the cluster with minimal preference for all studied foods.

In all clusters, levels of individual carcinogenic risk, mainly due to arsenic entering in median concentrations, corresponded to the third range, which is unacceptable, and was the highest in the ‘high-calorie’ second cluster. The level of carcinogenic risk due to arsenic intake in maximum concentrations (‘pessimistic scenario’) also corresponded to the third range and

was the highest in the second cluster. The level of carcinogenic risk due to combined intake of all three analyzed contaminants in maximum concentrations corresponded to the third range in all five clusters. The maximum risk due to arsenic intake in median concentrations was found in the second cluster, 1.03 per 10,000 people over 70 years; for the 90th percentile, 1.6 new cases per 10,000 people over 70 years, which is several times higher than the risk due to cadmium and lead intake.

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SUBSTANTIATION OF WAYS TO REDUCE CONTAMINATION BY BACTERIA OF THE GENUS CRONOBACTER OF DRY SPECIALIZED PRODUCTS FOR BABY FOOD DURING THEIR PRODUCTION

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Prevention of morbidity in the child population from septic foodborne infections caused by the new bacterial pathogen Enterobacter sakazakii (according to the new classification - Cronobacter spp.) is becoming increasingly relevant due to an expanding contingent of susceptible individuals and the proven ability of low doses of the pathogen to quickly increase a population in dry specialized products for formula feeding after rehydration.

In this regard, it is important to assess the risk of accumulation of thermoresistant coliform enterobacteria, including Cronobacter spp., in residual microflora of such products during their production in order to determine ways to minimize it.

To identify a hazardous factor in specialized infant formula of domestic production, we summarized and analyzed expert data on contamination of 245 samples of infant formula and 182 cereals with the entire spectrum of coliform enterobacteria, which were previously identified as Enterobacter sakazakii (Cronobacter spp.). Cronobacter spp. was detected in 4 samples of instant formula (1.6 %) in amounts ranging from 0.04 to 0.5 CFU/g, which is above the hazardous level (≥ 0.003 CFU/g) for susceptible children. No pathogen was isolated from dry mixtures for cooking and instant porridges produced by dry mixing but the content of heat-resistant Enterobacter spp. was 10 times higher than those produced during the full cycle.

Using a risk process model and assuming the content of coliforms in raw milk at the level of the regulated microbial number, probability of pathogen survival in dry mixtures was assessed under standard parameters of spray drying technology. The calculation results showed that under this scenario of raw material contamination, 0.3–0.5 CFU of heat-resistant E.sakazakii (Cronobacter spp.) can be retained in 1 g of a finished product. This substantiates the necessity to introduce the strongest possible requirements for the microbiological quality of raw milk.

Keywords: *Enterobacter sakazakii (Cronobacter spp.), enterobacteria, food safety, microbial contamination, instant milk powder formulas, infant food products, microbiological risk assessment, risk process model.*

Provision of microbiological safety of specific food products used in infant formula feeding and prevention of their contamination with an emergent bacterial pathogen *Enterobacter sakazakii* (*Cronobacter* spp. according to the latest classification) are top priorities along the whole chain of supplying such products to infants.

Cronobacter spp. is a gen. nov created within *Enterobacteriaceae* family by reclassification of a genetic variant of *Enterobacter sakazakii* into separate *species C. sakazakii*

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ssps. *sakazakii & malonaticus*, *C. Turicensis*, *C. muytjensii*, *C. dublinensis* [1]. They are officially labeled by the WHO as obligate pathogens that can cause infections in neonates.

Cronobacter spp. and, primarily, *C. sakazakii* are able to cause necrotizing enterocolitis (NEC), meningitis, bacteremia and sepsis in infants; the diseases can be registered both as sporadic cases and outbreaks as well. The total number of such diseases is unknown since *Cronobacter*-associated infections are not still subject to registration as independent nosologies in most countries worldwide, Russia included [2]. G.L. Linchevskiy with colleagues point out that over the last 20 years the agent has been identified in 70 % of the patients with NEC [3]. Neonates are at the highest risk, especially low birth weight and premature ones. Incidence associated with *C. sakazakii* accounts for 13 and 25 % of the total infection cases respectively according to K. Abdesselam и F. Pagotto [4]. The case fatality rate reaches 60 % among infected neonates with low birth weight and outcomes of the disease (intellectual disability and hydrocephaly) result in permanent disability.

Epidemiological evidence has been provided for an association between *C. sakazakii*-related incidents and powdered breast milk substitutes but a dose of the infectious agent has not been definitely established yet. Experts believe it to be extremely low (below 1 CFU/g) and the infectious agent is considered to be able to form colonies in the intestines due to their immaturity in neonates, absence of protection provided by breast milk and low diversity of gut microbiota [5].

Cronobacter spp. do not differ from allied coliforms as per their cultural characteristics but they are closer to invasive enterobacter species as regards their certain metabolic properties. *Cronobacter* spp. are more resistant to heat and drying than the latter, can survive low pasteurization, able to increase a population in reconstituted formula very rapidly (over 4 hours) even from single cells and within a wide temperature range between 5.5 and 45 °C. They effectively form biofilms on surfaces of bottles, nipples, syringes, and polymer tubes for enteral feeding [6].

A hygienic regulation has been fixed as a measure to manage health risks in the CU TR 021/2011 On Food Safety[1]. It stipulates absence of *E. sakazakii* in 300 grams of powdered infant formulas. Control over occurrence of this pathogen is to be performed in case of detection of *Enterobacteriaceae*, not belonging to *E. coli* and salmonellas, in rated masses (the two-stage approach).

Group and individual prevention of *Cronobacter*-associated infections puts main emphasis on product consumption as the final stage, namely, on preventing the pathogen from growing in reconstituted powdered formulas or on their re-contamination from the environment. Recommendations have been developed for healthcare workers and parents on how to store and prepare formulas, including duration of safe storage of ready-to-feed formulas for healthy children or prohibition of any delayed use for sick ones [7–9].

These measures can need certain revisal and actualization given the contemporary demographic and economic processes. Thus, a population group susceptible to *Cronobacter* spp. is growing in Russia: since 2000, the number of premature newborns has increased by 1.5 times against 1990 and starting from 2012, in accordance with WHO recommendations, neonates born after 22 weeks of gestation have also been considered premature [10]. Moreover, imported infant formulas used to dominate the market in the past but recently the situation has changed and now domestic production of such products has grown considerably. This requires the strictest

[1] TR TS 021/2011. O bezopasnosti pishchevoi produktsii: Tekhnicheskii reglament Tamozhennogo soyuza (s izmeneniyami na 25 noyabrya 2022 goda), utv. Resheniem Komissii Tamozhennogo soyuza ot 9 dekabrya 2011 goda № 880 [CU TR 021/2011. On Food Safety: Technical Regulations of the Customs Union (with latest alterations made on November 25, 2022), approved by the Decision of the Customs Union Commission on December 9, 2011 No. 880]. *KODEKS: electronic fund for legal and reference documentation.* Available at: https://docs.cntd.ru/document/902320560 (November 03, 2023) (in Russian).

assessment of safety of manufactured powdered infant formulas and their components as regards the analyzed infectious agent. It is also necessary to improve control of products imported from South-East Asia and China where applied production technologies might not be reliable enough as regards contamination with *Cronobacter*.

Given all the aforementioned and to substantiate ways to minimize contamination of powdered infant formulas with the analyzed infectious agent, it is important to investigate risk factors associated with *Cronobacter* spp., which can have certain impacts on effectiveness of managing than at the very first stage, namely, during production.

Materials and methods. We analyzed and generalized data reported in foreign and Russian publications and results of our own sanitary-epidemiological inspections about quantitative characteristics of contamination by thermal resistant enterobacter species, including coliforms and those from *Cronobacter* genus, identified in powdered breast milk substitutes, cereals for infants and components for their production.

We analyzed typical domestic technological instructions on how to produce instant powdered infant formulas to assess impacts of technological factors on levels of microbial contamination in products. On this basis, a schematic risk process model (RPM) was created in conformity with the Methodical Guidelines MR 2.1.10.0067-2012[2] at the production stage.

Results. ***Analysis of prevalence and quantitative characteristics of contamination by thermal resistant enterobacter species, including those from Cronobacter genus, in powdered infant formulas.*** Cronobacter spp. are identified (as a rule, when testing coliform occurrence) in a in a wide variety of cereal-based foods, vegetables, herbs, spices, ready-to-eat foods, and foods from other categories. This pathogen was also found in cultivation environments, such as soils, compost, animal feces, rice and vegetable crops, as well as food processing industries, and domestic environments, thus demonstrating possible contamination routes for them to occur in ready-to-feed formulas [11]. Biological properties and behavior of Cronobacter spp. in different objects have been studied well enough; however, despite this fact, there are only scarce data in literature about their prevalence, quantities and concrete species occurring in baby formulas sold on the consumer market. Table 1 summarizes data on Cronobacter spp. identification in powdered infant formulas and their components in different countries. This includes studies where such data were collected within control of products incriminated during outbreaks of Cronobacter-associated infections.

Data analysis indicates that *Cronobacter* spp. can be found everywhere in instant powdered infant formulas and supplementary feeds for infants, including those used as part of dietetic therapy. In America, frequency of *Cronobacter* spp. identification in powdered formulas (when a sum of positive samples was recalculated per their sum for a specific product) equaled 22.5 % in the USA, 8.6 % in Brazil, and 6.25 % in Chile. In Eurasia (Russia, Jordan, and Egypt), it varied between 2.5 and 17.5 %. In China, powdered formulas were contaminated only slightly (less than 1 %) whereas cereals were contaminated in 13 % of cases. It is worth noting that contamination identified in rice flour and flour made of other cereals was 26.6 and 14 % accordingly and infant formulas and cereals in China are reported to be made of basic components used in manufacturing mass food products instead of some specialized ones. *Cronobacter* spp. contamination was identified in 120 samples of

[2] MR 2.1.10.0067-2012. Otsenka riska zdorov'yu naseleniya pri vozdeistvii faktorov mikrobnoi prirody, soderzhashchikhsya v pishchevykh produktakh. Metodicheskie osnovy, printsipy i kriterii otsenki [Assessment of health risks caused by exposure to microbial factors in food products. Methodical essentials, assessment principles and criteria]: methodical guidelines, approved by the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, the RF Chief Sanitary Inspector on August 10, 2012. Moscow, the Federal Center for Hygiene and Epidemiology of Rospotrebnadzor, 2012, 53 p. (in Russian).

Table 1

Cronobacter spp. identification in powdered infant formulas and their components

Product	Number of samples	Share of contaminated		Association with disease (cases)	Year	Country	Reference
		abs.	%				
1	2	3	4	5	6	7	8
PIFs (younger than 6 months)	14	0	0	Not proven	2022	USA	[2]
PIFs (6–12 months)	8	0	0				
PIFs	80	5	6.25	n.d.	2018–2020	Chile	[12]
Powdered milk	20	7	35	n.d.	2020	Serbia	[13]
PIFs (younger than 12 months)	4050	7	0.17	n.d.	2014–2019	China	[14, 15]
Supplementary cereal-based feeds	8055	1048	13				
Rice flour	410	109	26.6				
Cereal flour	85	12	14				
PIFs	400	70	17.5	n.d.	2017–2018	Egypt	[16]
Manufactured herbal infusions	500	45	9				
PIFs (younger than 6 months)	47	0	0	n.d.	2016–2018	Brazil	[17]
PIFs (6–12 months)	30	0	0				
Dry cereals	75	13	17.3				
PIFs	71	21	29.5	71	1961–2018	USA	[18]
PIFs (for premature/low birth weight neonates)	14	3	21.4	2	2012	Brazil	[19]
PIFs (0–6 months)	15	3	20				
PIFs (6–12 months)	7	6	85.7				
PIFs (0–12 months)	6	0	0				
Fortified powdered milk	5	0	0				
PIFs	40	1	2.5	n.d.	2008	Jordan	[20]
PIFs (for children with malabsorption)	1 lot	n/a	-	3	2001	USA, Tennesy	[21]
Instant PIFs	2	2	100	Not analyzed	2005	RF	[22]
Instant PIFs (0–12 months)	157	2	1.3	Not analyzed	2007	RF	[3]

Note: PIFs are powdered infant formulas; n.d. means no data available.

powdered infant formulas out of total 891 (that is, 13.5 %). The pathogen was detected in powdered milk, a basic component of such formulas, much more frequently, namely in 7 out of 25 cases (28 %).

Obviously, all aforementioned comparisons are formal in their essence, both due to analyzed samples being rather small and use of different analysis techniques in different studies. Also, data on frequency of the pathogen identification were obtained by alternative investigation in all foreign studies and no data are provided on quantity of the pathogen per 1 gram of a product, including cases of

[3] Sheveleva S.A. Analiz mikrobiologicheskogo riska kak osnova dlya sovershenstvovaniya sistemy otsenki bezopasnosti i kontrolya pishchevykh produktov [Analysis of microbiological risk as grounds for improving the system for safety assessment and control of food products]: dissertation … for the Doctor of Medical Sciences degree. Moscow, 2007, 329 p. (in Russian).

outbreaks. When the same approach was used (calculating a sum of 33 positive samples out of 137 samples analyzed during outbreaks (Table 1)), frequency of *Cronobacter* spp. identification on average did not exceed 24 %. Similarly, any association with the pathogen was confirmed only in 24 cases out of 84 incidences with analyzed products (28.6 %). Considering a usually big size of a sample analyzed to identify *Cronobacter* spp. (300 grams of a product), we can state that negative results of the test aimed at the pathogen detection in epidemiologically proven incidents provide another evidence that extremely low content of the pathogen in powdered infant formulas (≤ 0.003 CFU/g) can still pose a serious threat for infants who consume them.

Given that, it seemed important to get a clear idea about frequency of potentially hazardous doses of *Enterobacter sakazakii* (*Cronobacter* spp.) for infants in domestic powdered infant formulas and to substantiate ways to minimize this contamination. To achieve that, we searched for data that provided quantitative characteristics of contamination. However, practically no research works on the subject have been published in the RF since 2008. Given that, we relied on generalizing and analyzing our own retrospective data obtained during sanitary-epidemiological inspections of such products in the process of their registration to be permitted for sale on the consumer market in the RF.

The sample includes results of tests performed on 247 samples of instant powdered infant formulas and 182 instant cereals, both milk and cereal-based ones, that had to be boiled prior to consumption. The tests were aimed at identifying the whole range of coliforms with *Enterobacter sakazakii* (*Cronobacter* spp.) being identified in their structure. For comparison, we also analyzed data on contamianiton by such pathogens in another group of specialized products for infants, namely, fermented milk products for babies.

Data on coliforms in a mass (volume) of these products obtained by an alternative way were transformed into CFU/g. While doing it, we assumed that a sample with no growth identified in 1 gram of it was considered as a clean one, not containing one single intact microbial cell. If coliforms were not identified in 0.1 and 0.01 gram of a product, their number was considered to be above 0 but below 10 and 100 CFU/g accordingly; in 10, 100 grams, above 0 but below 0.1 and 0.01 accordingly. Results were given as a mean value of a sum of the upper and lower boundaries of established ranges[4].

Table 2 provides quantitative characteristics of coliform enterobacter pathogens detected in residual microflora of infant formulas and foods for babies.

Obviously, *Enterobacter* species were the major contaminant identified in all ready-to-feed instant powdered products out of all analyzed coliform enterobacter pathogens. They prevailed over *E. coli, Citrobacter, Klebsiella* spp. and other gram negative bacteria (non-fermenting, Acinetobacter) as regards both frequency and contents. Starting from the 90-th percentile, levels of bacteria belonging to this species, which had previously included *Cronobacter* spp., varied between 0.04 CFU/g in formulas and 5 CFU/g in cereals.

Identification of isolated *Enterobacter spp.* strains revealed that *E. Aerogenes* was the prevailing species among those contaminating instant powdered breast milk substitutes. Its average contents in products equaled 0.11 CFU/g (0.5 CFU/g as per the 95-the percentile). *E. sakazakii* (*C. sakazakii*) was isolated from 4 samples of instant infant formulas in quantities ranging between 0.04 and 0.5 CFU/g (in the 95-th percentile of the sample), that is, above the level established by the WHO as hazardous for susceptible groups among infants.

[4] Sheveleva S.A. Analiz mikrobiologicheskogo riska kak osnova dlya sovershenstvovaniya sistemy otsenki bezopasnosti i kontrolya pishchevykh produktov [Analysis of microbiological risk as grounds for improving the system for safety assessment and control of food products]: dissertation … for the Doctor of Medical Sciences degree. Moscow, 2007, 329 p. (in Russian).

Table 2

Levels of contamination by coliform enterobacter pathogens identified in infant formulas and food products for babies

Species	Number of contaminated samples		CFU/g						
			Range		*M*	*Me*	75%-perc.	90%-perc.	95%-perc.
	abs.	%							
Powdered breast milk substitutes									
Tasteless instant powdered formulas reconstituted under 50 °C and below, *n* = 126									
E.coli	11	8.9	0	5	0.08	0	0	0	0.5
Enterobacter spp.	19	**16.6**	0	5	0.2	0	0	0.05	0.5
Citrobacter spp.	9	7.25	0	0.5	0.02	0	0	0	0.05
Klebsiella spp.	1	0.8	0	0.5	0.004	0	0	0	0
Other gram(-) bacteria	9	7.25	0	5	0.18	0	0	0	0
Instant powdered formulas reconstituted under 70 °C, *n* = 33									
E.coli	2	6.1	0	5	0.3	0	0	0	5
Enterobacter spp.	4	**12.1**	0	0.5	0.06	0	0	0.5	0.5
Citrobacter spp.	3	9.1	0	0.5	0.045	0	0	0	0.5
Klebsiella spp.	2	6	0	0.5	0.03	0	0	0	0.5
Other gram(-) bacteria	2	6	0	0.5	0.045	0	0	0	0.5
Formulas to be boiled, *n* = 88									
E.coli	6	6.8	0	49.5	0.84	0	0	0	5
Enterobacter spp.	50	**56.8**	0	49.5	4.3	5	5	5	5
Citrobacter spp.	7	7.95	0	5	0.4	0	0	0	5
Klebsiella spp.	5	5.7	0	5	0.3	0	0	0	5
Other gram(-) bacteria	27	30.7	0	5	0.57	0	0	0.04	0.04
Dry supplementary feeds									
Instant milk cereals, *n* = 142									
E.coli	2	1.4	0	0.5	0.007	0	0	0	0
Enterobacter spp.	16	**11.3**	0	5	0.49	0	0	0.46	5
Other CA(+) coliforms, total	2	1.4	0	0.13	<0.001	0	0	0	0
Other gram(-) bacteria	7	4.9	0	0.04	0.007	0	0	0	0
Instant cereals, *n* = 40									
E.coli	4	10	0	5	0.387	0	0	0.25	5
Enterobacter spp.	6	**15**	0	5	0.75	0	0	5	5
Other CA(+) coliforms, total	0	0	0	0	0	0	0	0	0
Other gram(-) bacteria	4	10	0	0.08	0.12	0	0	0	0
Liquid fermented milk products, *n* = 234									
E.coli	3	1.3	0	100	0.47	0	0	0	0
CA(+) coliforms, total	0	0	0	0	0	0	0	0	0
Gram(+) microbes (*Enterococcus spp.*, yeast and mold)	22	9.4	0	1610	51.1	0	0	0	0

Note: 0 means not identified in bacterial inoculation.

E. cloacea prevailed in formulas to be boiled prior to consumption. They were isolated in 22 samples and occurred in the 76-th percentile of the series in a quantity equal to 5 CFU/g.

It should be emphasized that tests aimed at detecting all species of enterobacter pathogens in instant infant formulas involved a stage of preliminary non-selective fortification.

Analyzed fermented milk products were only slightly contaminated with coliforms in general; *Enterobacter* spp. were not identified in them at all. This most probably indicates that high active acidity typical for such products due to active fermenting microflora and occurrence of its metabolites create rather unfavorable conditions for the development of these enterobacter pathogens.

Contents of enterobacter pathogens contaminating powdered instant formulas and cereals depended on a technology. For example, contents of *Enterobacter* spp. in formulas reconstituted under 70 °C and cereals made by dry mixing of prepared components were 10 times higher than in formulas reconstituted under 50 °C and below and in milk cereals produced in a full cycle process accordingly.

Given solid evidence of cause-effect relations between low doses of certain *Enterobacter* spp. and *Cronobacter* spp. species and infections in infants and weakened people [23, 24], the obtained results indicate there is a necessity to perform profound examination of technologies facilitating their concentration in instant products and possible ways to reduce it.

Assessing likelihood of E. sakazakii (Cronobacter spp.) survival in a risk process model (RPM). The task was to assess likelihood of *Enterobacter sakazakii* (*Cronobacter* spp.) survival during production of powdered breast milk substitutes manufactured using spray drying, the most common technology in the sphere, as well as a risk of contamination by them in ready products. To do that, we created an element of the stage I in microbiological risk assessment, a risk process model (RPM), in accordance with the MR 2.1.10.0067-2012[5]. Parameters of the spray drying technology (modules) were introduced into the RPM for powdered instant formulas reconstituted in water under temperature below 50 °C. The model also covered data available in literature about basic microbiological processes occurring in different stages in production (including data on how enterobacter pathogens from raw milk behave under heating) since at present no data are available in literature as regards such characteristics of *Cronobacter* spp. [25–27]. The Figure below presents the scheme.

Next, we assumed that raw milk was contaminated only or predominantly with coliforms and predicted contents of their thermal resistant specimen in a ready formula made of milk, which conformed to the safety requirements established by the CU TR 033/2013 On Safety of Milk and Milk Products[6] as per microbiological indicators.

The RPM scheme obviously shows that only those enterobacter pathogens that can survive temperatures ranging between 72 and 80 °C (in milk) and between 78 and 82 °C (in cream) at the stage I (pasteurization) can mostly persist in residual microflora in a ready product given the outlined interchanging thermal processes. Literature data outlined above indicate that *Enterobacter* spp. are the most likely to persist among such microorganisms. Since the entire milk microflora was assumed to be represented by coliforms, then we can believe their initial contents to equal 300,000 CFU/ml (*lg* 5.47) for raw milk used in infant formula production category and 500,000 CFU/ml (*lg* 5.69) for milk or cream sold on the consumer market.

These figures were considered as well when we included critical control points (CCP) and CP (control points) into the RPM. Obviously, pasteurization reduces *Enterobacter* spp. contents by 5 *lg*-orders at the first CCP (pasteurization) [28, 29]. Accordingly, by the moment CP2 is reached (evaporation), 0.47–0.69 *lg* CFU/ml are left of the initial population. In accordance with the RPM, a mean

[5] MR 2.1.10.0067-2012. Otsenka riska zdorov'yu naseleniya pri vozdeistvii faktorov mikrobnoi prirody, soderzhashchikhsya v pishchevykh produktakh. Metodicheskie osnovy, printsipy i kriterii otsenki [Assessment of health risks caused by exposure to microbial factors in food products. Methodical essentials, assessment principles and criteria]: methodical guidelines, approved by the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, the RF Chief Sanitary Inspector on August 10, 2012. Moscow, the Federal Center for Hygiene and Epidemiology of Rospotrebnadzor, 2012, 53 p. (in Russian).

[6] TR TS 033/2013. O bezopasnosti moloka i molochnykh produktov [CU TR 033/2013. On Safety of Milk and Milk Products]: Technical Regulations of the Customs Union (with latest alterations made on September 23, 2022), approved by the Decision of the Customs Union Commission on October 9, 2013 No. 67. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/499050562 (November 05, 2023) (in Russian).

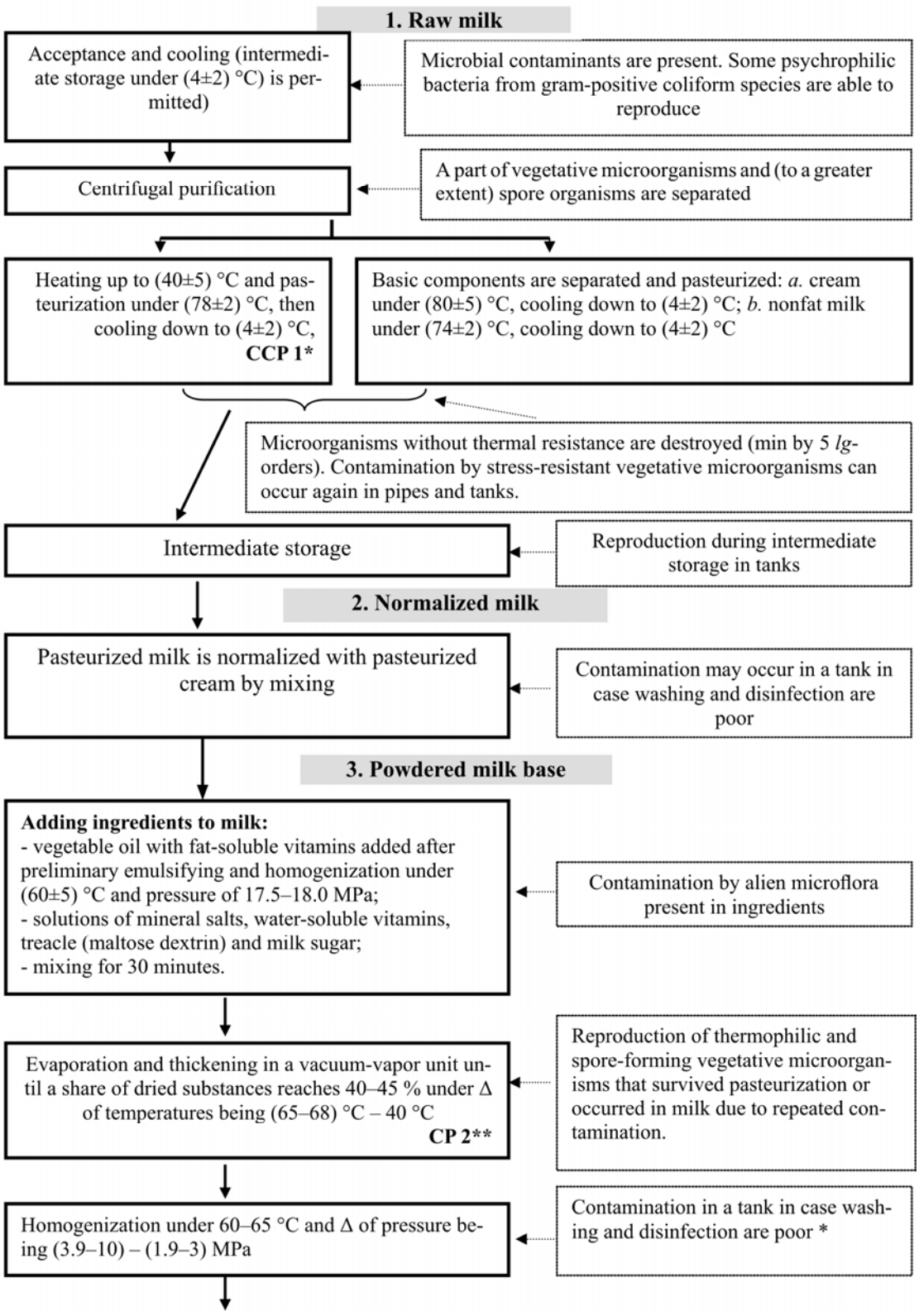
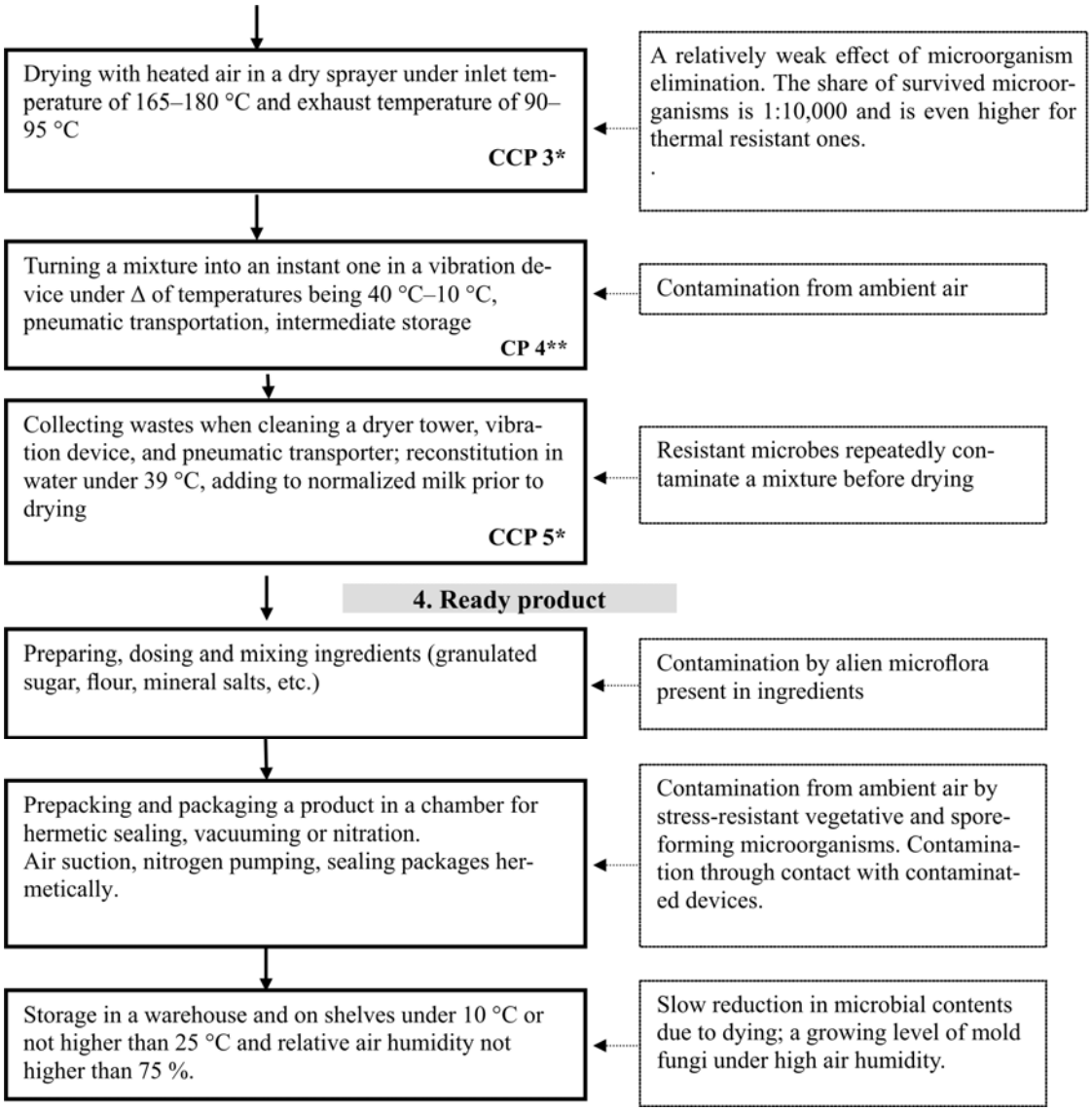


Figure. The risk process model for survival of *Enterobacter sakazakii* (*Cronobacter* spp.) in powdered breast milk substitutes produced by using spray drying technology: *CCP are critical control points at different stages in the technological process where contents of coliforms, enterobacter pathogens included, should be checked; **CP are critical points at different stages in the technological process where contents of coliforms, enterobacter pathogens included, should be checked; CCP 1 is a tank for storing milk after heating; CP 2 is at the exhaust from an evaporator to a tank; CCP 3 is a powder collector; CP 4 is at the exhaust from a vibration device; CCP 5 is at a centrifugal collector



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evaporation temperature is within 52.5–54 °C (53.25 °C). If we again assume that a death rate fixed for *Enterobacter* species in instant formula for 56 °C [30], which is close to 53.25 °C, is correct, then their population reduces by one *lg*-order, that is, down to 0.047–0.069 *lg* CFU/ml at this production stage over 19.1 minutes. If other variables are neglected, then these contents correspond to 0.3–0.5 CFU of *Enterobacter* species, *E. sakazakii* included, in 1 gram of a ready product manufactured under conventional production conditions. Obviously, the calculation results are fully consistent with the actual data on contamination of powders by *Enterobacter* spp. ($M_{cp.}$ = 0.2 CFU/g) since the figures are within one *lg*-order given authentically higher frequency of their occurrence among all other coliform enterobacter pathogens.

Undoubtedly, results of such calculations depend on initial contents of *Enterobacter* species in raw materials. If this estimation and assumptions are correct, then absence of all *Enterobacter*, including *Enterobacter sakazakii*, in 1 gram of a ready product can be ensured under the outlined production conditions only by using milk with coliform contents not exceeding 100,000 CFU/ml (*lg* 5.0). Use of milk with coliform contents ranging between 300,000 and 500,000 CFU/ml does not ensure their absence in powdered instant formulas.

Therefore, use of a simple qualitative risk process model as an element of microbial risk assessment made it possible to objectively identify behaviors of the most thermal resistant enterobacter pathogens *Enterobacter* spp., including pathogenic *Enterobacter sakazakii* (*Cronobacter* spp.) that contaminate milk during production of instant powdered instant formulas and to substantiate a relationship between contamination by them in a ready product and initial levels of microbial contamination in raw milk. Accordingly, manufactures of powdered instant formulas should aim at using raw milk with the lowest possible contents of coliform enterobacter pathogens in it.

Conclusion. Biological properties of a new emergent bacterial pathogen *Enterobacter sakazakii* (*Cronobacter* spp.) include thermal resistance, resistance to drying, and fast growth activation due to rehydration. They have actually become selection factors in technological parameters of production and use of powdered breast milk substitutes and supplementary feeds due to their ability to create risks of severe infections in susceptible infants. Therefore, this study is an attempt to substantiate that, apart from microbiological regulation of the pathogen in such products and development of relevant prevention activities provided for their practical use in healthcare organization and at home, it is also vital to perform investigations aimed at assessing microbiological risks when developing, implementing or improving technologies applied in their production.

In this study, we used some elements of simple qualitative microbiological risk assessment, such as identification of a hazard factor represented by thermal resistant enterobacter pathogens from *Enterobacter* species including *E. sakazakii* (*Cronobacter* spp.); we also analyzed their taxonomic identity, quantitative indicators of their frequency and contents in CFU/g in detail and estimated impacts exerted on these contents by technological parameters by using a risk process model. As a result, we confirmed a priority association between these bacteria and powdered instant formulas and cereals. In addition to that, this methodology made it possible to predict likely accumulation of thermal resistant enterobacter pathogens in residual microflora of ready-to-feed instant powdered infant formulas. This substantiates a recommendation to introduce the strongest possible requirements for the microbiological quality of raw milk into HACCP plans as a prevention measure aimed at reducing microbial contamination.

The results obtained by analyzing available data on microbial contamination of ready products and examination data that are evidence of high frequency of thermal resistant *Enterobacter* spp., *E. sakazakii* (*Cronobacter* spp.) included, in instant serials produced by spray drying indicate the necessity to perform a profound investigation of production technologies and their impacts on the analyzed hazard factor. This is necessary for developing targeted measures aimed at reducing contamination and for achieving more effective control of cereal-based components by introducing relevant laboratory tests in addition to assessment of covering documents.

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Competing interests. The authors declare no competing interests.

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Research article

ON ASSESSMENT OF THE PROBABILITY OF VARIOUS COMORBIDITIES IN WORKERS OF ALUMINUM AND REFRACTORY INDUSTRIES

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Recent findings in occupational medicine have demonstrated that physical diseases are one of the main factors determining poor health of industrial workers. Non-occupational disorders also have a significant impact on timing of occupational disease onset.

Our objectives were to assess the likelihood of comorbidities in cases of occupational diseases of various etiologies and to compare their profiles.

The study was conducted retrospectively. We created a database of medical records of aluminum and refractory workers and analyzed all diagnoses and systemic disorders identified during the clinical examination of these patients using SPSS Statistics 23. The comorbidity index was used to determine the degree of the disease burden of the subjects. We assessed transnosological and transsystemic multimorbidity, as well as the relationship between multimorbidity and occupational diseases. The Kolmogorov – Smirnov test was used to test the null hypothesis that the set of data came from a normal distribution, after which parametric estimation, Student's t-test, and one-way analysis of variance were applied for data analysis. We established comorbidities that were significantly more frequent among the patients suffering from fluorosis or silicosis.

Exposure to occupational hazards in different industries affects the profile of comorbidity. We observed a pronounced polysystemic nature of lesions in aluminum industry workers and the predominance of comorbid diseases of the respiratory system in refractory workers. The level of multimorbidity among the workers of the refractory industry was significantly lower than that in the aluminum production, thus showing a more pronounced negative impact of the combined occupational risk factors in the latter on workers' health.

Keywords: *occupational disease, comorbidity index, fluorine toxicity, silicosis, combination of occupational hazards, transnosological multimorbidity, transsystemic multimorbidity, aluminum industry, refractory industry.*

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Over the second half of the 20th century, significant progress was made in reducing mortality from acute diseases, shifting the focus on chronic diseases. As the number of deaths from acute diseases decreased, the prevalence of chronic conditions accumulating over time rose. This trend was particularly noticeable in the world where a deteriorating environment made people more vulnerable in the long term (World Health Organization on behalf of the European Observatory on Health Systems and Policies, 2011).

In the 21st century, healthcare systems around the world face the rising burden of chronic diseases posing one of their greatest challenges. According to the World Health Report (2002), longer life expectancy, "modernization" of the lifestyle accompanied by an increasing number of risk factors for many chronic diseases, and growing opportunities of saving lives of people who were previously terminally ill, lead to a change in the structure of morbidity, which in turn affects healthcare in different countries.

The World Health Organization (WHO) recognizes that chronic conditions "require ongoing management over a period of years or decades". This category includes a variety of diseases and disorders that fall outside the standard definition of a "chronic disease," i.e. coronary heart disease (CHD), diabetes mellitus, or bronchial asthma [1].

In the context of the pandemic of chronic diseases, the relationship between them is widely discussed being one of the key areas of research in various fields of medicine. "In patient with a particular index disease, the term co-morbidity refers to any additional co-existing ailment", either with pathogenetic interplay or common chronometric features[1].

Comorbidity types include the following [2–4]:

1. Causal comorbidity, which occurs when different organs and systems are affected by the same pathological mechanism;

2. Complicated comorbidity, which is the outcome of the index disease and its consequences;

3. Iatrogenic comorbidity, which manifests itself following complications of medical treatment or examination, provided that their danger is known in advance;

4. Unspecified comorbidity, which suggests the presence of common mechanisms for the development of diseases in this combination, but requires additional research to confirm the hypothesis; and

5. "Random" comorbidity representing a random combination of diseases lacking logical reasoning.

Many authors stick to this classification [5–8].

There exist several scales for assessing comorbid disorders, such as the Cumulative Illness Rating Scale (CIRS), the Cumulative Illness Rating Scale for Geriatrics (CIRS-G), Kaplan–Feinstein index (KFI), the Index of Coexistent Diseases (ICED), the Geriatric Index of Comorbidity (GIC), Charlson comorbidity index (CCI), the Total Illness Burden Index (TIBI), the Chronic Disease Score (CDS), the Adjusted Clinical Groups (ACG) system, the Functional Comorbidity Index (FCI), etc.[2] [3, 9–17]. These scales help analyze the condition

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of patients, including the elderly ones, and predict mortality. Comorbidity indices play an important role in managing the impact of comorbid diseases on patients in the long term. Each of these indices has its own advantages and disadvantages and is used in different clinical situations.

We have come across only few articles discussing combinations of occupational and general diseases in workers exposed to occupational dangers and hazards [18–20].

Here we consider the relationship between general physical disorders, occupational risk factors, and the development of occupational diseases in workers of aluminum and refractory industries.

Inorganic fluorine compounds, high concentrations of which are detected in the workplace air, are among the main hazards in aluminum production. Working conditions of the core personnel (electrolysis operators and anode makers) correspond to Classes 3.3 and 3.4 [21]. Chronic fluorine poisoning, or occupational fluorosis, ranks highest in the structure of occupational diseases in the industry.

With various routes of exposure to inorganic fluorine compounds, their toxic effects are attributed to the resorption of fluorine ions. Fluorine chemicals can induce a variety of metabolic disorders, including those of lipid and carbohydrate metabolism, by suppressing the activity of enzyme systems inside cells. Acting as a multienzyme poison, the fluorine ion is believed to suppress the activity of more than 60 enzymes. In the clinical picture of occupational diseases, there is such a condition as fluorosis – a chronic poisoning that develops following long-term and high-dose exposure to fluorine and its compounds. A characteristic and specific sign of fluorosis is damage to the musculoskeletal system described as fluorine osteopathy [22]. At the same time, other organs and systems, including hepatobiliary, cardiovascular, autonomic, nervous, endocrine, and digestive ones, may be involved in the pathological process. In most cases, the disease develops after ten years of occupational exposure (depending on the airborne levels of fluorine compounds and their ability to dissolve). Currently, the mean latent period of occupational fluorosis is 20 years[3]. Given the present-day concentrations of fluorine compounds in the workplace air, the disease may develop much earlier in highly sensitive workers.

The core personnel involved in the production of aluminum by electrolysis are molten salt electrolysis operators, anode makers, and bridge crane operators. Service personnel, such as electricians and equipment repair workers, spend up to 76.3 % of their shift time near shop-floor equipment and are exposed to the same occupational hazards as the core workers, but receive different doses.

S.V. Shcherbakov was the first to predict the likelihood of developing occupational chronic fluorine poisoning depending on the cumulative dose of fluorine since the first contact[4]. Multivariate analysis techniques were used to substantiate indicators for diagnosing the initial stage of occupational fluorosis out of many symptoms describing the state of the musculoskeletal system and metabolism. The analysis, however, did not reveal specific clinical signs of its early stage, thus necessitating consideration of both radiological and clinical parameters ensuring an individual approach to particular cases.

Respiratory diseases are one of the key issues in contemporary occupational medicine [23]. Lung injuries caused by exposure to industrial aerosols rank second in the structure of occupational diseases. According to the current classification, pneumoconioses are a group of interstitial lung diseases with known etiology.

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[3] Zhovtyak E.P., Odinokaya V.A., Semennikova T.K., Yarina A.L. [et al.]. Khronicheskaya professional'naya intoksikatsiya ftorom i ego soedineniyami – flyuoroz: posobie dlya vrachei [Chronic Occupational Poisoning with Fluorine and Its Compounds – Fluorosis: A Manual for Physicians]. Yekaterinburg, 2003, 16 p. (in Russian).

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Refractory workers are exposed to a combination of risk factors, the main of which are highly fibrogenic aerosols. Dust is generated at each stage of the production of refractory materials.

Press, mill, and conveyor operators, mechanics and other workers serving grinding and molding machines are exposed to the highest levels of dust at work [24]. Dinas refractories are the most common type of refractory products. Dinas production involves the extensive use of silica and induces occupational lung diseases in the modern production of silicate products. Other risk factors of refractory manufacturing include irritant gases, resinous substances, hot microclimate, and heavy physical work [25]. The combination of the above risk factors poses a higher risk of occupational diseases of the bronchi and lungs.

The **objectives** of our study were to assess the likelihood of developing comorbidities in patients with different occupational diseases and to compare their profiles.

Materials and methods. We applied a retrospective approach including the analysis of all diagnosed diseases regardless of their status (index or concomitant) in each patient. The disease burden was determined using the multimorbidity index, where the number of diseases was divided by the number of patients [26]. We also assessed multimorbidity by nosology (the number of different physical diseases) and by system (the number of affected systems in each patient) [6].

The Kolmogorov – Smirnov test was used to test the null hypothesis that the set of data came from a normal distribution, after which parametric estimation, Student's *t*-test, and one-way analysis of variance were applied. The results are presented as $M \pm m$ where m is the error of the arithmetic mean M. The level of significance was set at 0.05 ($\alpha = 0.05$ or $p < 0.05$).

Results and discussion. We did a multivariate analysis of medical records of 192 male workers aged 32 to 75 years (mean: 53.48 ± 0.57 years) with the mean occupational exposure of 22.58 ± 0.42 years (range: 7 to 35 years) employed in the aluminum industry. The case group consisted of 93 patients (48.5 %) with occupational fluorosis (mean age: 57.85 ± 0.65 years; mean occupational exposure duration: 22.74 ± 0.65 years). The reference group included 99 workers without occupational poisoning (mean age: 49.35 ± 0.70 years; mean occupational exposure duration: 22.61 ± 0.56 years). The analysis showed no statistical difference between the groups in terms of exposure duration ($p = 0.874$). Yet, the patients suffering from occupational fluorosis were found to be significantly older ($p < 0.001$; Mann – Whitney U test).

We also analyzed medical histories of 172 workers of Pervouralsk Dinas Plant OJSC examined in the Occupational Health Clinic of the Yekaterinburg Medical Research Center for Prophylaxis and Health Protection in Industrial Workers. The main group included 75 patients with a confirmed diagnosis of silicosis; 97 experienced workers without occupational diseases were matched by sex (the proportion of men in the groups was 53 and 68 %, respectively, $p = 0.052$) and duration of dust exposure (21.11 ± 1.03 vs 20.85 ± 1.05 years, respectively, $p = 0.862$) as controls. Workers from the main group were older (55.84 ± 0.96 vs 49.72 ± 0.84 years, respectively, $p < 0.001$).

The study cohorts are described in Table 1.

Table 1

Description of the study cohorts

Parameter	Aluminum production	Refractory production
Workers, *n*	192	172
Mean age, years	53.48 ± 0.57	55.84 ± 0.96
Mean work experience, years	22.58 ± 0.42	21.11 ± 1.03

The number of comorbid diseases (nosological multimorbidity) per patient with

fluorosis was 6.95 ± 0.26, and 5.18 ± 0.22 per experienced worker ($p < 0.001$). The number of affected body systems (systemic multimorbidity) per patient with occupational fluorine poisoning was 5.71 ± 0.20 and 3.98 ± 0.16 per control ($p < 0.001$).

The following comorbid diseases and conditions were significantly more prevalent in the fluorosis cases compared to the controls: obesity (47 % vs 31 %, respectively, $p = 0.018$), type 2 diabetes mellitus (17 % vs 4 %, $p = 0.003$), arterial hypertension (68 % vs 45 %, $p = 0.001$), heart failure (28 % vs 4 %, $p < 0.001$), atrial fibrillation (15 % vs 0 %, $p < 0.001$), atrophic gastritis (65 % vs 24 %, $p < 0.001$), hyperuricemia (41 % and 13 %, $p < 0.001$), fatty liver disease (48 % vs 24 %, $p = 0.003$), serum creatinine level (84.45 ± 1.98 vs 76.85 ± 1.30 μmol/L, $p = 0.002$), and chronic kidney disease (73 % vs 27 %, $p < 0.001$).

Fluorine exposure indicators also differed statistically in terms of the frequency of hydrofluoride levels above the maximum allowable concentration (MAC) (36 % vs 11 %; $p = 0.002$) and above 2 MAC (90 % vs 60 %, $p < 0.001$), which had probably determined the development of occupational fluorine poisoning in the case group.

In the reference group of experienced workers, no cases of atrial fibrillation were registered. Yet, the development of pneumoconiosis was significantly more often observed in them than in the fluorosis cases (7 % vs 0 %, respectively, $p = 0.007$).

X-ray changes corresponding to Stage 1 fluorosis were registered in 39 % of the workers with fluorosis ($p = 0.002$), and those corresponding to Stage 2 fluorosis were registered significantly more often in fluorosis cases (75 % vs 36 %, $p < 0.001$). X-ray images characteristic of Stage 3 fluorosis were obtained only for four workers with occupational fluorine poisoning (4.3 %).

We observed, on the average, 4.27 ± 0.22 comorbid diseases per silicosis case and 2.39 ± 0.17 diseases per experienced worker ($p < 0.001$). As for systemic multimorbidity, patients with pneumoconiosis and experienced workers had, on the average, 3.76 ± 0.19 and 2.21 ± 0.15 affected systems, respectively ($p < 0.001$).

The following functional respiratory disorders were statistically more frequent in the silicosis cases compared with the workers without occupational diseases: decreased vital capacity (VC) of the lungs – 83.42 % vs 93.34 % ($p = 0.003$); reduced forced expiratory volume per second (FEV1) – 2.33 ± 0.08 L/sec vs 3.77 ± 0.83 L/sec ($p = 0.89$); relative FEV1 decline – 77.8 ± 2.36 % vs 89.84 ± 1.9 % ($p < 0.001$); decreased forced vital capacity (FVC) – 3.70 ± 0.11 m^3 vs 2.89 ± 0.12 m^3 ($p < 0.001$), and relative FVC decline – 78.39 ± 2.59 % vs 93.35 ± 2.15 % ($p < 0.001$), respectively.

The rates of the following comorbidities were also statistically higher in the group of workers with occupational diseases: left ventricular hypertrophy (LVH) (48 % vs 20 %, $p = 0.003$), heart failure (25 % vs 2 %, $p < 0.001$), and arrhythmia (15 % vs 1 %, $p = 0.018$).

The 8-hour time weighted average dust concentration was found to be statistically higher in the group of workers with silicosis (3.19 ± 0.26 vs 1.87 ± 0.13 mg/m^3, respectively, $p < 0.001$) and might have caused the development of pneumoconiosis in those workers.

To assess the probability of developing multimorbidity in fluorosis cases and the coefficient of multimorbidity (integrated comorbidity), we built a model using logistic regression and determined the predictors of the regression equation. To exclude correlations between the predictors that could negatively affect the quality of the model (i.e., the identifiability of equation parameters), we used the method of step-by-step variable selection - Forward LR.

The obtained coefficients of the logistic regression equation are presented in Table 2.

Table 2

Coefficients of the logistic regression equation used to predict the development of multimorbidity (multimorbidity coefficient)

Predictors	B	SE	Sig.	exp (B), odds ratio
BMI	0.199	0.084	0.017	1.221
Fluorosis	5.720	1.622	0.000	305.032
HDL	-4.234	1.410	0.003	0.014
CMD	2.665	1.008	0.008	14.363
Constant	-2.053	2.807	0.465	0.128

N o t e s: B – coefficient in the logistic regression equation for the corresponding predictor; SE, standard error of the mean; Sig. – statistical significance of coefficient B; exp (B) – odds ratio per unit change in the predictor (factor); BMI, body mass index; HDL, high-density lipoproteins; CMD, carbohydrate metabolism disorders.

The formula (1) for the logistic regression equation and further calculation of the probability of developing multimorbidity in the workers of interest is as follows:

$$y = -2.053 + 0.199 \cdot \text{BMI} + 5.720x_1 - 4.234 \cdot \text{HDL level} + 2.665x_2, \quad (1)$$

where $x_1 = 1$ for the diagnosis of fluorosis and $x_1 = 0$ for its absence; $x_2 = 1$ for carbohydrate metabolism disorders and $x_2 = 0$ for their absence in the worker.

Then the probability (P) of developing multimorbidity (multimorbidity coefficient) will be calculated as follows:

$$P = \exp(y) / (1 + \exp(y)). \quad (2)$$

The formula for assessing the likelihood of developing multimorbidity covers the following factors: body mass index, high-density lipoprotein levels, diagnosed fluorosis, and the presence of carbohydrate metabolism disorders. According to the classification table, the constructed model has a high overall predictive ability (86.7 %). Moreover, in the case of predicting the outcome of interest, the model has high specificity (90.4 %) and high sensitivity (80.6 %).

Based on the results of assessing comorbidities among workers in hazardous industries, the highest prevalence of comorbid diseases and conditions was registered among the aluminum industry workers. The maximum nosological comorbidity in them equaled 6.95, meaning that almost seven comorbid diseases or conditions were diagnosed in patients with fluorosis, such as: hypertension, type 2 diabetes mellitus, obesity, heart failure, atrial fibrillation, atrophic gastritis, fatty liver disease, abnormal serum creatinine levels, and/or chronic kidney disease.

This implies that, of the nine diseases or conditions listed, five (55.5 %) were cardiovascular disorders, two were gastrointestinal diseases, and the other two were diseases of the excretory system. Systemic multimorbidity in the workers with fluorosis was 5.18 ± 0.22, meaning that more than five systems were affected in each patient: the cardiovascular and excretory systems, liver, kidneys, and metabolism. Such a wide profile of comorbid diseases and affected systems is related to the fact that fluorine is a multienzyme, multisystem poison.

In the reference group, the number of comorbid diseases per experienced worker was 5.18 ± 0.22, i.e. significantly lower than in patients with fluorosis ($p < 0.001$). The number of affected body systems (systemic multimorbidity) per experienced worker was 3.98 ± 0.16, which was also significantly lower than in the fluorosis cases ($p < 0.001$). This pattern is probably due to the fact that fluorine exposure of workers with fluorosis was statistically higher. The absence of chronic kidney disease and atrial fibrillation

in the reference group was potentially related to its lower exposures since the pathogenetic basis of these disorders includes fibrosis and inflammation.

In the silicosis cases, we established, on the average, 4.27 ± 0.22 comorbid diseases per patient, while in the reference group this number was 2.50 ± 0.27 ($p < 0.001$). As for systemic multimorbidity, 3.53 ± 0.22 systems on the average were affected in the pneumoconiosis patients compared to 2.20 ± 0.22 in the controls ($p < 0.001$). That is, more than four of the following comorbidities were registered per silicosis case: hypertension, silicosis, respiratory failure, coronary heart disease, obesity, lipid metabolism disorders, etc.

When comparing comorbid disorders in refractory workers without occupational diseases, we noticed the absence of left ventricular hypertrophy (LVH), underweight, type 2 diabetes mellitus, elevated levels of interleukins 4 and 8 in them. On the other hand, in the group of workers with silicosis, there were no cases of urolithiasis, increased intima-media thickness, or kidney cysts. In the workers with occupational silicosis, compared with experienced refractory workers, decreased vital capacity of the lungs (82.7 ± 2.9 % vs 93.1 ± 3.9 %, $p = 0.034$), FEV1 (54 % vs 29 %, $p = 0.017$), and FVC (76.1 ± 3.4 % vs 90.5 ± 3.9 %, $p = 0.07$) were statistically more frequent.

The number of affected body systems (systemic multimorbidity) per patient with pneumoconiosis was 3.53 ± 0.22 vs 2.20 ± 0.22 per an experienced worker ($p < 0.001$). We assume that a more frequent development of general diseases and a greater number of affected systems in the group of workers with pneumoconiosis (silicosis) are associated with a higher 8-hour time weighted average dust concentration in the workplace (2.40 ± 0.25 vs 1.72 ± 0.23 mg/m^3, respectively, $p = 0.051$).

It is worth mentioning that the level of both nosological and systemic multimorbidity in refractory workers is significantly lower than that in the workers of aluminum industry, which allows us to conclude that the combination of occupational hazards in refractory manufacturing has a less pronounced negative impact on workers' health and mainly induces comorbid diseases of the respiratory and cardiovascular systems, and metabolic disorders. The likelihood of developing pneumoconiosis depends on several factors, occupational dust exposure being of greatest importance, followed by a high cumulative exposure dose of inorganic dust and genetic predisposition to dust-induced pulmonary fibrosis. If the exposure level, chemical composition and dispersion of dust give an idea of working conditions in various industries, then the rates of nosological and systemic comorbidity help establish the extent of health problems and lesions characteristic of various industries.

Here are the examples of using the model to calculate probability.

Patient A: BMI = 26 kg/m^2, HDL = 1 mmol/L, has carbohydrate metabolism disorders but no fluorosis. For patient A, according to formula (1), we have:

$$y = 0.199 \cdot 26 - 4.234 \cdot 1 + \\ + 2.665 - 2.053 = 1.552$$

Using formula (2), the probability of developing multimorbidity in patient A is estimated as follows:

$$P = \exp(y) / (1 + \exp(y)) = 0.825, \text{ or } 82.5\ \%$$

Patient B: BMI = 23 kg/m^2, HDL = 1.2 mmol/L, no carbohydrate metabolism disorders or fluorosis. For patient B, we have:

$$y = 0.199 \cdot 23 - 4.234 \cdot 1.2 - 2.053 = -2.5568$$

The probability of developing multiple long-term conditions in this patient is as follows:

$$P = \exp(y) / (1 + \exp(y)) = 0.0719, \text{ i.e. } 7.19\ \%$$

Conclusions:

1. At present, the structure of morbidity is dominated by chronic, multifactorial diseases,

characterized by multimorbidity and multisystemic lesions.

2. Combinations of occupational risk factors in various industries form different profiles of comorbidities. In the aluminum industry, we observed a pronounced polysystemic nature of lesions, while respiratory diseases prevailed in refractory workers.

3. The fluorosis cases have a significant number of comorbid and systemic diseases: more than six comorbidities with more than four systems affected on the average, which is probably due to the properties of fluorine compounds as a multienzyme and multisystem poisons.

4. Risk factors of refractory manufacturing have a less pronounced negative impact on workers' health (silicosis cases have, on the average, slightly more than four comorbid diseases with 3.5 systems affected).

5. The use of such indicators as nosological and systemic multimorbidity allows not only to assess the individual degree of health impairment, but also to compare characteristics of lesions specific for different industries.

Compliance with ethical standards. The study complied with ethical standards of the World Medical Association Declaration of Helsinki on the Ethical Principles of Scientific Medical Research Involving Human Subjects as amended in 2000 and the "Rules of Clinical Practice in the Russian Federation" adopted by Order of the Ministry of Health of the Russian Federation No. 266 of June 19, 2003. It was approved by the Ethics Committee of the Yekaterinburg Medical Research Center for Prophylaxis and Health Protection in Industrial Workers (protocol No. 7 of October 3, 2022).

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Research article

HYGIENIC ASSESSMENT OF HEALTH RISKS FOR EMPLOYEES OF THE OMSK AMBULANCE SERVICE DUE TO TOBACCO SMOKING

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The results of many studies indicate that there is a cause-effect relationship between active tobacco smoking and risks of various diseases, lung and bronchial cancer (C34) and coronary heart disease (I25) being the most common among them. These diseases are one of the main causes of death in working age.

The aim of this study was to perform hygienic assessment of risks of lung and bronchial cancer and coronary heart disease due to active tobacco smoking. Healthcare workers employed at the Omsk ambulance station were chosen as the research object. Additional risk levels were calculated for lung and bronchial cancer and coronary heart disease in accordance with the methodical guidelines MR 2.1.10.0033-11 Assessment of Risks Associated with Impacts of Lifestyle Factors on Public Health.

Smoking was a health risk factor for 27.5 % of emergency medical services workers, including 42.5 % of men and 21.3 % of women. Sixty-six point seven percent of men aged between 31 and 40 years smoked. Prevalence of smoking among the females in the sample did not depend on age. The risk analysis revealed that smokers, equally men and women (p > 0.1) were the most likely to have lung and bronchial cancer and coronary heart disease. The corresponding median levels of additional risk equaled 1.45E-05 and 9.0E-06. The proportion of people with unacceptable levels of additional risks of the analyzed diseases (> 1.4E-04) equaled 43.3 and 53.3 % respectively among people older than 40 years. Likelihood of lung and bronchial cancer and coronary heart disease statistically significantly depends on the intensity of smoking.

Keywords: *hygiene, risk, smoking, tobacco, incidence of the population, coronary heart disease, malignant neoplasms, healthcare workers.*

Smoking is the most common form of tobacco use. Carcinogens and substances with pronounced toxic properties have been found in tobacco smoke [1]. Tobacco smoking increases the risk of respiratory infections due to structural changes in the respiratory tract and decreased immune response [2, 3] and is one of the main causes of chronic bronchopulmonary diseases [3–12].

Arterial hypertension and coronary heart disease (CAD) are significantly more frequently registered among smokers [6, 12]. Smoking is one of the main factors determining the prognosis of death from cardiovascular diseases (CVD) in the modern adult population of the Russian Federation (RF) [8]. Tobacco smoking makes a major contribution (more than 90 %) to the risks of CAD development among tobacco and alcohol users [10]. In Australia, 25 % of hospitalizations with acute coronary syndrome among persons under 65 years of age are related to smoking [11]. A direct correlation has been found between smoking intensity and the magnitude of the risk of death due to CAD[1].

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The results of numerous epidemiologic and experimental studies suggest a cause-effect relationship between tobacco use and the risks of malignant neoplasms [3, 5, 9, 13–18]. Tobacco smoking is one of the main etiologic factors in the pathogenesis of lung and bronchial cancer [5, 9, 13–15, 18, 19]. Women, all other things being equal, have a higher risk of developing lung cancer from smoking than men [13, 19], which may be due to interaction between tobacco smoke carcinogens and female sex steroids [13]. Smoking is one of the significant causes of premature death [1, 3, 11, 19, 20]. The tobacco epidemic causes significant economic losses due to treatment of smoking-related diseases as well as premature deaths due to the same cause [1].

Smoking is primarily a male habit[2] [5, 8–10, 21, 23–25, 28, 29, 32]. In 2020, 36.7 % of men and 7.8 % of women living on the planet used tobacco [1]. In 2018, the smokers accounted for 46.4 % among men and 14.6 % among women in the Russian Federation[2]. In 2022, 47 % of men and 21 % of women smoked according to the results of a monitoring survey of the country's population conducted by the All-Russian Center for Public Opinion Research (ARCPOR) [32].

The age factor has a significant impact on prevalence of smoking. This addiction is quite widespread among young people [23, 24, 26, 32]; many of them start smoking at school [24, 29]. In 2022, according to ARCPOR [32], the highest share of smokers, 37 %, was established in the aged group of 25-29 years. With age, the proportion of smokers decreases, regardless of sex [9, 21, 23, 32].

Data on the prevalence of tobacco smoking among healthcare workers are of particular interest as they are a "model" society group in terms of creating a healthy image [7, 25–30]. The level of tobacco use remains high in this occupational group [7, 23, 28, 29]. A significant proportion of smoking doctors take up the habit when getting higher medical education [24]. Very low prevalence of tobacco use has been identified among specialists in obstetrics and gynecology [25].

Predictors of giving up smoking include higher education [5, 7, 9, 21, 23, 29, 32], awareness of the consequences of smoking [7, 22, 25, 27, 29], pregnancy and having diseases that respondents believe are caused by smoking [5, 9, 32], and high prices of tobacco products [26, 32].

In 2008, World Health Organization proposed a package of measures to effectively reduce prevalence of tobacco smoking [31]. In 2013, the Federal Law "On protection of citizens' health from exposure to tobacco smoke, consequences of tobacco use or consumption of nicotine-containing products" was issued[3]. The share of smokers went down by 3.7 % among the adult population of the Russian Federation, including 4.3 % among men, from 2013 to 2018[4]. Among the taken measures, implementation of tax and price policy, social advertising and medical assistance in overcoming this bad habit made the greatest contribution to the reduction of smoking prevalence rates [30]. According to ARCPOR [32] since 2013, the proportion of smoking Russians decreased by 7 % by 2022 and amounted to 33 %. The total share of smokers among 18–24-year-olds decreased from 48 to 29 %.

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[2] Itogi vyborochnogo nablyudeniya povedencheskikh faktorov, vliyayushchikh na sostoyanie zdorov'ya naseleniya v 2013 i 2018 gg. [The results of sampling observation of behavioral factors influencing public health in 2013 and 2018]. *The Federal State Statistics Service*. Available at: https://rosstat.gov.ru/itog_inspect (October 04, 2023) (in Russian).

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According to the results of a large-scale study in 10 regions of the Russian Federation [30], it was found that from 2013 to 2019 there was a statistically significant decrease in the rate of hospitalization for angina pectoris (by 16.6 %), myocardial infarction (by 3.5 %) and pneumonias (by 14.3 %).

The purpose of the study was to perform hygienic assessment of the risks of lung and bronchial cancer and ischemic heart disease in connection with active tobacco smoking among the employees of the emergency medical service (EMS) of the city of Omsk.

Materials and methods. Health risks for the employees of the emergency medical service in connection with active smoking were assessed in accordance with methodical guidelines MR 2.1.10.0033-11 Assessment of Risks Associated with Impacts of Lifestyle Factors on Public Health[5].

According to the results of a survey of 411 people, the median (*Me*) age was 33 years; the first quartile (Q_1) and the third quartile (Q_3) were 26 and 55 years, respectively. The analysis was conducted for 3 age groups: up to 30 years inclusive; from 31 years to 40 years inclusive; from 41 years and older. The main results of the survey are summarized in Table 1.

The intensity of smoking among smoking respondents (n = 113) was indirectly assessed by the average daily nicotine intake (F^S, mg). After the procedure of removing the so-called "pop-ups", 105 individual F^S values were further developed, which, depending on the position relative to the quartiles Q_1 (1.43 mg) and Q_3 (4.0 mg), were divided into three subgroups of SI: low, medium and high.

At the stage of factor-effect analysis using recurrent equations[5], individual values of additional risk (R_i) of developing diseases were calculated: lung and bronchial cancer (LBCa), oral cavity cancer (OCCa), esophageal cancer (ECa), gastric cancer, pancreatic cancer (PCa), bladder cancer (BCa), cervical cancer (CCa), coronary heart disease (CAD), and chronic bronchitis (CHB).

Individual values of additional risk of diseases caused by active smoking were qualitatively assessed in accordance with the criteria specified in Clause 8.6. MR 2.1.10.0033–11[5].

The Mann – Whitney (U), Kruskel – Wallis (H) and λ-test proposed by A.N. Kolmogorov and N.V. Smirnov were calculated to assess the statistical significance of the differentces between the independent groups. A p value of no more than 0.05 was taken as the critical level of statistical significance.

Table 1

EMS employees' attitudes towards smoking: survey results

Age, years	Total			Men			Women			p
	n	smokers		n	smokers		n	smokers		
		n	%		n	%		n	%	
Younger than 30	180	41	22.8	49	14	28.6	131	27	20.6	> 0.1
31–40	101	39	38.6	36	24	66.7	65	15	23.1	< 0.001
41 and older	130	33	25.4	35	13	37.1	95	20	21.1	< 0.05
Total	411	113	27.5	120	51	42.5	291	62	21.3	< 0.001

[5] MR 2.1.10.0033-11. Otsenka riska, svyazannogo s vozdeistviem faktorov obraza zhizni na zdorov'e naseleniya: Metodicheskie rekomendatsii, utv. Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii G.G. Onishchenko 31 iyulya 2011 g. [Assessment of Risks Associated with Impacts of Lifestyle Factors on Public Health: Methodical guidelines, approved by G.G. Onishchenko, the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Well-being, the RF Chief Sanitary Inspector on July 31, 2011]. *KODEKS: electronic fund for legal and reference documentation.* Available at: https://docs.cntd.ru/document/1200111974/titles (February 08, 2023) (in Russian).

Results and discussion. As shown in Table 1, smoking is a health risk factor for 27.5 % of EMS employees, including 42.5 % of men and 21.3 % of women ($p < 0.01$). Among men aged between 31 and 40 years, 66.7 % smoked, which is significantly higher than among men in the "younger" and "older" age subgroups (28.6 %); $p < 0.001$) and over 40 years of age (37.1 %; $p < 0.01$). Prevalence of smoking among women was not significantly associated with age ($p > 0.1$).

The proportion of smokers among doctors and paramedical workers was 28.3 % and 28 %, respectively ($p > 0.1$). In the group of doctors, 35.5 % of men and 20.7 % of women smoked ($p > 0.1$). In the paramedical group, 45.5 % of men smoked, while only 21.6 % of women smoked ($p < 0.01$).

The intensity of smoking among men and women (Table 2) was almost the same ($U = 1066$; $p > 0.1$). The age factor did not have a statistically significant effect on the SI of smoking EMS employees either ($H = 3.1$; $p > 0.1$), although there is a slight downward trend in median SI values from the "junior" to the "senior" subgroup, both in general and among men and women.

According to Table 3, the distribution of F^S values among men is shifted towards high smoking intensity (29.5 %) due to a decrease in the proportion of persons with relatively low and medium SI to 25.0 % and 45.5 %, respectively. The female part of the sample is dominated by employees with low and medium SI. In general, however, the sex difference in the distribution of individual SI values in the analyzed sample is insignificant ($\lambda = 0.93$; $p > 0.1$).

According to the data given in Table 4, smoking employees of the EMS are most likely to develop LBCa and CAD. The median additional risk values for these diseases were 1.4E-05 and 9.1E-06, respectively. Likelihood of other diseases associated with smoking was significantly lower: from 9.9E-07 (pancreatic cancer) to 2.6E-06 (chronic bronchitis).

Table 2

Distribution of smoking employees by smoking intensity depending on age and sex (F^S, mg/day)

Age, years	All smokers				Including								p
					men				women				
	n	Me	Q_1	Q_3	n	Me	Q_1	Q_3	n	Me	Q_1	Q_3	
Younger than 30	38	3.22	1.43	4.00	11	3.60	1.71	5.57	27	3.14	1.27	3.80	> 0.1
31–40	37	2.29	1.14	4.69	22	2.29	1.14	4.77	15	2.40	1.57	3.94	> 0.1
41 and older	30	1.26	1.14	3.14	11	1.59	1.23	5.20	19	1.20	1.14	2.80	> 0.1
p		> 0.1				> 0.1				> 0.1			
Total	105	2.29	1.14	4.00	44	2.29	1.27	5.3	61	2.23	1.14	3.77	> 0.1

Table 3

Distribution of smoking employees of the EMS depending on the intensity of smoking and sex

SI	F^S, mg/day		All smokers		including:				p
					men		women		
	min – max	*Me*	n	%	n	%	n	%	
low	0.29–1.14	0.97	31	29.5	11	25.0	20	32.8	> 0.1
average	1.2–4.69	2.6	54	51.4	20	45.5	34	55.7	
high	4.8–10.13	7.54	20	19.0	13	29.5	7	11.5	
total	0.29–10.13	2.29	105	100	44	100	61	100	> 0.1

Table 4

Indicators of individual additional risk of certain diseases in the group of smoking employees of the Omsk Secondary Health Care Department, in relative units

Indicator	LBCa	CAS	SCa	OCCa	ECa	CCa	BCa	PCa	CHB
n	105	105	105	105	105	61	105	105	105
Me	1.4E-05	9.0E-06	1.4E-06	2.0E-06	1.9E-06	2.3E-06	2.4E-06	9.9E-07	2.6E-06
Q_1	6.2E-06	3.3E-06	6.0E-07	8.6E-07	9.0E-07	7.8E-07	1.1E-06	4.4E-07	1.3E-06
Q_3	3.9E-05	3.9E-05	3.9E-06	5.1E-06	4.6E-06	1.1E-05	6.8E-06	2.4E-06	5.8E-06

Given that the recurrence equations used in the calculation of the additional risk associated with smoking are of the same type and differ only in the value of the empirical coefficients reflecting likelihood of a particular disease, as well as the above-mentioned literature data, we considered it possible to limit ourselves analyzing the dependence between LBC and CAD risks in smoking employees of the EMS and such factors as sex, age, and smoking intensity. The main results are presented in tables 5 and 6.

All individual values of R_{LBCa} in smoking EMS employees ranged from 3.20E-07 to 1.09 E-03 (n = 105; *Me* = 1.4E-05). Sex had no statistically significant effect on the risk of CAD (U = 1122.5; $p > 0.1$), although the median values of R_{LBCa} among men overall (1.6E-05) were slightly higher than those of their female smokers (1.2E-05).

Of the analyzed factors, age had the greatest influence on LBC likelihood in smokers: overall (H = 64.5; $p < 0.01$); among men (H = 20; $p < 0.01$) and women (H = 39.5; $p < 0.01$). In the "younger" age subgroup, there were no individuals with unacceptable R values of LBC (> 1.0E-04), while in the "older" subgroup, the proportion of individuals with such risk levels was 43.3 % (45.5 % and 42.1 %, respectively, among men and women). Sex differences between R_{LBCa} values turned out to be statistically insignificant in all compared age subgroups ($p > 0.1$).

Table 5

Some results of analyzing LBC and CAD risks in smoking employees of the EMS depending on age and sex

Age, years	All smokers			Including:						p
				men			women			
	Me	People with R_i > 1.0E-04		*Me*	People with R_i > 1.0E-04		*Me*	People with R_i > 1.0E-04		
		n	%		*n*	%		*n*	%	
Lung and bronchus cancer										
Younger than 30	5.8E-06	0	0.0	7.5E-06	0	0.0	4.2E-06	0	0.0	>0.1
31–40	1.9E-05	1	2.7	1.7E-05	0	0.0	2.1E-05	1	6.7	>0.1
41 and older	7.5E-05	13	43.3	4.2E-05	5	45.5	7.5E-05	8	42.1	>0.1
p	<0.01			<0.01			<0.01			
total	1.4E-05	14	13.3	1.6E-05	5	11.4	1.2E-05	9	14.8	>0.1
Coronary heart disease										
Younger than 30	2,8E-06	0	0.0	3.3E-06	0	0.0	1.8E-06	0	0.0	>0.1
31–40	1,3E-05	1	2.7	1.2E-05	0	0.0	1.4E-05	1	6.7	>0.1
41 and older	1,5E-04	16	53.3	6.4E-05	5	45.5	1.6E-04	11	57.9	>0.1
p	<0,01			<0.01			<0.01			
total	9,0E-06	17	16.2	1.2E-05	5	11.4	7.1E-06	12	19.7	>0.1

Table 6

Some results of analyzing LBC and CAD risks in smoking employees of the EMS depending on smoking intensity and sex

SI	All smokers			including:						
				men			women			p
	Me	People with R_i > 1.0E-04		*Me*	People with R_i > 1.0E-04		*Me*	People with R_i > 1.0E-04		
		n	%		*n*	%		*n*	%	
Lung and bronchus cancer										
low	9.4E-06	2	6.5	9.4E-06	0	0.0	5.9E-06	2	10.0	>0.1
medium	1.3E-05	6	11.1	1.7E-05	2	10.0	1.1E-05	4	11.8	>0.1
high	3.7E-05	6	30.0	4.1E-05	3	23.1	3.4E-05	3	42.9	>0.1
p	<0.01			<0.01			<0.05			
total	1.4E-05	14	13.3	1.6E-05	5	11.4	1.2E-05	9	14.8	>0.1
Coronary heart disease										
low	7.4E-06	5	16.1	7.4E-06	0	0.0	5.3E-06	5	25.0	>0.1
medium	7.7E-06	6	11.1	1.2E-05	2	10.0	6.6E-06	4	11.8	>0.1
high	2.6E-05	6	30.0	3.0E-05	3	23.1	2.0E-05	3	42.9	>0.1
p	<0.05			>0.1			>0.1			
total	9.0E-06	17	16.2	1.2E-05	5	11.4	7.1E-06	12	19.7	>0.1

CAD risks in smoking employees of the EMS (n = 105; *Me* = 9.0E-06) ranged from 1.1E-07 to 3.7E-03. Men had slightly higher risks (*Me* = 1.2E-05) than their female counterparts (*Me* = 7.1E-06) but the differences were not significant (U = 1103.5; $p > 0.1$).

The “Age” factor had a considerable statistically significant effect on CAD likelihood in smoking employees of the EMS: in general (H = 75.9; $p < 0.01$); men (H = 28.0; $p < 0.01$); women (H = 24.6; $p < 0.01$). In the “younger” age subgroup, there were no individuals with unacceptable R_{CAD} values, while in the “middle” and "senior" subgroups, the proportion of individuals with such risk levels was 2.7 % and 53.3 %, respectively. Sex differences between values of R_{CAD} the compared age subgroups were insignificant ($p > 0.1$).

Smoking intensity had a statistically significant effect (H = 15.2; $p < 0.01$) on likelihood of lung and bronchial cancer in smoking EMS: median R_{LBCa} values consistently increased as smoking intensity increased, from 9.4E-06 in the subgroup of employees with relatively low individual F^S values to 1.3E-05 and 3.7E-05 in the subgroups with medium IR and high IR. In the subgroup of employees with high IR, the proportion of individuals with unacceptable R_{LBCa} values was 30 %, which was significantly higher than in the subgroup of employees with relatively low SI (6.5 %; $p < 0.001$) and medium SI (11.1 %; $p < 0.05$).

Likelihood of coronary heart disease in smoking employees showed a slightly lower, but still statistically significant direct correlation with SI (H = 7.8; $p < 0.05$); median R_{CAD} values were almost equal in the subgroups with relatively low and average SI (7.4E-06 and 7.7E-06, respectively), and the median was 2.6E-05 only in the subgroup of employees with high SI. The proportion of individuals with unacceptable R_{CAD} values was almost equal in all subgroups with different SI ($p > 0.1$).

Conclusion. Smoking is a health risk factor for 27.5 % of emergency medical service personnel, including 42.5 % of men and 21.3 % of women. Smokers accounted for 66.7 % among men aged between 31 and 40 years. Prevalence of smoking did not de-

pend on age in the female part of the sample. The proportion of smokers among physicians and paramedics was 28.3 % and 28 %, respectively ($p > 0.1$). Smoking intensity of the respondents did not show statistically significant dependence on sex and age factors. Based on the results of risk analysis, it was found that smokers were most likely to develop lung and bronchial cancer and ischemic heart disease. The proportion of people with unacceptable levels of additional risks of the analyzed diseases (> 1.4E-04) equaled 43.3 % and 53.3 % respectively among people older than 40 years. Likelihood of lung and bronchial cancer and coronary heart disease was statistically significantly related to smoking intensity.

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Research article

THE RISK OF COLORECTAL CANCER INCIDENCE IN A COHORT OF INDIVIDUALS OCCUPATIONALLY EXPOSED TO IONIZING RADIATION

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The increased risk of colorectal cancer following ionizing radiation exposure was demonstrated in a number of epidemiological studies. Earlier, no impact of occupational radiation exposure on colorectal cancer incidence or mortality was observed in a cohort of workers of the nuclear industrial facility, Mayak Production Association (PA). Extension of the follow-up of the cohort and improvement of dose estimates for personnel made it possible to update the earlier findings.

The study objective is to assess the risk of colorectal cancer incidence associated with chronic occupational radiation exposure taking into account non-radiation factor effects.

The study cohort included 22,377 workers employed at the reactor, plutonium-producing and radiochemical plants of Mayak PA (hiring period 1948–1982; follow-up period ended on December 31, 2018). Using the Poisson regression (EPICURE software), the relative risks (RRs with 95 % confidence intervals, (95 % CI)) of colorectal cancer incidence were estimated depending on the most significant non-radiation factors (sex, age, smoking, alcohol consumption, excessive body mass and obesity, intestinal polyps, chronic colitis). These values were also calculated for certain ranges of occupational exposure doses relying on data provided by 'The Mayak Worker Dosimetry System – 2013'. The linear model was used to analyze the dose-response relationship.

In the study cohort, the RR of colorectal cancer incidence was lower in females than in males: 0.72 (95 % CI: 0.55; 0.96) for colon and 0.48 (95 % CI: 0.34; 0.67) for rectum. The increased RR of the rectum cancer incidence was observed for cases with intestinal polyps: 3.42 (95 % CI: 1.68; 6.19). The colon cancer incidence risk increased with increasing age of workers, but other non-radiation factors were not shown to affect the results. This study supported the earlier results: no association was observed between the risk of colorectal cancer incidence and doses of occupational external gamma-ray or internal alpha-particle exposures.

Keywords: *colon cancer, rectum cancer, external gamma-ray exposure, internal alpha-particle exposure, risk factors, nuclear workers, Poisson regression, analysis of dose-response relationship.*

Colorectal cancer (colon and rectum cancer) occupies a significant place in incidence and mortality caused by malignant tumors (MTs) [1]. Over the last decades, incidence of colorectal cancer has been growing in most countries, Russia included [1, 2]. Given that, etiology of colorectal cancer has been given a lot of expert attention.

Age older than 50 years, male sex, specific lifestyles (dietary patterns, smoking, alcohol consumption, and low physical activity), and obesity are the most significant risk factors of colorectal cancer [3–7]. Approximately 25–30 % of patients with colorectal cancer (CRC) have a family history of the disease attributed to genetically-determined high sensitivity to environmental exposures as well as habitual behaviors [8], and about 5 % of all colorectal cancer cases are caused by hereditary mutations [9].

The International Agency for Research on Cancer (IARC) lists colon and rectum MTs as cancer sites with evidenced associations between tumor progression and exposure to ion-

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izing radiation [10]. An elevated risk of colorectal cancer was reported for atomic bomb survivors exposed to acute gamma-neutron radiation in Japan (an LLS cohort) as well as for patients who had once been prescribed radiotherapy to treat MTs in organs of the pelvis minor [11–16].

Some growth in the excess relative risk of colorectal cancer was identified for nuclear workers in France, Great Britain and the USA (INWORKS); however, a significant relationship with an occupational exposure dose was established only for rectum cancer [17]. No relationships between exposure doses and incidence (in 1948–2004) or mortality (1948–2008) caused by colorectal cancer were established in the cohort made of workers employed at Mayak Production Association (Mayak PA), the first nuclear enterprise in Russia [18–19]. Extension of the follow-up of the cohort and improvement of dose estimates for Mayak PA personnel made it possible to update the earlier findings by conducting the present study [20].

The aim of this study was to assess effects of chronic occupational radiation exposure and non-radiation factors on the colorectal cancer risk in a cohort of nuclear workers.

Materials and methods. The analyzed cohort includes workers employed at reactor, radiochemical and plutonium-producing plants of Mayak PA (the hiring date is within 1948–1982) and covers the period up to December 31, 2018. The analyzed period was limited to the date of the last medical entries for workers who dropped out of observation or a date of death for deceased workers. The total number of people in the cohort is 22,377; women account for 25 % in it. Previous studies [21] describe in detail how the medical follow-up of the Mayak PA personnel is organized, sources and methods for obtaining data on incidence and non-radiation factors as well as the 'Clinic" database, which is a valuable resource for conducting epidemiological studies. Complete data on incidence were collected for 21,679 (97 %) of the cohort members. Forty-three workers were excluded from analysis of the colorectal cancer risk related to chronic radiation exposure; in the first years of the Mayak PA operation, they had been exposed to acute gamma radiation at high doses, which had led to acute radiation sickness (Table 1).

Table 1

The description of the analyzed cohort

The cohort structure	**Number of workers (%)**
Number of people in the cohort	22,377
Dropped out of observation	698
Suffered from acute radiation sickness	43
Are included in the study	21,636 (100 %)
Occupational exposure	***Me*** **($Q_{25\%}$–$Q_{75\%}$)**
A dose of external gamma-ray exposure absorbed in the colon wall, Gy	0.163 (0.047–0.527)
A dose of internal alpha-particle exposure absorbed in the colon wall, Gy	0.00018 (0.00005–0.0007)

N o t e: *Me* is median, $Q_{25\%}$–$Q_{75\%}$ is interquartile range.

By the end of the observation period, 43 % of the people in the analyzed cohort were older than 60 years. Sixty-three percent of the workers were hired at the nuclear enterprise in 1948–1960 when the production was in the process of formation and occupational exposure doses were the highest [20]. Duration of occupational radiation exposure exceeded 20 years for 33 % of the analyzed workers.

Workers employed at the reactor plant (24 % of the cohort members) experienced only external gamma-ray exposure whereas workers of the radiochemical (42 % of the cohort members) and plutonium-producing (35 % of the cohort members) plants were additionally exposed to alpha-active plutonium-239 aerosols. Individual doses of external gamma-ray exposure are known for all cohort members whereas doses of internal alpha-particle exposure are available only for 36 % of workers exposed to plutonium-239. This is due to peculiarities related to implementation of occupational radiation exposure monitoring at Mayak PA [20].

Total doses of external gamma-ray exposure and internal alpha-particle exposure (hereinafter gamma- and alpha-doses) absorbed in the colon wall were provided by the Mayak Worker Dosimetry System – 2013 [20] as of the date when colorectal cancer was diagnosed (the end of the observation period for workers without cancer in the cohort), a lag period was 0 years. In addition to that, a lag-period of 10 years was used to estimate the excess relative risk per unit dose (ERR/Gy). In this case, doses accumulated over the first 10 years of employment at Mayak PA were included into the zero-dose category. Characteristics of exposure doses (the lag period is 0 years) for the workers are provided in Table 1.

Risks were analyzed separately for colon and rectum cancer. We calculated relative risks (RR) of colorectal cancer incidence associated with non-radiation factors as well as for certain categories of occupational radiation exposure doses. The following non-radiation factors were taken into account: sex, age, smoking status, alcohol consumption, body mass index (BMI = weight (kg) / height (m^2)), chronic colitis as well as intestinal polyps in medical history.

Comprehensive data on non-radiation factors were available for most cohort members: smoking status, 99 %; alcohol consumption, 96 %; BMI values, 82 % of the analyzed workers. Smoking status was estimated as of the end of the follow-up period. Alcohol consumption was classified as follows: 'rarely' and 'moderately', if the workers used the same definitions when describing their drinking habits; 'alcohol abuse', if 'binge drinking' or 'chronic alcoholism' were diagnosed in a worker by an addiction specialist within the follow-up period. Two BMI categories were considered, namely BMI < 25 kg/m^2 (normal weight) and ≥ 25 kg/m^2 (overweight or obesity).

At early stages, a tumor can develop either under disguise of another disease or without any clinical manifestations; therefore, data on chronic colitis as well as intestinal polyps were taken into account if an interval between these diagnoses and diagnosed colorectal cancer (the end of the follow-up for workers without it) was not shorter than 2 years. A similar approach (a 2-year lag) was used in BMI calculation. Workers without available information on any analyzed factor were included into a separate category ('unknown').

Risks of colorectal cancer incidence were estimated based on the Poisson regression using the AMFIT module; to group the data and calculate person-years at risk, the DATAB module of the EPICURE software[1] was used. While estimating RR, the stratification by age and sex was applied.

The following model was used to estimate ERR/Gy for colorectal cancer incidence:

$$\lambda = \lambda_0 (s, a, x_1 \ldots .x_n) \times (1 + \beta D),$$

where λ_0 is the background risk, β is excess relative risk per dose unit (ERR/Gy), and D is gamma dose or alpha dose.

When calculating the background risk (λ_0), we applied stratification to take into account the impact of sex, s; age, a; and other factors mentioned above, $x_1 \ldots .x_n$. This includes an adjustment for an alpha dose in the analysis of the incidence risk due to gamma dose and vice versa. The maximum likelihood technique was used to calculate 95 % confidence intervals (95 % CI) for *RR* and ERR/Gy. In case CI boundaries were not identified, the abbreviation 'n/a' was used. The obtained estimates were considered statistically significant at $p < 0.05$.

Results and discussion. As of December 31, 2018, colorectal cancer was diagnosed in 409 members of the analyzed cohort; several colorectal MTs of different sites were identified in 19 of them during the follow-up period. For these workers, the earliest diagnosed cancer case was considered within risk analysis. Therefore, risk analysis included 225 colon cancer cases (66 % males and 34 % females) and 184 rectum cancer cases (74 % males and 26 % females). Diag-

[1] Preston D.L., Lubin J.H., Pierce D.A., McConney M.E. Epicure Users Guide. Seattle, WA, Hirosoft International Corporation, 1993.

nosed colorectal cancer was histologically verified in 89 % of workers.

The colorectal cancer risk was lower for women than men in the analyzed cohort; the *RR* = 0.72 (95 % CI: 0.55–0.96) was estimated for colon cancer and the *RR* = 0.48 (95 % CI: 0.34–0.67) was estimated for rectum cancer (Table 2). The colorectal cancer risk increased with age and reached its maximum in the age group of 70–79 years. We established a significant increase in the rectum cancer risk, *RR* = 3.42 (95 % CI: 1.68–6.19) for workers who had intestinal polyps. We did not establish any significant relationships between the colorectal cancer risk and smoking status, alcohol consumption, chronic colitis, or BMI values in the analyzed cohort (Table 2).

Table 2

Relative colorectal cancer risk (*RR*)

Factor	Colon cancer			Rectum cancer		
	Cases	Person-years	*RR* (95 % CI)	Cases	Person-years	*RR* (95 % CI)
Sex:						
men	148	413,534	1	136	414,023	1
women	77	176,022	0.72 (0.55–0.96)	48	176,398	0.48 (0.34–0.67)
Age:						
< 50	13	360,317	0.02 (0.01–0.03)	12	360,584	0.02 (0.01–0.04)
50–59	45	108,115	0.20 (0.14–0.30)	36	108,260	0.21 (0.14–0.33)
60–69	74	73,273	0.51 (0.37–0.70)	63	73,496	0.57 (0.40–0.83)
70–79	73	37,678	1	53	37,873	1
≥ 80	20	10,173	1.05 (0.62–1.69)	20	10,207	1.52 (0.89–2.51)
Smoking status:						
never	105	253,806	1	68	254,393	1
quit smoking	62	123,324	1.1 (0.74–1.64)	60	123,482	1.46 (0.95–2.30)
smoke	55	205,044	1.06 (0.70–1.60)	54	205,135	1.46 (0.93–2.32)
unknown	3	7382	1.55 (0.38–4.14)	2	7410	1.51 (0.25–4.83)
Alcohol consumption:						
rarely	68	154,229	1	46	154,554	1
moderately	107	268,936	0.88 (0.61–1.28)	95	269,168	0.92 (0.6–1.43)
abused	43	144,720	0.78 (0.49–1.24)	38	145,013	0.78 (0.46–1.3)
unknown	7	21,669	1.08 (0.44–2.26)	5	21,684	0.94 (0.32–2.21)
Body mass index:						
normal	32	99,242	1	21	99,338	1
above normal	98	268,849	0.95 (0.64–1.44)	83	268,972	1.30 (0.82–2.16)
unknown	95	221,465	1.03 (0.70–1.56)	80	222,110	1.38 (0.87–2.30)
Intestinal polyps:						
no	221	586,679	1	174	587,421	1
yes	4	2876	1.13 (0.35–2.68)	10	2999	3.42 (1.68–6.19)
Colitis:						
no	162	501,668	1	141	502,026	1
yes	63	87,888	0.95 (0.69–1.28)	43	88,394	0.8 (0.55–1.13)
Gamma-dose, Gy:						
0–0.2	103	316,989	1	71	317,455	1
> 0.2–0.5	53	109,360	1.08 (0.77–1.51)	45	109,621	1.25 (0.85–1.82)
> 0.5–1.0	36	72,710	1.02 (0.69–1.48)	34	72,737	1.32 (0.86–1.99)
> 1.0	33	72,337	0.89 (0.59–1.32)	34	72,444	1.24 (0.81–1.86)
Alpha-dose, Gy:						
0–0.0001	46	178,043	1	31	178,259	1
> 0.0001–0.0005	62	89,208	1.30 (0.89–1.93)	29	89,538	0.87 (0.52–1.46)
> 0.0005–0.001	16	26,647	0.96 (0.53–1.67)	21	26,692	1.80 (1.01–3.13)
> 0.001	27	38,494	0.93 (0.57–1.50)	29	38,546	1.46 (0.87–2.45)
unknown	74	249,465	1.03 (0.71–1.50)	74	249,687	1.46 (0.97–2.25)

Categorical analysis did not reveal any impacts of gamma- and alpha-doses on the colorectal cancer risk for workers in the analyzed cohort. A significant increase in the rectum cancer, *RR* = 1.80 (95 % CI: 1.01–3.13), was detected only for internal alpha-particle exposure at a dose within 0.0005–0.001 Gy (against 0.0–0.0001 Gy) but the reasons for that need further clarification (Table 2).

The dose-response relationship was analyzed based on a linear model and this analysis confirmed the results obtained by categorical analysis (Tables 3 and 4). ERR/Gy estimates varied between -0.03/Gy and 0.04/Gy (colon cancer) and between 0.17/Gy and 0.29/Gy (rectum cancer) for the lag period of 0 years and with the use of background risk models with sets of different non-radiation factors. The results were not significant (Table 3).

ERR/Gy of alpha-dose varied within -5.73/Gy and -4.78/Gy (colon cancer) and between -5.69/Gy and -4.80/Gy (rectum cancer) for the 0-year lag period but it did not reach statistical significance either (Table 4). Analysis based on occupational exposure doses, which considered the 10-year lag period, did not demonstrate any relationship between occupational radiation exposure and the colorectal cancer risk (Tables 3 и 4).

Table 3

Excess relative risk (*ERR*/Gy) of colorectal cancer: external gamma-ray exposure

Factors considered in the background risk model	*ERR*/Gy (95 % CI)	
	Colon cancer	Rectum cancer
0-year lag period		
Age, sex	0.01 (-0.13–0.21)	0.17 (-0.08–0.55)
Age, sex, smoking	0.01 (-0.14–0.20)	0.17 (-0.08–0.56)
Age, sex, smoking, alcohol consumption	0.03 (-0.13–0.24)	0.22 (-0.06–0.65)
Age, sex, smoking, alcohol consumption, body mass index	0.04 (-0.12–0.25)	0.20 (-0.07–0.62)
Age, sex, smoking, alcohol consumption, body mass index, intestinal polyps, colitis	0.02 (-0.14–0.23)	0.18 (-0.09–0.62)
Age, sex, smoking, alcohol consumption, body mass index, intestinal polyps, colitis, alpha-dose	-0.03 (-0.20–0.21)	0.29 (-0.06–0.93)
10-year lag period		
Age, sex	0.02 (-0.13–0.23)	0.16 (-0.09–0.54)

Table 4

Excess relative risk (*ERR*/Gy) of colorectal cancer: internal alpha-particle exposure

Factors considered in the background risk model	*ERR*/Gy (95 % CI)	
	Colon cancer	Colon cancer
0-year lag period		
Age, sex	-5.73 (n/a–37.61)	-4.80 (n/a–76.58)
Age, sex, smoking	-4.97 (n/a–33.06)	-5.25 (n/a–72.78)
Age, sex, smoking, alcohol consumption	-4.92 (n/a–34.82)	-5.34 (n/a–79.45)
Age, sex, smoking, alcohol consumption, body mass index	-5.69 (n/a–38.41)	-5.30 (n/a–85.37)
Age, sex, smoking, alcohol consumption, body mass index, intestinal polyps, colitis	-5.16 (n/a–32.61)	-5.28 (n/a–87.76)
Age, sex, smoking, alcohol consumption, body mass index, intestinal polyps, colitis, gamma-dose	-4.78 (n/a–46.65)	-5.69 (n/a–79.55)
10-year lag period		
Age, sex	-9.05 (n/a–64.79)	-9.24 (n/a–125.7)

N o t e: n/a means limits of the CI interval were not identified.

We observed elevated colorectal cancer risks for older age groups as well as for men compared to women in the analyzed cohort. Our findings are consistent with results of other epidemiological studies where 90 % of malignant tumors of this localization were reported in patients older than 50 years [1, 5]. Men have 1.4–1.5 times higher risks of colorectal cancer than women; this fact is explained by differences in the prevalence of lifestyle factors in male and female populations [5, 6].

Smoking plays a significant role in colorectal cancer etiology, which is especially relevant for tumors in the proximal colon and the rectum. Levels of risk depend on smoking intensity and duration and are different for specific molecular subtypes of colorectal cancer [22, 23]. Some epidemiological studies suggest that even moderate regular drinking increases the colorectal cancer risk by 20–40 % against people who drink rarely or even do not drink alcohol at all [24].

Chronic inflammatory bowel diseases (CIBD) are a significant risk factor of colorectal cancer and approximately 10–15 % of CIBD patients die due to malignant tumors of this localization [25]. An elevated colorectal cancer risk in obese people is also explained by inflammatory changes in intestinal epithelium due to metabolic disorders [26]. Changes in organization and structure of intestinal epithelium induced by inflammation promote growth of adenomatous polyps which can undergo malignant transformation in 10–20 % cases [27].

In this study, we established an elevated rectum cancer risk in patients with intestinal polyposis but did not reveal any impacts of such factors as smoking, alcohol consumption, chronic colitis, overweight and obesity on colorectal cancer incidence among the analyzed cohort of nuclear workers. It is noteworthy that according to accumulated research data, microbiota in the large intestine has considerable influence on metabolism of ethanol and tobacco smoking products as well as on development and outcome of inflammatory reactions. This microbiota is considered a carcinogenesis mediator [28]. Byproducts of gut microbiota can have either carcinogenic or anti-tumor properties and this can modify effects produced by carcinogenic factors in some individuals. State of gut microbiota largely depends on nutrition [29].

Large-scale epidemiological studies observed effects of ionizing radiation on colorectal cancer incidence and mortality; however, estimated risk levels differ for MTs of the colon and rectum. In the LSS cohort, a positive significant relationship was demonstrated between doses of acute gamma-neutron exposure and the colon cancer risk in atomic bomb survivors [11–13]. *ERR*/Gy estimates adjusted for smoking, alcohol and meat consumption, and body mass index were calculated for 70-year old people who had been exposed at the age of 30 years (both sexes). The results were as follows: colon cancer (all sections), *ERR*/Gy = 0.63 (95 % CI: 0.34–0.98); the proximal colon, *ERR*/Gy = 0.80 (95 % CI: 0.32–1.44); the distal colon, *ERR*/Gy = 0.50 (95 % CI: 0.04–0.97). These estimates were not significant for rectum cancer: *ERR*/Gy = 0.023 (95 % CI: -0.081–0.13) [11].

Previously, no effects of acute gamma-neutron exposure were observed in the LSS cohort for rectum cancer incidence (1958–1998) and mortality (1950–2003) [12, 13]. Estimates of radiation-related colon cancer risks adjusted for sex, age and age of exposure (without taking into account other non-radiation factors) were the same: *ERR*/Gy = 0.54 (90 % CI: 0.30–0.81) for incidence and *ERR*/Gy = 0.54 (90 % CI: 0.23–0.93) for mortality [12, 13].

Meta-analysis of findings reported in studies of patients who were treated with radiotherapy for prostate cancer revealed an increase in relative risk (*RR*) of rectum cancer, *RR* = 1.64 (95 % CI: 1.39–1.94) and colon cancer, *RR* = 1.33 (95 % CI: 1.02–1.76) compared to those patients who had never received the radiotherapy [14]. Elevated colon cancer risks were established 8 years after and rectum cancer risks 15 years after radiotherapy for cervical cancer [15]. The colon cancer risk was *RR* = 2.00 (95 % CI: 1.43–2.80) in these female patients; the rectum cancer risk was

RR = 4.04 (95 % CI: 2.08–7.86). The observed *RR* values remained the same during the next 20 years of the follow-up [15]. An elevated colorectal cancer risk was also observed for patients who had undergone the radiotherapy at doses between 20 Gy and 29.99 Gy for whom odds ratio was 7.8 (95 % CI: 1.3–56.0) compared to those who had never received the radiotherapy [16].

Elevated risks of rectum cancer mortality were reported for nuclear workers of the United Kingdom (the UK) as well as in the joint INWORKS study, which included cohorts of occupationally radiation-exposed workers from France, the UK and the USA [17, 30]. Cumulative exposure doses absorbed in the large intestine were 0.4–19.8 mGy in INWORKS workers and the risk of rectum cancer mortality calculated using maximum likelihood technique based on the Poisson regression was *ERR*/Gy = 1.87 (90 % CI: 0.04–4.52) [17]. When the analysis was performed by using hierarchical regression, *ERR*/Gy estimates for rectum cancer were not significant. The INWORKS did not reveal a relationship between radiation doses from occupational exposure and the risk of colon cancer mortality [17].

Epidemiological studies conducted in various countries did not report any findings indicating an association between internal alpha-particle exposure and the colorectal cancer risk in industrial workers exposed to plutonium or radium; in patients who had been treated with radium- or thorium-based medications, either diagnostic or therapeutic ones; as well as in individuals exposed to radon (miners and general population) [31–36]. It is noteworthy that doses of alpha-active nucleotides absorbed in the intestine were very low in all cases mentioned above [31–36].

Previously, incidence [18] and mortality [19] due to MTs of various localizations were analyzed in the cohort of Mayak PA workers. The analysis did not reveal any relationship between occupational exposure doses (gamma and alpha radiation) and colorectal cancer. A study of cancer incidence included workers hired at the reactor, plutonium-producing and radiochemical plants of Mayak PA in 1948–1982 and covered the follow-up period until December 31, 2004 [18]; a study of cancer mortality also included personnel hired at auxiliary production of Mayak PA and covered a longer follow-up period up to the end of 2008 [19]. Occupational exposure doses were provided by the 'Mayak Worker Dosimetry System – 2008'; sex, age, and smoking status were considered in the baseline risk calculations.

In this study, the follow-up period was extended up to 14 years for the same cohort; occupational exposure doses were provided by the improved 'Mayak Worker Dosimetry System – 2013' [20]; we used a wider set of non-radiation factors in the baseline risk modeling (alcohol consumption, intestinal polyps, chronic colitis, and BMI). This analysis, similarly to the previous one, did not reveal any significant relationship between occupational radiation exposure doses and the colorectal cancer risk.

It is noteworthy that the number of colorectal cancer cases included in this study was relatively small. In addition to that, we did not consider workers' dietary habits, physical activity, other individual peculiarities (genetic predisposition, state of gut microbiota), or interactions between specific risk factors. This might affect the study findings.

Conclusions:

1. This study did not find any impact of chronic occupational external gamma-ray exposure or internal alpha-particle exposure on the colorectal cancer risk in the cohort of Mayak PA workers.

2. We observed a significant increase in the colorectal cancer risk in older age groups as well as in males compared to females; in addition to that, the rectum cancer risk was higher in workers diagnosed with intestinal polyposis.

3. We did not establish any associations between the colorectal cancer risk in the study cohort and such factors as smoking, alcohol consumption, overweight and obesity, or chronic colitis.

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THE SIGNIFICANCE OF RISK FACTORS FOR ACQUIRING HEPATITIS B AND C VIRUS INFECTIONS IN CHILDREN WITH ONCOLOGICAL AND HEMATOLOGICAL DISEASES AND IMMUNODEFICIENCIES

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Patients with oncological and hematological diseases are at high risk of nosocomial bloodborne infections (hepatitis B, hepatitis C, and HIV) due to their immunosuppressed condition and highly invasive treatment. The aim of our study is to identify the key risk factors of acquiring bloodborne infections among patients with hematological and oncological diseases and to determine the causes of uneven prevalence of hepatitis B and C among main clinical groups of patients.

The study was carried out from 2021 to 2023. The study cohort consisted of 500 patients, with 100 patients in each clinical group: primary immunodeficiencies PID), disorders of the blood and blood-forming organs (BD), hematological malignancies (HM), malignant solid tumors (MST), benign tumors (BT).

The median burden of invasive procedures per patient in the patients with HM, MST, BD, BT, and PID amounted to 10.9, 6.2, 5.1, 4.1, and 2.2 invasive interventions a day, respectively. The median infusion/injection burden was 8.3, 4.0, 2.7, 2.7, and 0.6 drugs a day, respectively. The median blood sampling burden amounted to 2.0, 1.7, 1.7, 1.3, and 1.6 samples a day, respectively. The median transfusion burden was 0.14, 0.07, 0.25, 0, and 0 units of transfused blood components a day, respectively. The median surgery burden was 0, 0.15, 0, 0.17, 0 surgical procedures a day, respectively. The medians for other medical procedures in all clinical groups amounted to 0.

The patients with PID representing a clinical group of patients with the highest prevalence of hepatitis B and C infections (2.5 % and 2.3 %, respectively) have the lowest level of invasive burden. It should be supposed that the major risk factor of acquiring HBV or HCV among patients with oncological and hematological diseases is the level of immunocompetence together with the impact of risk factors associated with invasive procedures such as blood transfusions, the use of venous catheters (for intravenous administration of drugs and blood sampling), and extensive surgeries.

Keywords: *risk factors, bloodborne infections, prevalence of HBV, prevalence of HCV, seroprevalence of HBV, seroprevalence of HCV, children with oncological and hematological diseases, transfusion-associated hepatitis, risk factors of acquiring nosocomial HBV and HCV infections.*

Patients with oncological and hematological diseases as well as patients undergoing hemodialysis are at high risk of nosocomial bloodborne infections (hepatitis B, hepatitis C, and human immunodeficiency virus (HIV)) due to their immunosuppressed condition associated with the underlying disease and specific treatment [1–8]. Factors

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most commonly considered to be involved in the transmission of bloodborne infections among patients with oncological and hematological diseases are blood transfusions, unsafe injections and infusions, surgeries and other invasive diagnostic and treatment procedures [9–19].

Testing for hepatitis C virus (HCV) infections of patients with oncological and immunological diseases admitted to the D. Rogachev NMRCPHOI of Ministry of Healthcare of the Russian Federation (hereinafter referred to as the Center) from different regions of Russia showed high prevalence of these infections among them. From 2014 to 2020, it amounted to 1.7 % which is 50 times higher than the average national prevalence reported for children. The prevalence of HCV infection among patients with different oncological and hematological diseases was found to be high in patients with PID (2.8 %), BD (2.2 %), MST (1.9 %), HM (1.6 %) [20].

Materials and methods. The aim of the study was to identify possible causes of uneven prevalence of hepatitis B virus (HBV) and HCV infections among patients with oncological and hematological diseases, namely causes of high HCV and HBV prevalence among patients with PID and other clinical groups of patients (BD, MST, and HM). The objectives of the study were to assess the burden of invasive procedures, to correlate it with the prevalence of HCV and HBV infections among patients from the main clinical groups and to hypothesize the possible causes and risk factors for acquiring these infections.

In our study, we assessed the burden of invasive procedures in patients who had undergone treatment at the Center from 2021 to 2023. The study sample included 500 patients (100 patients in each clinical group: PID, BD, HM, MST, BT). To analyze the burden of invasive procedures in the patients, we assessed the infusion burden (the number of drugs infused), the frequency of diagnostic blood sampling (the number of blood tubes collected), the burden of blood transfusions (the number of units of blood and blood components transfused), surgery burden (the number of surgeries), the frequency of bone marrow aspirations and lumbar punctures and diagnostic endoscopic procedures (the number of invasive procedures per patient per day).

In order to correlate the results of our assessment of invasive burden with the prevalence of HBV and HCV, we used the retrospective data on the prevalence of these infections among patients who had received treatment at the Center from 2014 to 2022 (13,500 patients). These retrospective data included the results of laboratory testing for HBsAg, anti-HCV, HCV RNA, and HBV DNA performed at admission to the Center. All patients with HCV and HBV from this retrospective cohort were infected before admission to the Center. There were no cases of HBV or HCV infections acquired at the Center during the analysis period.

The analyzed group of patients was characterized by prior hospitalizations at the place of residence, the need for complex and technologically advanced diagnostic and treatment modalities that are unavailable in other regions of the country, and severe condition at admission to the Center.

The statistical analysis was conducted using Microsoft Excel. The significance of differences in quality parameters was assessed by using contingency tables and the calculation of χ^2 tests (95 % confidence intervals). A statistical comparison of the medians was made using the Mann – Whitney U test.

Results and discussion. It was revealed that the patients with HM experienced the highest burden of invasive procedures: the median daily burden among the patients with HM was 2 times higher than in the whole cohort of interest (n = 500) (10.9 vs 5.4, $p < 0.001$). The lowest median burden of invasive procedures was observed among the patients with PID; it amounted to 2.2 invasive procedures per patient per day, which is 5 times lower than in the patients with HM ($p < 0.001$) and 2.5 times lower than the average burden of invasive procedures per patient per day in the whole cohort of interest ($p < 0.001$) (Table 1, Figure 1).

Table 1

The median number of invasive procedures per 1 patient per day (2022)

Invasive procedures / Clinical diagnosis	Injections, infusions (drugs)	Blood sampling (tubes)	Blood transfusions (units)	Surgeries	Lumbar punctures/bone marrow aspirations	Diagnostic endoscopic procedures	Total burden
HM	8.3	2.0	0.1	0	0	0	10.9
MST	4.0	1.7	0.1	0.15	0	0	6.2
BD	2.7	1.7	0.3	0	0	0	5.1
BT	2.7	1.3	0	0.17	0	0	4.1
PID	0.6	1.6	0	0	0	0	2.2
All clinical groups	3.3	1.6	0	0	0	0	5.4

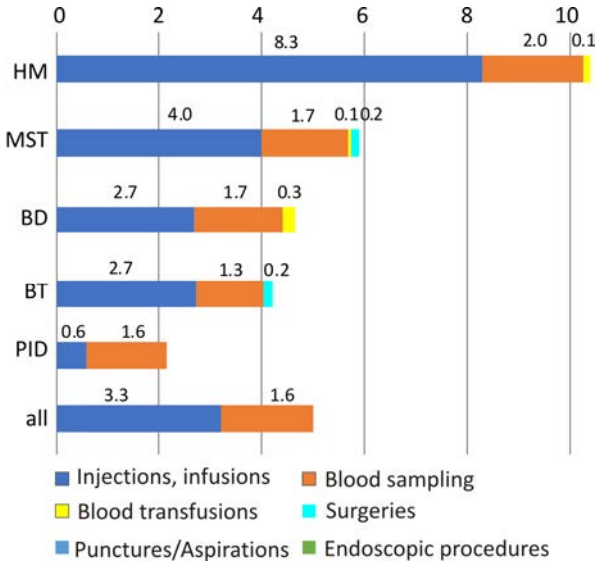

Figure 1. The median number of invasive procedures per 1 patient per day according to the type of procedures and clinical groups

We carried out a thorough analysis of each type of invasive interventions in all the clinical groups of patients. Parenteral administration of drugs was the most common invasive procedure in the patients with oncological and hematological diseases. To assess the burden of injections and infusions, we calculated the number of medications administered by the following parenteral routes: intravenous (IV) (intermittent (push or short) infusions and continuous infusions), subcutaneous (SC), intramuscular (IM), intrathecal (IT), and intraventricular (IVT).

The median number of medications administered to all patients from the cohort of interest was 3.3 per patient per day. The median number of medications administered per day to the patients with HM, MST, BD, BT, and PID was 8.3, 4.0, 2.7, 2.7, and 0.6, respectively. The patients with HM received the highest number of injections and infusions during treatment which is 2.5 times higher than the whole cohort of interest and statistically significantly higher than the patients from other clinical groups ($p < 0.05$). The patients with PID received the lowest number of parenteral medications, which is 14 times lower than the patients diagnosed with HM ($p = 0.00028$) and 6 times lower than the whole cohort of interest (Table 1, Figure 1).

At the Center, the most commonly used venous access for both intermittent and continuous infusions of medications was a central venous catheter (CVC).

The patients with HM received 5.1 medications per day administered as short infusions; the patients with MST, 3.3 medications; the patients with BT, 2.6; the patients with BD, 2.2; and the PID cases, 0.2. The patients with HM received the largest number of medications via short infusions which was twice as high as the median number of drugs administered this way at the Center (2.6). The patients with PID were given the smallest number of drugs as short intravenous infusions which was 16 times lower than the median number of medications administered this way at the Center, and 31 times lower than the number of drugs received by the patients with HM ($p = 0.00028$). The patients with HM received 2.8 drugs per day via continuous intravenous infusions, the patients with BD – 0.5 drugs, MST cases – 0.2, BT – 0, PID – 0 (Figure 2). The largest number of drugs administered via this route was given to the patients with HM.

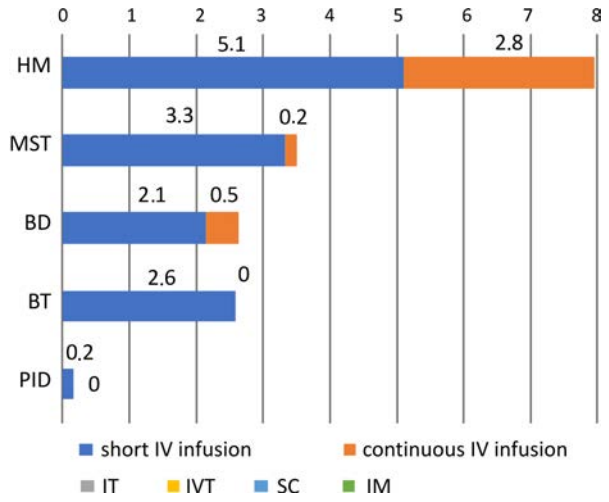

Figure 2. The median number of drugs per patient per day according to the disease and route of administration

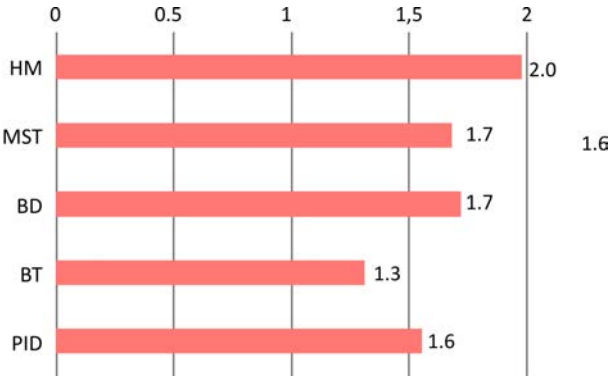

Figure 3. The median number of blood samples collected per patient per day according to the disease

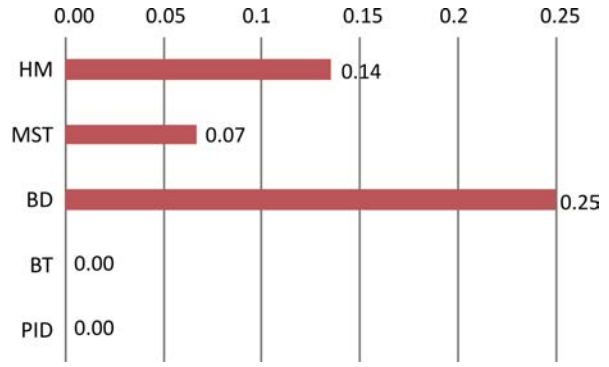

Figure 4. The median number of blood transfusions (doses of blood and its components) per patient per day according to the patient clinical group

The median number of drugs administered subcutaneously, intrathecally, intramuscularly and intraventricularly was 0 (Figure 2). Intrathecal and intraventricular routes were mostly used in the patients with HM.

The maximum burden of parenteral drug administration was registered in the patients with HM, with both the number of drugs and the route of their administration taken into account. Meanwhile, the patients with PID had the lowest injection/infusion burden.

Blood sampling was the second most frequent invasive procedure performed at the Center, after parenteral drug administration. In order to reduce the invasive and psychological burden in the patients, blood was collected from a central venous line in 89–99 % cases.

When assessing blood sampling burden, we discovered that the patients with HM underwent diagnostic blood testing more often than the others: the median number of blood specimens per patient per day was 2, and in the patients with PID this parameter was 1.3 times lower (1.6 vs. 2, $p = 0.017$) (Table 1, Figure 3). All the clinical groups experienced high invasive burden but the patients with HM were the most affected group.

The analysis of the burden of blood transfusions, namely, of the median amounts of transfused blood components, showed that the highest amount of blood was received by the patients with BD and HM: 0.25 and 0.14 doses of blood or its components per patient per day, respectively; while the patients with MST received 0.07 doses, and the patients with PID and BT – 0. The patients with BD underwent 1.8 times more blood transfusions than the patients with HM ($p > 0.05$) and 3.8 times more transfusions than the patients with MST ($p < 0.001$) (Table 1, Figure 4).

Since donor blood components with short shelf life (platelet concentrates, red blood cell containing components, granulocyte concentrates) are considered to be the most unsafe blood products, we decided to compare the number of transfusions of these components with that of quarantined ones among the different clinical groups. The patients with HM, MST and BD had the same median amount of transfused red blood cell containing components, namely, 0.06 dose. In the patients with HM and BD, the median amounts of transfused platelet concentrates were 0.03 and 0.06 doses per patient per day ($p = 0.89656$),

Table 2

The median number of doses of blood and its components transfused to 1 patient per day according to the patient clinical group and the transfused blood component

Blood component / Clinical diagnosis	Platelet concentrate	Red blood cell containing components	Granulocyte concentrate	Plasma	**All the blood components**
HM	0.03	0.06	0	0	0.14
MST	0	0.06	0	0	0.07
BD	0.06	0.06	0	0	0.25
BT	0	0	0	0	0
PID	0	0	0	0	0
All the patients	0	0	0	0	0

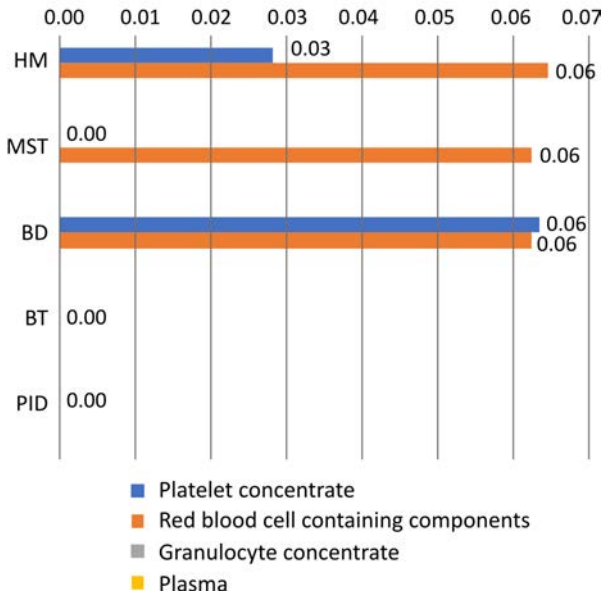

Figure 5. The median number of doses of blood and its components transfused to 1 patient per day according to the patient clinical group and the transfused blood component

respectively. The median amounts of other transfused blood components in the patients with HM, MST and BD as well as the median numbers of doses in the other groups (BT and PID) equalled 0 (Table 2, Figure 5). All the patient groups were at risk of acquiring bloodborne infections since most patients received blood components with short shelf life. The percentage of blood components with short shelf life transfused to the patients with HM was 83 %, the patients with MST – 79 %, BD – 83 %, BT – 74 %, PID – 95 %.

Thus, the highest burden of blood transfusions was registered in the patients with BD and HM, due to extensive replacement therapy with blood components that can potentially carry bloodborne pathogens.

Surgery burden assessment revealed that the median number of surgeries in the patients with MST was 0.15, while the patients with BT underwent a median of 0.17 surgeries per patient per day ($p = 0.5485$). In the other clinical groups, the median number of surgeries amounted to 0. The median number of surgeries undergone by the study cohort was also 0 (Table 3).

Since more extensive surgeries are associated with a higher risk of transmission of bloodborne infections, we analyzed the median numbers of surgeries stratified according to their complexity using the surgical complexity classification developed at the Center:

- Level I. Very low-risk surgeries: surgeries performed on the surface of the body without involving the inner structures;
- Level II. Low-risk surgeries: surgeries performed on the surface of the body with a few incisions, major surgeries without internal organ involvement, laparoscopy, oral surgeries, and limb reconstruction;
- Level III. Moderate-risk surgeries: surgeries on the internal organs and the intestines, open joint surgery, laparoscopy involving parenchymal organs, thoracoscopy, and microsurgery;
- Level IV. High-risk surgeries: extensive surgeries involving several organs or systems, surgery on the CNS;
- Level V. Extremely high-risk surgeries: surgeries on vital organs and systems in critically ill patients.

Table 3

The median number of surgeries per patient per day according to the clinical diagnosis and surgical complexity

	Level I	Level II	Level III	Level IV	Level V	Total number
HM	0	0	0	0	0	0
MST	0	0	0	0	0.08	0.15
BD	0	0	0	0	0	0
BT	0	0	0	0	0	0.17
PID	0	0	0	0	0	0
All the patients	0	0	0	0	0	0

An analysis of the number of surgeries stratified in accordance with their complexity showed that the median number of level V complexity surgeries was significant only in the patients with MST, amounting to 0.08 surgeries per patient per day. In the other clinical groups, the median number of surgeries of various complexity was 0 (Table 3).

Since the medians equalled 0, we had to analyze the distribution of the number of various complexity surgeries (Figure 6) in order to evaluate surgery burden in the different clinical groups. All the patients were shown to experience surgery burden to some extent but significant surgery burden was evident only in the patients with MST and BT, which was also demonstrated by the medians of the number of surgeries in these groups. Since the patients with MST underwent extensive level V complexity surgeries, the surgery burden in this group was judged to be higher than that in the BT patients. Fifty percent of the surgeries undergone by the patients with MST had level V complexity. The lowest surgery burden was registered in the patients with PID (Figure 6).

The median number of lumbar punctures and bone marrow aspirations was 0 in all the clinical groups. In this view, we set out to compare the distribution of the number of punctures/aspirations among the patient groups. The patients with HM were found to experience the highest burden of invasive procedures: 18 % of the patients underwent more than 0.1 punctures / aspirations per day (Figure 7).

The median number of endoscopic procedures was 0 in all the clinical groups. Our distribution analysis revealed that the highest number of endoscopic procedures was carried out in the patients with PID: 24 % of the patients underwent over 0.1 procedures per day (Figure 8).

Thus, the highest burden of endoscopy was registered in the patients with PID, while the patients from the other clinical groups experienced a minimal burden of invasive procedures.

When analyzing the prevalence of HBV and HCV in the main clinical groups of patients, we found that the most infected group was the one with the PID patients (HBV – 2.5 %, HCV – 2.3 %). HBV and HCV prevalence in the patients with PID was statistically significantly higher than in the patients with HM, BD and MST ($p < 0.05$). No significant difference in HCV prevalence was observed among the patients with HM, BD and MST (1.3 %, 1.3 %, 1.2 %, $p > 0.05$). There was no significant difference in HBV prevalence among the patients with HM and BD (0.9 %, 0.8 %, $p > 0.05$), but it was higher than in the patients with MST (0.2 %) ($p < 0.05$) (Figure 9).

Our analysis shows that invasive procedures have different significance depending on the clinical group of patients according to the special aspects of the organization of the D. Rogachev Center's work. Even though the results in other clinics may differ, our data can be taken into consideration when investigating cases of contracting bloodborne infections and instituting preventive and epidemic control measures among immunocompromised patients.

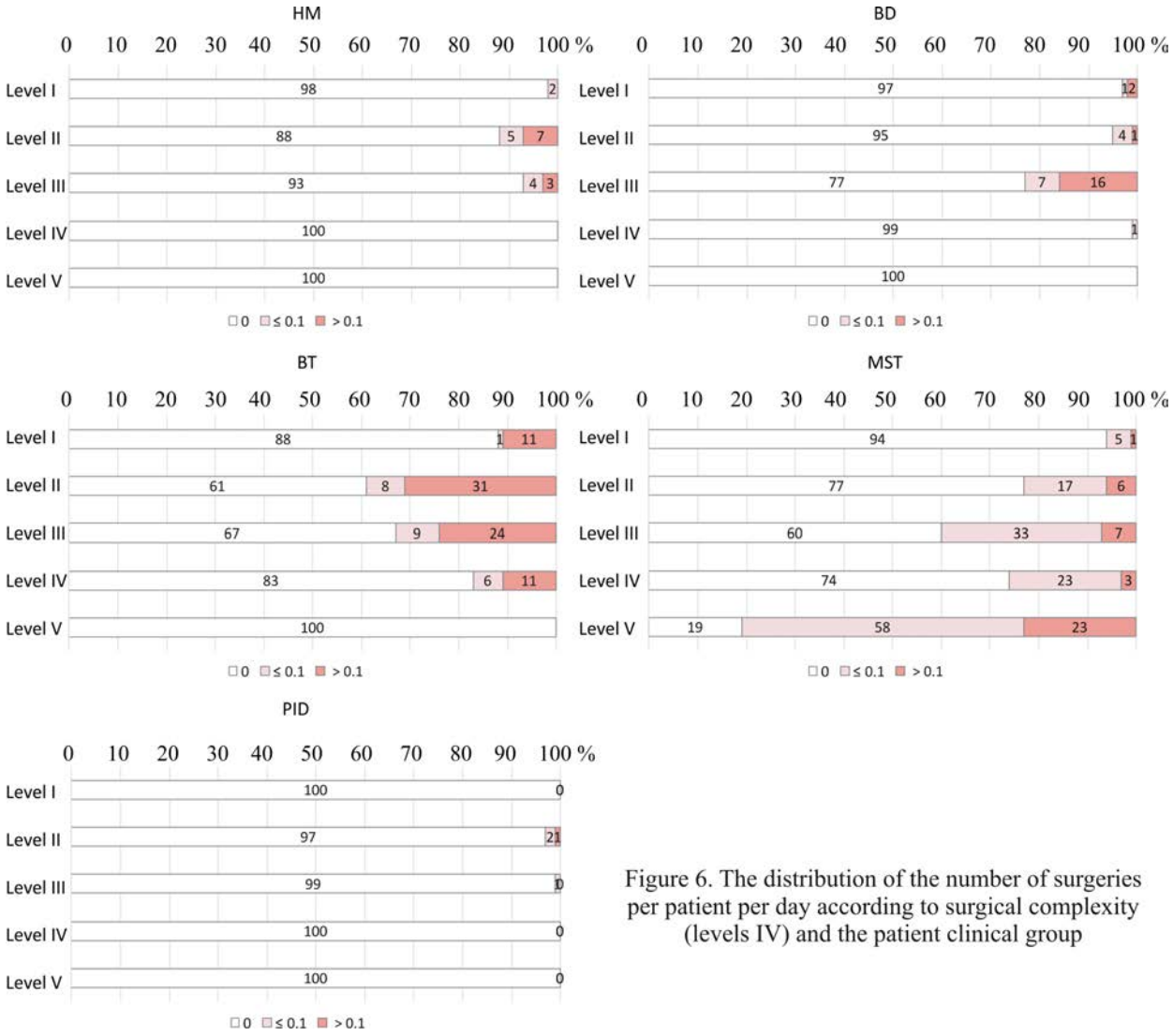

Figure 6. The distribution of the number of surgeries per patient per day according to surgical complexity (levels IV) and the patient clinical group

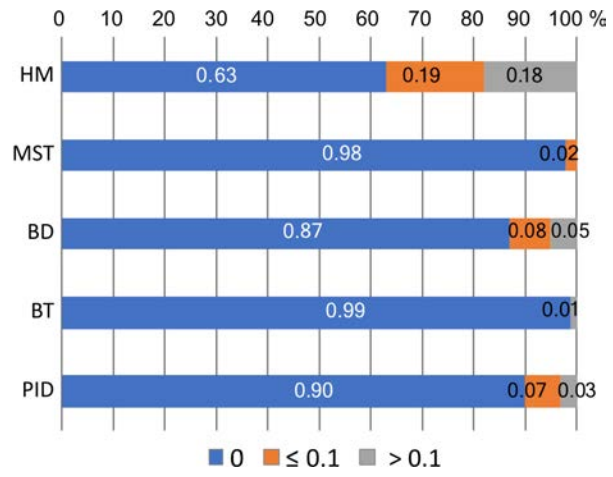

Figure 7. The distribution of the number of lumbar punctures and bone marrow aspirations per patient per day according to the clinical diagnosis

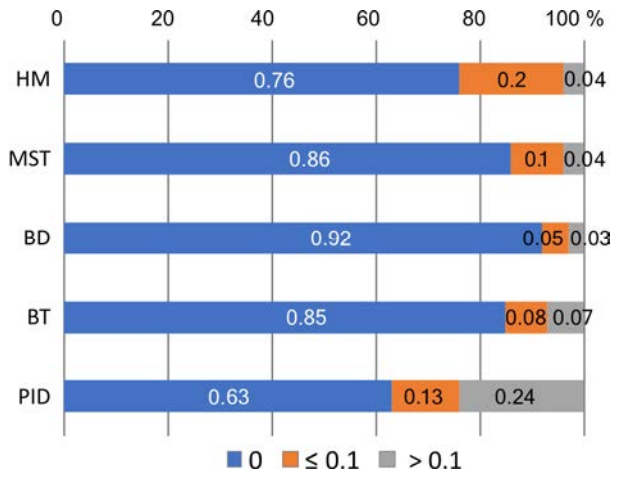

Figure 8. The distribution of the number of endoscopic procedures per patient per day according to the clinical diagnosis

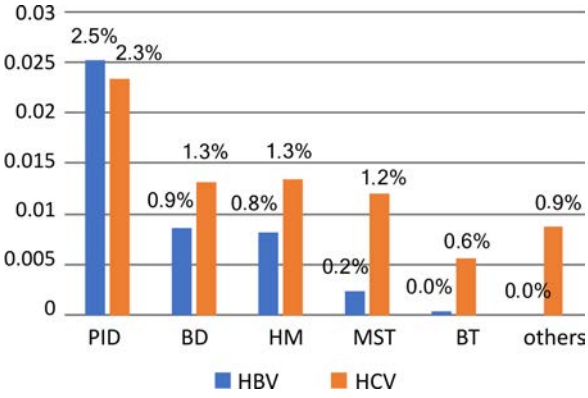

Figure 9. The prevalence of HBV and HCV infections in the main clinical groups of patients treated at the D. Rogachev NMRCPHOI, from 2014 to 2022 (n = 13 500)

Our analysis showed that the highest burden of invasive procedures among the main clinical groups of patients with oncological and hematological diseases and immunodeficiency conditions was observed in the patients with HM which underwent 10.9 invasive procedures per day, while the patients with PID experienced the lowest burden of invasive procedures, 2.2 invasive procedures per day, which is 5-fold lower than in the patients with HM and 2.5-fold lower than the average burden of invasive procedures at the Center (5.4 invasive procedures per patient per day).

When assessing certain types of invasive procedures, we found that the patients with HM had the highest infusion/injection burden in terms of the number of drugs administered. Routes of drug administration have varying degrees of invasiveness and therefore the risk of bloodborne infection transmission. The highest risk of getting infected is observed in case of intravenous drug administration using a catheter by intermittent infusions, since it involves numerous procedures with both the catheter and secondary IV accesses. Thus, in the patients with HM, the largest number of drugs was administered by intermittent intravenous infusions.

Another type of invasive procedures associated with miltifactorial risks of transmitting bloodborne infections is blood sampling. During blood sampling, all clinical groups of patients experienced high burden of invasive procedures but the highest burden was observed in the patients with HM.

The patients with BD and HM had the highest burden of blood transfusions both in terms of the number of units of transfused blood components and their safety (the number of unsafe platelet concentrates and red blood cell containing components).

The highest surgery burden was observed in the patients with MST and BT; in addition, the patients with MST underwent a higher number of extensive surgeries than patients from other clinical groups. The percentage of the patients with MST who underwent level V surgeries was 50 %.

The largest number of lumbar punctures and bone marrow aspirations was carried out in the patients with HM.

The lowest infusion/injection burden was observed in the patients with PID and was 14 times lower than in the patients with HM and 6 times lower than in the whole cohort of interest. The patients with PID had 1.3 times fewer blood samples collected daily than the patients with HB. The median numbers of blood transfusions, surgical interventions, punctures/aspirations and endoscopic examinations were 0 in the patients with PID. According to our analysis of the distribution of the number of surgeries and lumbar punctures/bone marrow aspirations, among all the clinical groups of patients, the PID patients had the lowest invasive burden associated with surgeries and lumbar punctures/bone marrow aspirations and the highest invasive burden associated with endoscopic procedures.

Our retrospective analysis demonstrated a high prevalence of bloodborne infections among patients with oncological and hematological diseases and immunodeficiency conditions admitted to the Center from different regions of the country. HBV and HCV prevalence among the patients treated at the Center was high; the highest prevalence was observed in the group of patients with PID.

When correlating the results obtained by assessing the burden of invasive procedures with the level of HBV and HCV prevalence, we found that the patients with PID who

experienced the lowest burden of invasive procedures, had the highest prevalence of HBV and HCV. We can assume that a lower dose of an infectious agent is required to infect patients with PID due to their immunodeficiency state. Moreover, the analysis of medical records revealed that the patients with PID have a longer time to diagnosis in outpatient clinics compared with the patients with HM and MST: they undergo numerous invasive procedures during their long stay in clinics not specialized in the treatment of immunocompromised patients until a final diagnosis is established.

In the previous studies, blood transfusions and medical procedures were considered the leading risk factors for contracting bloodborne infections in patients with oncological and hematological diseases[1]. Based on the data obtained from our study, it can be assumed that the leading risk factor for contracting HBV and HCV in patients with oncological and hematological diseases is the level of immunocompetence of patients in combination with the influence of risk factors associated with invasive procedures.

The next highest prevalence of HCV was observed among the patients with HM, BD, MST, most likely due to the high burden of invasive procedures during drug administration and blood sampling. In patients with induced immunosuppression, there might have been infection control breaches in the preparation of infusions, blood sampling and the management of IV catheters (the most commonly used venous access devices for drug administration in these patients). There were additional risk factors for contracting infections: numerous lumbar punctures and bone marrow aspirations in the patients with HM and a large amount of extensive surgeries in the MST patients. Despite the absence of immunosuppressive and / or chemotherapy, HCV prevalence was 0.6 % in the patients with BT, which exceeded the prevalence in the general pediatric population. The leading risk factors for the patients with BT included high surgery and infusion burden, which emphasizes that there might have been infection control breaches in the procedures carried out in in- and outpatient clinics. High prevalence of HBV in the patients with BD and HM who received extensive replacement therapy with blood components implies a residual risk of contracting post-transfusion HBV which is able to escape the capabilities of diagnostic test systems due to the presence of mutant forms of the virus. Despite the absence of induced immunosuppression, the prevalence of HCV in the patients with BD was at the same level as in the patients with HM and MST. As regards the prevalence of HBV among the patients with BD, it was at the same level as in the patients with HM but higher than in the patients with MST. The leading risk factors in the patients with BD were as follows: a high burden associated with transfusions of unsafe blood components, infusion/injection burden, and blood sampling. The prevalence of HBV and HCV in the patients with BD shows that blood transfusions are associated with the risk of HBV transmission and implies the unsafety of medical procedures.

Conclusions. Invasive procedures and transfusions of unsafe blood components in patients with immunosuppression are factors that place patients with oncological and hematological diseases and immunodeficiency conditions at increased risk of contracting bloodborne infections. Such invasive procedures include intravenous administration of medications, blood sampling and extensive surgeries.

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Research article

ANTHROPOMETRIC INDICES AND BIOIMPEDANCE BODY COMPOSITION AS ONTOGENETIC INDICATORS TO DESCRIBE RISK OF OBESITY

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The body mass index does not distinguish body fat mass from fat-free mass and does not capture changes in these parameters. The aim of this study was to establish an association between anthropometric indexes and bioimpedance indicators with age-specific obesity on the example of male population in the Magadan oblast. To achieve it, we examined 586 males who lived in the Magadan oblast by using conventional methods for assessment of physical development. The ROC analysis was performed and the area under the ROC curve (AUC) was measured.

The analysis of the obtained research data established a significant decrease in FFMI values with age (from young males to elderly ones) together with growing FMI, FMI/FFMI ratio, total body fat and the waist-to-hip ratio. To determine an optimal BMI value as an indicator eligible to diagnose obesity, a ROC-curve was built to describe a relationship between BMI and FMI/FFMI value < 0.4 cu. It showed that when BMI ranged between 22 kg/m^2 and 25.0 kg/m^2 in young males, bioimpedance values corresponded to the physiological norm; in the early maturity group, the optimal BMI cut-off point for diagnosing obesity was 26.5 kg/m^2; the optimal BMI range in the 2nd maturity group was 24.0–27.5 kg/m^2. It is noteworthy that the ROC-analysis turned out to have no predictive significance among elderly men; this indicates that BMI is hardly eligible for being used as an indicator of obesity risk in this period of ontogenesis.

Classical BMI ranges cannot be considered a clear indicator to diagnose obesity among males in the Magadan oblast whereas indicators obtained by bioimpedance analysis (FMI/FFMI ratios) can be used as relevant indicators when assessing risks of obesity and sarcopenia in the analyzed population.

Keywords: *BMI, bioimpedance analysis, anthropometric indices, age dynamics, physical development, male population, obesity, ROC-analysis.*

Nowadays, prevalence of obesity has reached an epidemic level and this poses a serious threat for population health in both developed and developing countries [1]. Obesity is considered a principal public health concern and ranked as the fifth foremost reason for death globally; another alerting fact is that obesity and overweight also lead to further health concerns and contribute to numerous chronic diseases, including cancers, diabetes, metabolic syndrome, cardiovascular diseases, hypercholesterolemia, and diseases of the musculoskeletal system [2–4]. Hence, obesity and its consequences affect quality of life, decrease work efficiency and lead to greater expenditure on healthcare [5].

At present, the body mass index (BMI) is widely used in clinical practices, especially for determining whether a patient has overweight or obesity [6, 7]. Although BMI is a rather informative indicator and correlates well with a growth in fat mass, its main drawback is that it does not differentiate precisely between fat and muscle mass and is

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also unable to capture the body composition and exact localizations of fat tissues. Moreover, it is a well-known fact that relative total fat to muscle mass ratios tend to differ significantly in people with the same BMI [8, 9]. This low diagnostic sensitivity of BMI results in impossibility to use it for identifying the body composition and, consequently, detecting people with so called normal weight obesity (hidden obesity). The latter is defined as a high fat percentage in the body under BMI values being within the reference range [10], which, in its turn, can be a risk of diseases associated with 'common' obesity [11, 12].

Previous studies have revealed that various components in the body composition can play quite the opposite roles as risk or protective health factors. Thus, in general, fat mass creates elevated risks of cardiovascular diseases whereas muscle mass, on the contrary, is a protective factor as regards chronic noncommunicable diseases [13]. Greater muscle mass may have a protective impact on high TC, high LDL cholesterol, hyperglycemia, and insulin resistance. This finding suggests that the "obesity paradox" may be partly explained by high muscle mass [14]. Chronic diseases associated with cardiometabolic dysfunction (insulin resistance, metabolic syndrome, diabetes mellitus, hypertension, dyslipidemia, and coronary artery disease) have been shown to be quite modifiable by changes in diets and lifestyles. Having an optimal body composition is a major modifiable risk factor; it is primarily achieved by reducing obesity and maintaining a proper ratio between fat mass and muscle mass [15].

Therefore, it is necessary to use alternative methods instead of BMI estimation to diagnose risks of obesity and metabolic disorders. Bioimpedance analysis is one of such methods. It is used in clinical diagnostics to assess the body composition. The method is simple, cheap, non-invasive and effective and allows estimating physical development as well as a wide range of physiological and morphological characteristics of the body [16, 17]. In addition to that, there are some indices such as fat-to-lean mass ratio, waist-to-hip ratio and others, which are recommended for assessing risks of obesity, sarcopenia and sarcopenic or abdominal obesity. Wide use of such methods and indices in clinical practice should result in establishing new criteria for obesity diagnostics, which will also be sex-dependent among adult population. A measured fat percentage in the body should become a conventional indicator in effective diagnostics as well as in obesity screening [18].

Therefore, the aim of this study was to assess how informative the body mass index was when assessing obesity among males in the Magadan oblast in the ontogenetic aspect based on investigating a combination of BMI and such indices as fat-free (FFMI) and fat (FMI) mass indices as well as their relationships with the total fat in the body and the waist-to-hip ratio.

Materials and methods. We analyzed 586 case histories of male patients provided by the Magadan Regional Center for Medical Prophylaxis. All patients lived in the Magadan oblast. Prior to inclusion in the study, each patient provided his informative voluntary consent; all patients' data were depersonalized prior to analysis.

The analyzed sample was divided into four groups in accordance with the age difference as of 1965: the first group was made of young males (158 people); the second one, men in early (first) maturity (154 people); the third one, men in the second maturity (163 people); the fourth group included elderly males (111 people). Then, each group was divided as per conventional BMI estimates where its value < 18.5 kg/m^2 was considered underweight; 18.5–24.9 kg/m^2, normal weight; 25–29.9 kg/m^2, overweight, and BMI values > 30 kg/m^2 meant obesity [19].

The following indices were input into the research database: height (cm), weight (kg), lean mass as per Durnin – Womersley (kg), fat mass as per Durnin – Womersley (kg), fat (%) (identified with ABC-02 MEDASS bioimpedance analyzer of metabolic processes and body composition, Russia), as well as waist-to-hip ratio (W/H, cu). Measurements of fat and fat-free mass were used to calculated fat mass index (FMI = fat mass index, kg/height (m)^2, kg/m^2) and fat-free mass index (FFMI = fat-free (lean) mass index, kg/height(m)^2, kg/m^2). FMI values ≥ 8.3 cu were

considered high fat mass and FFMI values ≤ 17.4 cu were considered low lean mass [20].

We calculated the FMI / FFMI ratio as well, which is ranked as metabolic health if its value is < 0.4 cu; obesity, if it is 0.4–0.8 cu; values > 0.8 cu mean sarcopenic obesity [20]. When interpreting the waist-to-hip (W/T) ratio, we considered its value > 0.90 cu as an indicator of abdominal obesity in the examined males.

A fat percentage in the body higher than its reference range was classified as follows according to the WHO recommendations: more than 19 % for young males, more than 21 % for men in the first and second maturity age, and more than 24 % for elderly males [21, 22].

The results were statistically analyzed with Statistica 7.0 applied software. Distribution of the measured variables was checked for normality by using the Shapiro – Wilk test. The results are given as mean and its standard error ($M \pm m$). We applied parametric one-factor disperse analysis (ANOVA) to perform multiple comparisons between normally distributed samples; next, we used a post-hoc Scheffe test to establish any significant difference between specific groups. The ROC analysis was performed and the area under the ROC curve (AUC) was measured. The ROC analysis was used to estimate whether BMI or FMI/FFMI made it possible to identify obesity in various age groups. Predictive capability was quantified through an area under ROC curve (AUC) where higher values indicated greater predictive capability[1]. Critical significance (p) was taken at 0.05; 0.01; 0.001.

Results and discussion. The analyzed indicators, calculated indices and statistical differences inside age groups can be found in Table 1. Table 2 provides significant differences between the analyzed age groups. The provided percentage of people with different BMI values indicates there is an age-specific decline in a number of people with underweight and normal weight (from young males to elderly ones). Hence, in the ontogenetic aspect, we can state that a number of people with overweight and obesity is growing with age among males in the Magadan oblast. It is noteworthy that overweight people prevail over obese ones in the first and second maturity group whereas percentages of overweight and obese men are practically the same among elderly males. Among young males, underweight, normal weight and overweight are typical though obesity is also detected, the percentage being as follows: 9 % / 72 % / 13 % / 6 % respectively; people with normal body weight apparently prevail in this age group. In the first maturity age, the percentages of normal weight and overweight are practically the same (3 % / 42 % / 43 % 12 %); obesity grows in the second maturity age (0 % / 26 % / 38 % / 36 %). The greatest number of males with overweight and obesity was identified in the elderly age group (0 % / 15 % / 45 % / 40 %).

Low FFMI values identified in young underweight males and males in the first maturity group indicate low muscle mass; these groups have no significant differences as per all analyzed indicators. The same situation occurs in the second maturity group and elderly people with normal body weight; it is worth noting that males in the second maturity group tend to have an elevated fat percentage and high FMI/FFMI values in elderly males indicate they have obesity even if their BMI appears to be normal.

We should also note that young males with overweight and obesity tend to have fat percentages above their reference range. Overweight males in the first maturity group have high FMI/FFMI values and fat percentages; obese men tend to have abdominal obesity against elevated FMI, FMI/FFMI values and total fat percentage, which confirms obesity in this age group.

Males in the second maturity group and elderly males, with BMI values indicating both overweight and obesity, tend to have elevated FMI, FMI/FFMI, W/H values and total fat percentage, which means marked obesity in each group. It is noteworthy that we have not identified any statistical differences between these two age groups as per all analyzed indicators under normal weight or obesity.

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Table 1

Analyzed indicators, their calculated indices and differences inside the analyzed groups, ($M \pm m$)

Young males										
	Underweight (1)	Normal weight (2)	Overweight (3)	Obesity (4)	1–2	2–3	3–4	1–3	2–4	1–4
N, people	15 (9 %)	113 (72 %)	21 (13 %)	9 (6 %)						
BMI, kg/m^2	17.7 ± 0.2	21.7 ± 0.2	26.9 ± 0.3	33.4 ± 0.7	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
FFMI, kg/m^2	15.3 ± 0.3	18.9 ± 0.8	20.7 ± 0.3	25.3 ± 0.3	$p < 0.001$	$p < 0.05$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
FMI, kg/m^2	2.4 ± 0.2	3.9 ± 0.2	6.1 ± 0.3	7.3 ± 0.7	$p < 0.001$	$p < 0.001$	$p = 0.13$	$p < 0.001$	$p < 0.001$	$p < 0.001$
FM/FFM, kg/m^2	0.16 ± 0.02	0.21 ± 0.01	0.30 ± 0.02	0.29 ± 0.03	$p < 0.05$	$p < 0.001$	$p = 0.76$	$p < 0.001$	$p < 0.01$	$p < 0.001$
W/H, cu	0.76 ± 0.02	0.79 ± 0.00	0.82 ± 0.01	0.84 ± 0.03	$p = 0.23$	$p < 0.01$	$p = 0.59$	$p < 0.01$	$p < 0.05$	$p < 0.05$
Fat percentage, %	13.5 ± 1.4	17.2 ± 0.6	22.8 ± 0.9	22.1 ± 1.6	$p < 0.05$	$p < 0.001$	$p = 0.73$	$p < 0.01$	$p < 0.01$	$p < 0.001$
First maturity										
	Underweight (1)	Normal weight (2)	Overweight (3)	Obesity (4)	1–2	2–3	3–4	1–3	2–4	1–4
N, people	5 (3 %)	64 (42 %)	66 (43 %)	19 (12 %)						
BMI, kg/m^2	17.6 ± 0.3	22.4 ± 0.2	27.3 ± 0.2	33.0 ± 0.6	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
FFMI, kg/m^2	15.3 ± 0.7	17.6 ± 0.2	19.5 ± 0.2	22.4 ± 0.5	$p < 0.01$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
FMI, kg/m^2	2.2 ± 0.5	4.9 ± 0.2	7.7 ± 0.2	10.7 ± 0.5	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
FM/FFM, kg/m^2	0.15 ± 0.04	0.28 ± 0.01	0.40 ± 0.01	0.48 ± 0.02	$p < 0.01$	$p < 0.001$	$p < 0.01$	$p < 0.001$	$p < 0.001$	$p < 0.001$
W/H, cu	0.80 ± 0.03	0.80 ± 0.01	0.86 ± 0.01	0.92 ± 0.01	$p = 0.93$	$p < 0.001$	$p < 0.001$	$p = 0.09$	$p < 0.001$	$p < 0.001$
Fat percentage, %	12.9 ± 2.9	21.2 ± 0.8	28.0 ± 0.7	32.2 ± 1.1	$p < 0.01$	$p < 0.001$	$p < 0.01$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Second maturity										
	Underweight (1)	Normal weight (2)	Overweight (3)	Obesity (4)	1–2	2–3	3–4	1–3	2–4	1–4
N, people	0 (0 %)	44 (26 %)	60 (38 %)	59 (36 %)						
BMI, kg/m^2	–	22.9 ± 0.2	27.1 ± 0.2	34.4 ± 0.5	–	$p < 0.001$	$p < 0.001$	–	$p < 0.001$	–
FFMI, kg/m^2	–	16.5 ± 0.2	18.3 ± 0.2	20.9 ± 0.4	–	$p < 0.001$	$p < 0.001$	–	$p < 0.001$	–
FMI, kg/m^2	–	6.4 ± 0.3	9.1 ± 0.4	12.7 ± 0.4	–	$p < 0.001$	$p < 0.001$	–	$p < 0.001$	–
FM/FFM, kg/m^2	–	0.39 ± 0.02	0.50 ± 0.02	0.62 ± 0.02	–	$p < 0.001$	$p < 0.001$	–	$p < 0.001$	–
W/H, cu	–	0.85 ± 0.01	0.91 ± 0.01	0.97 ± 0.01	–	$p < 0.001$	$p < 0.001$	–	$p < 0.001$	–
Fat percentage, %	–	27.5 ± 1.0	33.5 ± 1.2	36.5 ± 1.0	–	$p < 0.001$	$p < 0.05$	–	$p < 0.001$	–
Elderly males										
	Underweight (1)	Normal weight (2)	Overweight (3)	Obesity (4)	1–2	2–3	3–4	1–3	2–4	1–4
N, people	0 (0 %)	17 (15 %)	50 (45 %)	44 (40 %)						
BMI, kg/m^2	–	22.7 ± 0.5	27.4 ± 0.2	33.7 ± 0.6	–	$p < 0.001$	$p < 0.001$	–	$p < 0.001$	–
FFMI, kg/m^2	–	16.2 ± 0.3	17.7 ± 0.2	21.2 ± 0.5	–	$p < 0.001$	$p < 0.001$	–	$p < 0.001$	–
FMI, kg/m^2	–	6.6 ± 0.4	9.6 ± 0.2	12.6 ± 0.3	–	$p < 0.001$	$p < 0.001$	–	$p < 0.001$	–
FM/FFM, kg/m^2	–	0.41 ± 0.03	0.55 ± 0.02	0.61 ± 0.02	–	$p < 0.001$	$p < 0.05$	–	$p < 0.001$	–
W/H, cu	–	0.87 ± 0.01	0.93 ± 0.01	0.98 ± 0.01	–	$p < 0.001$	$p < 0.001$	–	$p < 0.001$	–
Fat percentage, %	–	28.7 ± 1.4	35.2 ± 0.7	37.4 ± 0.8	–	$p < 0.001$	$p < 0.05$	–	$p < 0.001$	–

Table 2

Statistical differences between the analyzed groups

	Young males – 1st maturity	1st maturity – 2nd maturity	2nd maturity – elderly males	Young males – elderly males
Underweight				
N, people	$p = 0.69$	–	–	–
BMI, kg/m^2	$p = 1.00$	–	–	–
FFMI, kg/m^2	$p = 0.76$	–	–	–
FMI, kg/m^2	$p = 0.84$	–	–	–
FM/FFM, kg/m^2	$p = 0.32$	–	–	–
W/H, cu	$p = 0.84$	–	–	–

End of the Table 2

	Young males – 1st maturity	1st maturity – 2nd maturity	2nd maturity – elderly males	Young males – elderly males
Normal weight				
N, people	$p < 0.05$	$p = 0.11$	$p = 0.76$	$p < 0.05$
BMI, kg/m^2	$p = 0.09$	$p < 0.001$	$p = 0.43$	$p < 0.01$
FFMI, kg/m^2	$p < 0.001$	$p < 0.001$	$p = 0.62$	$p < 0.001$
FMI, kg/m^2	$p < 0.001$	$p < 0.001$	$p = 0.62$	$p < 0.001$
FM/FFM, kg/m^2	$p < 0.05$	$p < 0.001$	$p = 0.11$	$p < 0.001$
W/H, cu	$p < 0.001$	$p < 0.001$	$p = 0.49$	$p < 0.001$
Overweight				
N, people	$p = 0.23$	$p = 0.49$	$p = 0.32$	$p = 0.16$
BMI, kg/m^2	$p < 0.001$	$p < 0.001$	$p < 0.05$	$p < 0.001$
FFMI, kg/m^2	$p < 0.001$	$p < 0.001$	$p = 0.23$	$p < 0.001$
FMI, kg/m^2	$p < 0.001$	$p < 0.001$	$p < 0.05$	$p < 0.001$
FM/FFM, kg/m^2	$p < 0.05$	$p < 0.001$	$p < 0.05$	$p < 0.001$
W/H, cu	$p < 0.001$	$p < 0.001$	$p = 0.23$	$p < 0.001$
Obesity				
N, people	$p = 0.69$	$p < 0.05$	$p = 0.32$	$p = 0.76$
BMI, kg/m^2	$p < 0.001$	$p < 0.05$	$p = 0.62$	$p < 0.001$
FFMI, kg/m^2	$p < 0.001$	$p < 0.001$	$p = 0.76$	$p < 0.001$
FMI, kg/m^2	$p < 0.001$	$p < 0.001$	$p = 0.62$	$p < 0.001$
FM/FFM, kg/m^2	$p < 0.01$	$p < 0.001$	$p = 0.62$	$p < 0.001$
W/H, cu	$p < 0.001$	$p < 0.01$	$p = 0.49$	$p < 0.001$

Figure 1 provides a graph showing dynamics of percentage distribution for people with normal weight as well as overweight and obesity (people with underweight as per BMI were excluded from the graph due to absence of such sub-group in the second maturity and elderly age groups).

Bearing in mind, that BMI did not identify obesity correctly in our investigations, we built a series of ROC-curves for the examined age-specific groups of males to estimate the optimal BMI cut-off point that meant no obesity in accordance with reference FMI/FFMI values (Figure 2).

The analysis of the obtained research data established a significant decrease in FFMI values with age (from young males to elderly ones) together with growing FMI, FMI/FFMI ratio, total body fat and the waist-to-hip ratio in males with normal body weight, overweight and obesity. This is consistent with findings reported by other authors [23]. Stratification of the examined males as per BMI made it possible to establish a significant ascending trend in the analyzed variables as BMI values grew in each age group. Higher muscle mass values in people with overweight and obesity are in line with findings reported by other authors who believe this fact to be related to anabolic activity due to the body overweight load on the musculoskeletal system [24]. It should be noted that we established age-specific changes in BMI ranges from its minimum to maximum values. Thus, BMI range was 16.15–36.33 kg/m^2 in young males; 16.36–41.4 kg/m^2 in the first maturity group; 19.02–48.52 kg/m^2 in the second maturity group; the bottom value shifted considerably among elderly males where the range started at 25.03 kg/m^2 and its upper value was 49.69 kg/m^2.

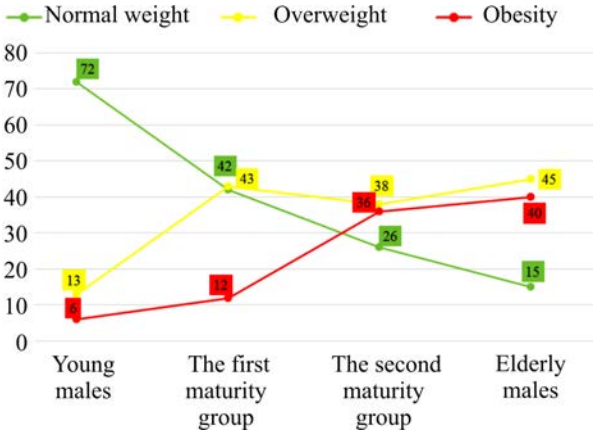

Figure 1. Distribution of the analyzed sample as per frequency of normal weight, overweight and obesity in different age groups

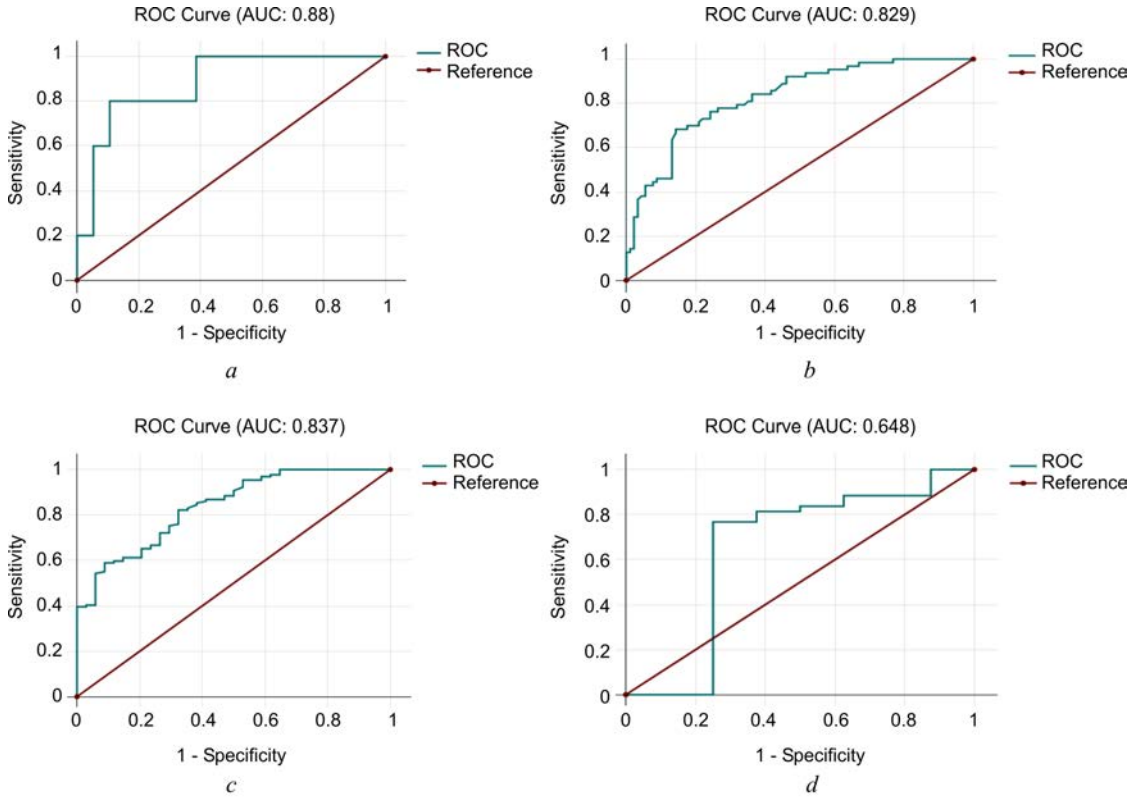

Figure 2. ROC-analysis in young males (a), the first maturity group (b), the second maturity group (c), elderly males (d)

Figure 1 obviously shows that normal body weight prevails among young males (72 %); overweight prevails in the first maturity group (43 %) and its percentage is higher than that of normal weight (42 %) whereas both obesity (36 %) and overweight (38 %) are quite frequent in the second maturity group and their percentages are higher than that of normal weight (26 %). Among elderly males, we established a considerable decrease in normal weight percentage (15 %) with growing overweight (45 %) and obesity (40 %). Data provided in Figure 1 give evidence of rather unfavorable manifestations in males' physical state, which become apparent through two crosspoints of the graph in the age aspect. In the first maturity group (the first crosspoint), they are characterized with the percentage of overweight people being higher than people with normal weight; in the second maturity group (the second crosspoint), obesity is more frequent than normal weight with a simultaneously high percentage of people with overweight.

Analyzing the research data, we should establish the fact that underweight in young males occurs due to low muscle mass. All analyzed indicators in people with normal weight were within the reference range but higher body fat percentages were identified in young males with overweight and obesity against optimal FMI and FFMI values and FMI/FFMI and W/H ratios. This allows us to conclude that BMI can be used to diagnose obesity in this age group.

Lower muscle mass was also detected in underweight males from the first maturity group whereas males with BMI values between 18.5 and 24.9 kg/m^2 (normal weight) were established to have excessive total fat in the body. The same fact was established for males from the second maturity group and elderly males; these changes in these two groups were combined with lower fat-free mass index (muscle component). Therefore, it is rather doubtful that BMI can be used as an indicator of normal body weight in these age groups. Several studies established that both high and

low BMI values were associated with risks of chronic non-communicable diseases and all-cause mortality [25]. A risk of incidence as per BMI was shown to create either a U- or J-like curve; that is, low or high BMI increased this risk in comparison with BMI closer to its medium values [26]. Our findings also confirm a U-like curve for BMI among young males and males from the first maturity group where low BMI values meant lower muscle mass and BMI values higher than 30 kg/m^2 indicated excessive body fat.

We should emphasize that we established a combined set of negative signs as regards the physical state in overweight people starting from the second maturity group and older. This manifested itself in obesity (high FMI/FFMI values), excessive total body fat and elevated fat mass index as well as signs of abdominal obesity (the waist-to-hip ratio > 0.90 cu). The identified trends aggravated further in obese people.

Overall, our findings indicate that classical BMI ranges determining obesity / underweight cannot serve an accurate parameter for identifying both obesity and underweight since they do not allow determining muscle mass deficiency or high fat percentage in the body in male population, especially in age-specific aspects. The issue was to identify those BMI values that could serve as markers of optimal FMI/FFMI ratio excluding obesity and sarcopenic trends in the analyzed groups. To do that, the research data were analyzed to determine their predictive significance by building a ROC-curve and calculating AUC value. It should be noted that FMI/FFMI ratio had significant and quite strong correlations with FMI and fat percentage (young males, 0.86 ($p < 0.001$) and 0.98 ($p < 0.001$); the first maturity group, 0.95 ($p < 0.001$) and 0.95 ($p < 0.001$); the second maturity group, 0.86 ($p < 0.001$) and 0.86 ($p < 0.001$); elderly people, 0.79 ($p < 0.001$) and 0.98 ($p < 0.001$) respectively) but not with FFMI. The latter did not have any significant associations with FMI/FFMI ratio in young males ($r = -0.07$, $p = 0.98$), males from the first maturity group ($r = 0.13$, $p = 0.47$), and males from the second maturity group ($r = 0.06$, $p = 0.84$) whereas we detected an inverse correlation between FMI/FFMI and FMI $r = -0.48$ ($p < 0.01$) in elderly males. The latter, in our opinion, reflects sarcopenic trends in this age group.

Figure 2 shows ROC-curves used to identify the marker BMI value under FMI/FFMI ratio > 0.4 cu, which means obesity. In young males, BMI higher than 25 kg/m^2 is shown to have high predictive value as regards obesity detection and this is evidenced by AUC equal to 0.88 ($p < 0.001$). It is worth noting that we detected one more marker in this curve, namely, BMI value of 22.0 kg/m^2. Another interesting fact was that a mean FFMI value equaled 14.8 ± 0.12 kg/m^2 in young males with BMI values below the foregoing threshold. This means lower muscle mass and can reflect some sarcopenic trends in the physical state. It is also worth noting that ROC-analysis data obtained for young males are confirmed by a rather high correlation coefficient between BMI and FMI/FFMI ratio ($r = 0.50$, $p < 0.001$), which was established together with a low percentage of people with FMI/FFMI ratio above the reference range. Frequency of such people equaled only 4 % in the examined group made of young males.

In the first maturity group, BMI cutoff point equal to 26.5 kg/m^2 turned out to have high predictive value as regards obesity detection (AUC = 0.829, $p < 0.001$) with a high correlation coefficient between BMI and FMI/FFMI, which was 0.68 ($p < 0.001$) and a 41 % percentage of people with FMI/FFMI values being higher than the metabolic health threshold.

In the second maturity group, the optimal BMI range between 24.0 and 27.5 kg/m^2 also had high predicative significance determined by AUC value equal to 0.837 ($p < 0.001$) where men with BMI below this bottom threshold had a decline in FFMI down to 16.9 ± 0.07 kg/m^2 (the reference level being 17.4 kg/m^2) whereas men with BMI higher than 27.5 kg/m^2 tended to have a growth in FMI up to 12.2 ± 0.9 kg/m^2 with its reference level being below 8.3 kg/m^2. It is worth noting that men with BMI between 24.0 and 27.5 kg/m^2

tended to have optimal FMI (7.98 ± 0.06 kg/m^2) and FFMI (17.8 ± 0.16 kg/m^2) and these values were totally within the reference range. We should also mention a high correlation coefficient between BMI and FMI/FFMI ratio (r = 0.60, p < 0.001) together with a growing percentage of people with FMI/FFMI reflecting obesity up to 78 % in the second maturity group.

Attention should be paid to the fact that the ROC-analysis turned out to have no predictive value for elderly males (AUC = 0.562). This indicates that BMI is hardly eligible for being used as an indicator of obesity risk in this period of ontogenesis and this is further confirmed by absence of any correlations between BMI and FMI/FFMI (r = 0.008, p = 0.54) and high frequency of men with FMI/FFMI > 0.4 cu, the percentage being 91 %. Our findings are in line with the results obtained by other researchers who revealed that elderly people tended to have a high fat percentage in the body under certain BMI values. That's why the established BMI threshold values can also be less accurate in elderly people (≥ 65 years) [23].

Conclusion. Stratification of the examined males as per BMI established a significant positive dynamics in the analyzed variables as BMI values grew in each analyzed age group together with age-specific decline in FFMI values from young males to elderly ones against growing FMI, FMI/FFMI, total body fat and waist-to-hip ratio in people with normal weight, overweight and obesity identified as per BMI.

Our findings allow us to conclude that classical BMI ranges cannot be considered a clear indicator to diagnose obesity among males in the Magadan oblast whereas indicators obtained by bioimpedance analysis (FMI/FFMI ratios) can be used as relevant indicators when assessing risks of obesity and sarcopenia in the analyzed population. This is confirmed by highly significant correlation coefficients between this indicator and the fat percentage in the body as well as fat mass index in each age group.

Overall, our study findings confirm the opinion that any assessment of physical state aimed to identify obesity should consider anthropometric indices that rely not only on a body weight related to height (BMI) but also on fat-free mass index (FFMI), fat mass index (FMI) as well as their ratio FMI/FFMI. At present bioimpedance analysis is widely available due to its low costs and simplicity; given that, it seems advisable to implement assessment of these indices in screening preventive and clinical practices. This will allow analyzing both absolute (kg) and relative (%) values of muscle and fat mass in the body for effective early diagnostics and prevention of obesity.

Limitations. Our study has certain limitations. The major one is that our participants were exclusively males and this does not allow describing the total population of northern regions. In addition to that, our results apply only to Caucasians as a specific ethnic group. To our best knowledge, this is the first study with its focus on males living in the north-eastern Russia and with its aim being to analyze whether anthropometric indices are eligible for assessing obesity and its types relying on fat mass index and free-fat mass index.

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Research article

ASSESSMENT OF THE RISK OF DEVELOPING CARDIOVASCULAR PATHOLOGY IN MEDICAL UNIVERSITY STUDENTS

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Diseases of the cardiovascular system (hypertension, coronary heart disease, and heart failure) occupy leading places in the overall pathology structure. A specific feature is a growing share of young people who suffer from cardiovascular diseases (CVDs) in the total population. This is facilitated by physical inactivity, unhealthy diets, elevated stress levels as well as genetic predisposition. Identification of leading risk factors at the latent stage can make for timely diagnostics of cardiovascular pathology in young people. This, in its turn, allows implementing relevant prevention as well as adjusting therapies thereby improving quality of life of each individual patient.

Given that, the aim of this study was to assess risk factors causing CVDs in medical university students; to determine severity of existing cardiovascular disorders as well as their relationships with factors that may have caused them. Eight hundred and seventeen students participated in the study. They all took part in a survey to identify risks of developing CVDs with certain adjustments made to an applied questionnaire to adapt it for use among students. Also, the study involved assessing basic anthropometric parameters (height, weight, and body mass index (BMI)), hypertension in family case history, physical activity, time spent with gadgets (use of smartphone), and alcohol consumption.

The study revealed that 30 % of the examined people had overweight; more than 54 % abused alcohol; 53 % of the respondents mentioned elevated stress levels. All this creates significantly elevated risks of cardiovascular diseases as well as their complications for young and middle-aged people. The study results clearly indicate elevated risks of cardiovascular pathology and this requires correction of risk factors at an early stage.

Keywords: *cardiovascular diseases, leading risk factors, young age, stress, physical inactivity, genetic predisposition, smoking, alcohol.*

In recent years, multiple studies have reported an increase in prevalence of cardiovascular pathologies among different age groups with unwaveringly growing mortality due to heart diseases and their complications. A distinct relationship is established between prevalence of risk factors that cause cardiovascular diseases (CVDs) and numbers of CVDs cases. Influence of behavioral factors on changes in a lifestyle and, consequently, on risks of CVDs has been given scientific evidence [1–3]. In particular, it is important to investigate significance of specific risk factors able to cause CVDs such as elevated neuro-psychic loads, unhealthy work and rest regime, alcohol consumption, smoking, overweight and others, including their combined effects. This will allow getting a better

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insight into reasons for CVDs development, identifying distinct regularities and possible regional peculiarities of prevalence of risk factors [4–7]. It is extremely alerting that in recent years CVDs have started to occur in much younger age groups. Notably, there has been a substantial growth in a number of young patients with changes in the cardiac muscle, which are a signal of undiagnosed CVDs, as well as patients who have suffered myocardial infarction at an age younger than 40 years [2, 8–10]. Occurrence and a constant growth in CVDs cases in adolescents, youth, and the first period of a middle age, that is, in people younger than 35–40 years are associated not only with an unhealthy lifestyle but also with permanently increasing neuro-psychic loads.

The Internet, television, and various electronic gadgets are undoubtedly an irreplaceable part of our everyday life. Still, they bring huge flows of diverse information into a person's life, especially in young and middle age. Under such conditions, uncontrollable emotional overloads, suppressed emotions and stress can promote higher levels of catecholamines (adrenalin and noradrenalin) in blood and, consequently, lead to occurring unmotivated anxiety, agitation, and fear. As a rule, functional state of the cardiovascular system has a drastic response to changes in mood and this can lead to irreversible pathological impairments and CVDs development. Multiple research works can help adjust data on risk factors and optimize a system for CVDs prevention for young people. According to literature data, correction of lipid metabolism disorders, fighting against smoking, sanitation of infection foci, optimization of physical activity and a lifestyle as a whole have turned out to be the most significant for preventing CVDs and their complications [11, 12]. Diseases of the cardiovascular system, especially in young patients, are often accompanied with impairments of the nervous system, which can have certain effect on a clinical course and outcome of a primary disease [13, 14]. Therefore, all this is a huge complex issue, both medical and social one, which requires a comprehensive approach and additional investigations.

The aim of this study was to assess risks of CVDs in medical university students, determine severity of existing cardiovascular disorders as well as establish their relationships with factors that may have caused them.

Materials and methods. We conducted an anonymous survey among students of various years and faculties who attended the Voronezh State Medical University named after N.N. Burdenko. Eight hundred and seventeen students, from the 1st to 5th year, participated in it. A questionnaire applied in the survey was based on a standard questionnaire for identifying hazards of CVDs [15] with certain adjustments to adapt it for use among students; namely, an age range was excluded, an age was given in figures, some so called trap questions were added to exclude students, who did not fill in the questionnaire conscientiously, from the data array for further analysis. Hazards of CVDs were assessed as per a total score sum according to the criteria describing a risk of cardiovascular pathology (Table 1). The obtained data were analyzed using several criteria: general data; data distributed as per a study year; analysis of Broca BM index (height – weight) to identify students with overweight; alcohol consumption; hypertension in family case history; susceptibility to stress or its actual occurrence; physical activity; diets; occurrence of various CVDs symptoms according to students' own subjective assessment. After excluding some forms, the total number of filled-in forms eligible for statistical analysis equaled 788.

Table 1

Criteria describing risks of cardiovascular diseases

CVDs hazard	Total score	Recommendations
High	46–59	You should contact your physician immediately to have a complex medical check-up and be prescribed a therapy.
Pronounced	31–45	Your health requires immediate medical correction. You should contact your physician to develop a suitable rehabilitation program.
Moderate	16–30	Your health is still in a fragile balance since it is being affected by harmful factors.
Absent	1–15	No hazards have been detected for your health. You successfully avoid any risk factors able to cause CVDs.

Statistical data obtained by the anonymous survey were analyzed and the most significant indicators were filled in relevant tables.

Results and discussion. All study results were divided into several conditional groups. The most indicative ones were selected out of 33 groups of questions and their main criteria include the following: data of CVDs risks and their analysis as per study years; dependence between CVDs risks and Broca body mass index, alcohol consumption and signs of stress. Each group was analyzed both separately and with regularities associated with combinations of different groups. Analysis of the total data array revealed that only 31 % of the respondents (249 students) had no risks of developing CVDs. Moderate risks were identified for 50 % of the respondents (397 students); pronounced risks, 17 % (131 students). High CVDs risks were identified for 2 % of the respondents (11 students) (Table 2). The most distressing was the fact that 49 % of the respondents (175 students) had moderate risks of developing CVDs already during their first study year and another 17 % (62 first-year students) had even pronounced CVDs risks. This might indicate that some changes in the cardiovascular system had occurred in those students when they had still been studying at school. Naturally, this is a very alerting and serious signal. It also indicates that unfavorable risk factors that can cause CVDs had previously been present in students' life and significantly affected their health. Our analysis of data on CVDs risks as per study years did not reveal any authentic dynamics associated with impairing students' health as indicators spread was within 3–5 %. This undoubtedly means that a young body stull has high adaptation capabilities and an education process is organized properly. Analysis of fifth-year students was especially indicative in this respect; although moderate risks were higher for them than for students of younger study years, pronounced risks turned out to be practically 2–2.5 times lower. This indicates that both adaptation processes are at work and proper education conditions have been provided for students.

Next, we analyzed a possible relationship between CVDs risks and body mass index. Already 30 % of the respondents (235 students) turned out to have overweight; still, despite overweight being an unfavorable predictive indicator, we did not identify any authentic increase in CVDs risks in students with overweight against their peers with normal body weight (Table 1).

The answers given to the questions related to alcohol consumption clearly indicate that more than a half of the respondents, namely 54 % (420 students), already drank alcohol with various periodicity. We re-

vealed a direct relationship between alcohol consumption and risks of developing CVDs. These risks were absent only for 11 % of the students who consumed alcohol whereas the share was 20 % among those who did not drink alcohol, that is, practically two time higher. A moderate risk of CVDs was 10 % higher among those students who drank alcohol and a pronounced risk turned out to be 2.5 times higher than among their non-drinking peers. According to some studies, a person starts consuming alcohol at an average age of 15.8 years. Also there are scientific proofs that recently a trend has been noted for growing risks of alcoholism to occur at younger ages [3, 16, 17]. Our research data, similarly to those obtained by other studies, provide clear evidence of an existing relationship between alcohol consumption and elevated CVDs risks (Figure 2).

Table 2

Analysis of CVDs risks as per study years

Study year	Total	CVDs risks, % (number)			
		Absent	Moderate	Pronounced	High
1	358	33 (117)	49 (175)	17 (62)	1 (4)
2	145	28 (41)	53 (77)	16 (23)	3 (4)
3	197	34 (67)	49 (97)	16 (31)	1 (2)
4	44	30 (13)	45 (20)	25 (11)	0 (0)
5	44	25 (11)	63 (28)	9 (4)	2 (1)

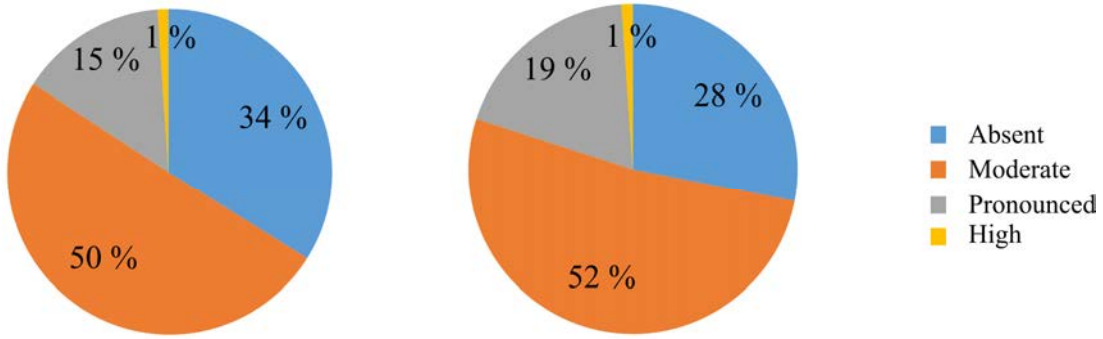

Figure 1. The relationship between CVDs risks and body mass index (Broca index):
(a) is normal body weight, (b) is overweight

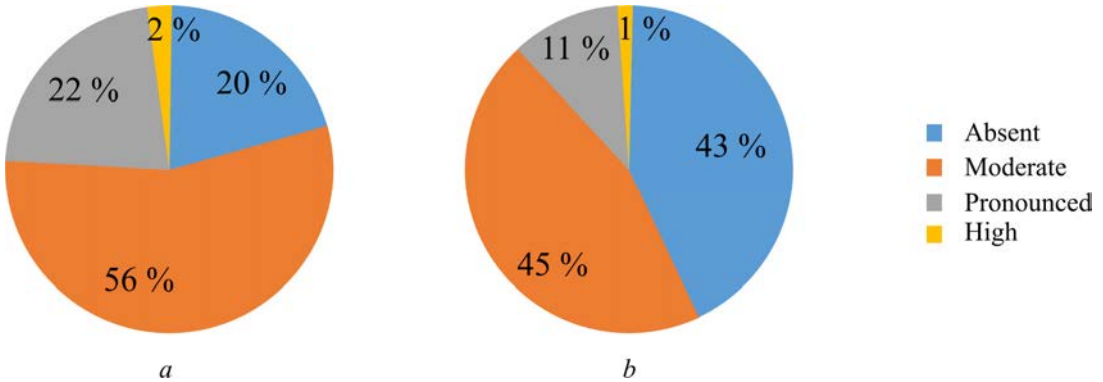

Figure 2. The relationship between CVDs risks and alcohol consumption:
(a) students who drink alcohol, (b) students who do not drink alcohol

Signs of stress were identified in 53 % out of all surveyed students (414 people), that is, in more than a half of the respondents. Assessment of CVDs risk established that only 13 % of the respondents did not have any CVDs risks in case signs of stress were identified in them. In case such signs were absent, CVDs risks were absent as well in 53 % of the respondents. This obviously huge difference clearly indicates that stress is a powerful negative factor able to cause CVDs. A moderate CVDs risk was comparable but data on a pronounced CVDs risk turned out to be much more alerting since it was identified for 27 % of the respondents with signs of stress and only for 4 % of those who did not have them. Our data correlate well with those obtained by other studies, which also report a considerable increase in levels of interleukins 1 and 6 in people under stress. The latter are able to damage cardiomyocytes and promote inflammatory changes in the vessel wall [18–22].

Conclusions. Therefore, relying on our study results, we can conclude that cardiovascular pathology is a huge complex issue and the most alerting thing is a rapidly growing tendency for it to occur at younger ages. Risks of developing CVDs occur not only in student years and later; primary changes in the cardiac muscle and cardiovascular system as a whole can develop already in schoolchildren, which was confirmed by data obtained through our survey of first-year students. It is public knowledge that fighting against bad habits, stress and psychoemotional loads in general still remains a huge relevant challenge. Its relevance is growing menacingly among young people. Overweight resulting from low physical activity and unhealthy 'fast-food' diets, an early age of being introduced to alcohol, and a hectic tempo of modern living often resulting in stresses and neurosis are all commonly known harmful factors able to cause not only cardiovascular pathology but also diseases of the nervous, endocrine and other systems of the body. This situation requires additional immediate attention as well as maximum efforts taken by both HEI administrations in order to control these factors and develop personalized prevention and school administrations in order to implement more comprehensive prevention programs for schoolchildren.

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Competing interests. The authors declare no competing interests.

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Research article

MEDICAL STUDENTS' MIGRATION INTENTIONS: RISK FACTOR AND CHALLENGE FOR THE HEALTHCARE SYSTEM IN KYRGYZSTAN

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Physician migration challenges healthcare systems in developing countries. The "Irish paradox" phenomenon, where doctor shortages persist despite numerous medical graduates, is emerging in Kyrgyzstan (KR). Limited research on this exists in Central Asia. The study explores medical students' migration intentions, offering insights for regional and global health authorities.

A cross-sectional study surveyed 526 final-year medical students in KR. We analyzed demographic characteristics, intentions to work abroad, future professional preferences, and "Pull and Push" factors for migrations that might influence students' decision to migrate.

86.1 % expressed willingness to emigrate. Intention to migrate was categorized by certainty of migration: 12.5 % "leave KR", 14.5 % "highly likely to leave KR", and 59.1 % "might leave KR". 13.9 % decided to stay in KR. The significant predictors of migration were marriage and rural living; the main migration destinations were Russia (41.5 %), Kazakhstan (18.8 %), and the EU (11.5 %). Pull and push factors significantly differed among groups. The main limitations of the study arose from the nature of the observational study.

The study results are alarming, uncovering the potential scale of physican migration in Central Asia. The majority of medical graduates in KR plan to migrate, posing a threat to healthcare sustainability. The presence of the "Irish paradox" amplifies the pressure on these processes in the country and should be considered in the development of migration policy. Monitoring students' intentions provides timely information for adjusting migration programs promptly, and the combined score of Pull and Push factors might serve as an express test to address the challenge more effectively. Migration programs should be developed jointly with the Russian Federation, as the main destination and give priority to professional development in the group with low migration intentions.

Keywords: *healthcare workers, physician migration, risk factor, brain drain, medical students' intention to migrate, pull and push factors, Kyrgyzstan, Central Asia.*

The disparity in the healthcare workforce distribution across various nations, particularly regarding physicians, is acknowledged by the United Nations and the World Health Organization (WHO). Given that human resources constitute the cornerstone of a healthcare system, the WHO underscores that the insufficiency of the healthcare workforce is a challenge for developing countries. This shortage significantly impacts the efficacy and efficiency of healthcare delivery systems and diminishes public satisfaction with the services provided [1, 2].

The migration of tertiary educated people from lower-middle-income countries (LMICs) has become an increasingly important issue in the time of the so-called "age of accelerations", turmoil, and the "post-COVID era". It is a challenge for LMICs to weigh the benefits and negative impacts of migration on economic, social, and political transformations. According to the Organization for Economic Cooperation and Development (OECD), the emigration of highly-skilled workers has been growing at a much faster rate than low-skilled workers recently

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[3, 4], and medicine is among the most mobile occupations [5, 6].

Physician migration from low to high-resource countries is a well-known process in the scientific literature with "two sides of the same coin". One side is the internalization of medical education and collaboration in research that provides undeniable benefits or "brain gain" [6, 7]. Specialists with new skills and ideas return to developing countries from academic centers and leading universities of high-resource countries. Another side is the negative impact of the process or "brain-drain" when the migration of specialists leads to a lack of qualified and efficient workforce in the healthcare system of developing countries [6, 8]. This process poses a risk to the effective operation of public health systems in any nation and presents a significant challenge for policymakers in the realm of migration policy. Hence, comprehensive examination and monitoring of migration processes provide a current state of evidence and help to develop recommendations for evidence-based migration policies of health professionals.

Kyrgyz Republic (KR) is a land-locked LMIC country in Central Asia with one of the highest labor migrations in the region [9]. The healthcare system in KR has been undergoing several rounds of partially successful reforms, mainly because of political and financial instability. Currently, the physician-to-population ratio is the second lowest ratio in Central Asia (2.0 per 100,000 people), with enormous variations from 4.0 per 100,000 people in some cities to 0.7 per 100,000 people in some secluded regions of the country[1]. The COVID-19 pandemic showed that one of the most common causes of health services disruption in KR was a problem with a lack of staffing [10, 11]. Health authorities announced that some health services in the biggest city had more than 25 % of vacant doctors' positions[2], despite the extensive number of medical graduates each year, equivalent to almost 20 % of all practicing physicians in KR[1].

Recently, new offers of medical study programs in English have attracted international students from India, Pakistan, and other countries in South Asia, doubling the number of medical students in KR. Most students complete their first degree in KR before moving home or to another country for internship and postgraduate specialty training. Thus, the healthcare system in the country encounters the phenomenon of the "Irish paradox" when healthcare institutions experience doctor shortages despite the high number of domestic and foreign medical graduates [12].

Analysis of physician migration is a multidimensional process, and one of the most significant aspects of this analysis is whether intentions to migrate could predict an actual future decision [13, 14]. Many scholars and our group believe that migration intention is crucial and a "trigger for real future migration" [15]. Comprehensive migration analysis cannot be done without this aspect because "migration intentions data holds advantages connected to both substantive and practical issues" of physician retention [16].

One of major drawbacks of recent scientific publications that examined medical students' and physicians' migration was attention to migration tunnels with the final destination countries such as the United States, the United Kingdom, and the European Union (EU) [5–7, 12–20]. Only the main "donor" countries for these destinations are well presented in the literature [17, 20]. Physician migration in some world regions, such as Central Asia, has not been explored yet. Another downside of research in the area is consideration of those who expressed willingness to migrate as a homogeneous group. Some studies examined and divided participants by preparation to migrate

[1] Zdorov'e naseleniya i deyatel'nost' organizatsii zdravookhraneniya Kyrgyzskoi Respubliki za 2021 god: ezhegodnyi sbornik [Population health and work of healthcare organizations in the Kyrgyz Republic in 2021: annual digest]. Bishkek, The Ministry of Health of the Kyrgyz Republic, 2021. Available at: https://bit.ly/3BHDjbL (November 27, 2023) (in Russian).

[2] Mikhailichenko K. Skol'ko medikov ne khvataet v Bishkeke? Vitse-mer nazvala tsifry [How many healthcare workers does Bishkek lack for? Vice-mayor has given the figure]. *Sputhik Kyrgyzstan: multimedia press center*, 2021. Available at: https://bit.ly/3fib7EI (December 03, 2023) (in Russian).

level; however, principal analysis was still conducted using a binomial approach, that is, contrasting students who were willing to migrate and those who did not [17–20].

The "Irish Paradox" refers to the situation where despite having a surplus of medical graduates, there are still significant shortages of doctors [12]. This effect was well described in Ireland and Romania [12, 14, 15, 17, 21, 22], two high-income countries that also became "educational hubs" for international medical students. Similar conditions in low or middle-income countries have not been reported in the literature, and examining the same settings in KR provided valuable insight into understanding the paradox.

The main goal of our research group was to examine physician migration processes in KR. We did not find publications investigating this issue in KR or the Central Asian Region. We aimed to examine Kyrgyz medical students' intention to migrate by exploring the heterogeneity of intentions, identifying the primary factors affecting a decision to migrate, and providing information to health authorities regionally and globally for future evidence-based migration policies.

Materials and methods. *Study design.* We conducted a cross-sectional study using survey data collected from 2 major universities of KR. The survey was conducted in 2021–2022 years. The study sample was 526 final-year medical students who studied medicine in Russian, the official language in KR. All students were interviewed in one university, and 74 % were interviewed in another because one student's batch was on a clinical rotation. The response rate was 98 %.

The self-administered questionnaire collected information on sex, age, place of living, marital and financial status, intentions to work abroad, future professional preferences, Pull and Push factors for migration, and possible retention factors that might influence students' decision to stay in Kyrgyzstan.

Family ties are powerful in Kyrgyzstan; most students live with their parents or are supported by them. Hence, we also collected some information about the parents of the participants.

The main structure and some questions of the questionnaire were adapted from a study with similar purposes that had been done in Romania [17]. However, this study was conducted in the Romanian language and examined migration by considering the current reality of the European Union. We translated and modified the questionnaire thereby adjusting it to Central Asia's current situation. Each part of the restructured questionnaire was validated in small groups and tested in a pilot study.

Participation of students was voluntary, and the purpose of the study was fully explained to them before the questionnaire was distributed. The participants were free to choose either a paper or an electronic version of the questionnaire. The questionnaire was distributed by the end of a lecture, and completed copies were collected on the spot. Students did not receive any incentives to participate in the study. We did not collect any personal identification information.

Identification of students' intentions to migrate. Students' post-graduation migration intentions were assessed in two steps using a composite outcome variable with four groups / levels. The first group, "Stay in KR", included those students who reported that they were "not going to leave" the country. The students who replied that they were going to leave the country after graduation were divided into three groups: those who "leave KR" with a definite plan to migrate; those who were "highly likely to leave KR" with a developed plan to leave the country; and those who "might leave KR" with a vague outline of migration.

The first step of identification was an answer to the following question: "Are you going to leave KR?" with five possible answers: "I do not have any plans to leave KR", "I thought about leaving KR but do not have an exact plan "when" and "where" to go", "I am going to leave the country after I earn my degree, finish internship and work for several years to gain some experience", "I will leave KR right after I will get my diploma", "I will leave the country after I earn a degree and finish my internship".

At the second stage, commitment of students to migrate or development of migration plans was assessed using a series of questions that helped to verify students' intention to leave. Thus, participants who replied that they are leaving KR right after they will earn the degree or after internships were assigned to the group "Leave KR" if they answered that they chose a country to migrate to, involved in a conversation with representatives of a particular university or health care facility where they might conduct an internship or continue their study or have a place to work. Otherwise, students were assigned to the group "highly likely to leave KR" along with those who decided to leave after gaining some experience working as doctors in KR if students chose a country to migrate to, constantly conducted an internet search, and participated at least in one program or job fair for international health care professionals abroad. Other students who replied that they would leave the country were assigned to the group "Might leave KR".

Push and Pull factors. We created a list of possible motivating factors (Pull and Push factors) to migrate or to stay in KR based on self-actualization Maslow's pyramid, which consists of six blocks. The framework for this approach was described by Dohlman and others [23]. The blocks were tested in a small pilot study group, and seven push and five pull factors were chosen for the survey. Each factor was presented in the form of a question with five possible answers on a Likert scale: from 1, 'this definitely, not an important reason for my decision to migrate / stay in KR'; to 5, 'this is the main reason for my decision to migrate / stay in KR'.

Statistical analysis. Descriptive, χ^2, and *t*-test statistics, along with logistic regression, were used to examine factors that might influence students' post-graduation migration intentions.

Missing values in almost every block of the questionnaire were less than 2 % and could not present any threats to our analysis. However, 11.2 % of participants refused to provide information about citizenship. We selected some participants from this group and conducted a personal interview. The results of the interview showed that the majority of these respondents applied for or received non-KR citizenship. As a part of sensitivity analysis, we also analyzed data considering these participants as those with non-KR citizenship.

We analyzed the answers to Pull and Push questions as interval-level data (between 1 and 5) and calculated the score that corresponds to each analyzed group of participants using mean and confidence intervals. The statistical difference was established using a t-test.

Logistic regression analyses independently examined the relationship between each variable and the main outcome using two approaches. The first approach explored migration intentions for those who stayed in KR and other participants who decided to migrate using binary outcomes. Another approach assessed the development of migration intentions using a cumulative logit model with an ordinary outcome[3].

The level of statistical significance was determined as 0.05. The data analysis was conducted using SAS 9.04 software (SAS Institute).

This study was approved by the Ethics Committee of International Higher School of Medicine.

Results. The final analytical sample constituted 526 students with more females than males (64.5 % versus 35.4 %, respectively) and mean age 23.4 (+/- 0.1) (Table 1). The percentage of married participants or common-law partners was two times less than that of those who were single or divorced (74.0 % versus 36.0 %, respectively). The number of individuals in the sample that reported the household economic situation as living in precarious conditions was 1.1 %, 31.5 % of the students could not afford everything needed for a normal life, 54.5 % could afford everything needed for a normal life, and 4.2 %

[3] Elkin E. PROC LOGISTIC to Model Ordinal and Nominal Dependent Variables. *Bitly Connections Platform*, 2012. Available at: https://bit.ly/3r6lZII (November 30, 2023).

Table 1

Socio-demographic characteristics and future occupational preferences of study participants by intention to migrate

	Study sample		Intention to migrate			
	Total *N* (col. %)	*P*-value	Leave KR *N* (row %)	Highly likely to leave KR *N* (row %)	Might leave KR *N* (row %)	Stay in KR *N* (row %)
Mean age of participants *Mean (SD)*	23.4 (1.17)		23.4 (0.4)	23.2 (0.1)	23.3 (0.4)	23.7 (0.2)
Sex						
Male	186 (35.4)		26 (13.9)	30 (16.1)	107 (57.6)	23 (12.4)
Female	339 (64.5)	<0.001	40 (11.8)	45 (13.3)	204 (60.2)	50 (14.8)
Missing values N (%)	1 (0.19)					
Place of living						
Living with parents	182 (34.6)		15 (8.2)	24 (13.2)	114 (62.6)	29 (16.0)
Living with relatives	51 (9.7)		3 (5.9)	4 (7.8)	35 (68.6)	9 (17.7)
Renting apartment or dormitory	186 (35.4)		35 (18.2)	35 (18.2)	98 (52.7)	18 (9.7)
Living in one's own apartment / house	107 (20.3)	<0.001	13 (12.2)	13 (12.2)	64 (59.7)	17 (15.9)
Missing values N (%)	0(0)					
Marital status						
Single	389 (74.0)		49 (12.6)	63 (16.2)	238 (61.2)	39 (10.0)
Married, no children	53 (10.1)		4 (7.6)	6 (11.3)	31 (58.5)	12 (22.6)
Married with children	57 (10.8)	<0.001	11 (19.3)	5 (8.8)	27 (47.4)	14 (24.6)
Cohabitating with a partner	27 (5.1)		2 (7.4)	2 (7.4)	15 (55.6)	8 (29.6)
Missing values N (%)	0 (0)					
Financial status						
Poor	6 (1.1)		1 (16.6)	1 (16.6)	3 (50.2)	1 (16.6)
Can't always afford the necessities	208 (39.5)		27 (13.0)	32 (15.4)	121 (58.2)	28 (13.5)
Can afford everything necessary	288 (54.8)	<0.001	35 (12.2)	40 (13.9)	177 (61.5)	36 (12.5)
Can afford anything without limitations	22 (4.2)		3 (13.6)	2 (9.1)	10 (45.5)	7 (31.8)
Missing values N (%)	2 (0.38)					
Future specialty						
Internal medicine	162 (30.8)		12 (7.4)	35 (21.6)	94 (58.0)	21 (13.0)
Surgery / gynecology	150(28.6)	0.026	23 (15.3)	23 (15.3)	80 (53.4)	24 (16.0)
Haven't decided yet	198 (37.7)		25 (12.7)	17 (8.6)	129 (65.1)	27 (13.6)
Missing values N (%)	16 (3.0)					
Out of those who haven't decided yet						
Will combine medicine with other non-medical activity	65(12.75)		12 (18.5)	6 (9.2)	37 (56.9)	10 (15.4)
Might not work at all	7 (1.4)		2 (28.5)	1 (14.3)	3 (42.9)	1 (14.3)
Citizenship						
KR	406 (77.2)		35(8.6)	45 (11.1)	256(63.1)	70 (17.2)
Not KR	61 (11.6)	<0.001	19 (31.5)	8 (13.1)	31 (50.8)	3(4.9)
Missing values N (%)	59 (11.2)		12(20.3)	23 (39.0)	24 (40.7)	0
Parents / family						
Parents' financial status						
Poor	5 (0.9)		2 (40.0)	0	1 (20.0)	2 (40.0)
Can't always afford the necessities	134 (25.5)		16 (11.9)	22 (16.4)	77 (57.5)	19 (14.2)
Can afford everything necessary	338 (64.3)	<0.001	39 (11.5)	48 (14.2)	209 (61.8)	42 (12.4)
Can afford anything without limitations	44 (8.4)		8 (18.2)	6 (13.6)	21 (47.7)	9 (20.5)
Missing values N (%)	5 (0.9)					
Brothers and sisters *Mean (SD)*	2.6 (1.33)		2.3 (0.2)	2.7 (0.2)	2.6 (0.1)	2.5 (0.2)

End of the Table 1

	Study sample		Intention to migrate			
	Total *N* (col. %)	*P*-value	Leave KR *N* (row %)	Highly likely to leave KR *N* (row %)	Might leave KR *N* (row %)	Stay in KR *N* (row %)
Parents' place of living						
Bishkek, the capital of KR	244 (46.4)		26 (10.7)	37 (15.2)	147 (60.3)	34 (19.3)
Other city	196 (37.3)		33 (16.8)	28 (14.3)	110 (56.1)	25 (12.8)
Urban settlement	79 (15.0)	<0.001	6 (7.6)	9 (11.4)	52 (65.8)	12 (15.2)
Missing values N (%)	7 (1.3)					
Parents' education						
Secondary school	39 (7.4)		5 (12.8)	4 (10.3)	23 (59.0)	7 (18.0)
Vocational education	146 (27.8)	<0.001	14 (9.6)	21 (14.4)	92 (63.0)	19 (13.0)
Higher education	336 (63.9)		47 (14.0)	51 (15.2)	192 (57.1)	46 (13.7)
Missing values N (%)	5 (0.9)					
Work in the healthcare system						
Yes	177 (33.7)		26 (14.7)	25 (14.1)	104 (58.8)	22 (12.4)
No	349 (66.3)	<0.001	40 (11.5)	51 (14.6)	207 (59.3)	51 (14.6)
Missing values N (%)	0 (0)					
Total (column / row %)	526 (100)		66 (12.5)	76 (14.5)	311 (59.1)	73 (13.9)

could afford anything without any restrictions. Most participants chose their future career path in internal medicine or surgery/gynecology (30.8 % versus 28.6 %, respectively). However, 198 (37.7 %) reported that they hadn't decided on a future career, and out of this number, 13.1 % would combine work in medicine with others unrelated to medicine work, and 1.5 % would possibly quit medicine.

Students with KR citizenship constituted 77.2 % of all students, and Non-KR citizenships 11.6 % (Table 1). Almost the same percentage (11.2 %) of students refused to answer this question. The following interview showed the majority of them were non-KR citizens or had double or applied for foreign citizenship.

Most respondents indicated their parents had higher education (63.9 %), 27.8 % of parents had more than secondary education, and 7.4 % had secondary or less than secondary education. The percentage of households with somebody working in health care was 33.7 %. The majority of the participants (72.6 %) described parents' household economic situation as "can afford everything needed for a normal life" and "can afford anything without any restrictions", and 26 % of households either live in precarious conditions or cannot afford everything needed for a normal life. The average number of children in a family was 2.6 (+/-0.1). Eighty-three point seven percent of the students reported that their families live in urban areas and 15.0 % in rural areas.

Overall, 86.1 % of the participants expressed a desire to migrate out of KR (Table 1). The strength of intention to migrate showed that 12.5 %, along with 14.5 % of the participants, had strongly formed decisions and developed plans to migrate, more than half (59.1 %) of the participants had thoughts and made some preparation to migrate. Only 13.9 % decided to stay and practice in KR. Females had less likely developed plans to leave KR compared to males (11.8 % vs.13.3 % and 13.3 % vs. 16.1 % who had developed plans to leave KR, correspondingly).

The least mobile group had the best economic situation: those students who "can afford anything without any restrictions" had the lowest percentage in all three groups except those that "stay in KR" (31.8 %). On the contrary, students who were renting apartments or living in a dormitory had the highest percentage in groups of "leaving KR" and "highly likely to leave" (18.2 % in both groups, correspondingly). We can observe the same situation among those who chose their career pass in surgery and gynecology (15.3 % in both

groups). Respondents who refused to provide information about citizenship were the most mobile group, with the highest percentage of all groups expressing willingness to migrate. This indirectly proved our interview findings with the group. Parents' financial status had almost the same pattern as the status of participants. The highest percentage of those staying in KR were in groups with the best and worst economic situations (20.55 and 40 %, correspondingly). Respondents who had parents with higher education had more developed plans to migrate compared to other groups (14.0 % and 15.2 %).

Table 2 presents push-and-pull or motivating and demotivating factors to migrate and stay in KR. The leading push factors were "the opportunity to get higher qualification abroad" (47 % put the highest score) and "better conditions to work as a physician abroad" (46.8 % put the highest score), with the highest mean score in all groups for these questions. Only 32.9 % indicated a better salary abroad as one of the leading factors for migration. The most important of all "pull" factors was family ties. Thirty-one point eight percent of the respondents indicated it as the main factor of motivation to stay in KR.

Table 2

Push-and-Pull factors of students with the intention to migrate

Factors	Leave KR (Mean/SE)	Highly likely to leave KR (Mean/SE)	Might leave KR (Mean/SE)	Total N (%) of students who put the highest grade (%)
Push factors				
There is a better salary abroad	4.3 (0.13)	3.8 (0.15)	3.8 (0.06)	149 (32.9)
There are more opportunities to get higher qualification	4.3 (0.13)	4.0 (0.13)	4.3 (0.06)	217 (47.9)
There are better conditions to work as a physician abroad	4.5 (0.10)	4.2 (0.12)	4.2 (0.06)	212 (46.8)
There are better opportunities to find a good place to work and be promoted abroad	4.2 (0.14)	3.9 (0.14)	3.9 (0.07)	165 (36.4)
My family is going to emigrate	3.3 (0.22)	1.9 (0.18)	2.0 (0.09)	62 (13.4)
I am not satisfied with the healthcare system in KR	4.0 (0.17)	3.7 (0.17)	3.7 (0.08)	163 (36.0)
I am not sure that I can find a decent position after an internship in KR	3.4 (0.20)	3.3 (0.18)	3.1 (0.09)	109 (24.1)
Pull factors				
My family and friends in KR	3.5 (0.19)	2.7 (0.23)	3.8 (0.09)	144 (31.8)
I do not have any means to go abroad	2.2 (0.17)	2.3 (0.2)	2.9 (0.08)	46 (10.2)
I am satisfied with healthcare in KR	1.6 (0.14)	1.8 (0.16)	1.9 (0.07)	12 (2.6)
I believe that healthcare reforms make the system better	2.0 (0.17)	1.9 (0.17)	2.4 (0.08)	32 (7.01)
I don't think I can find a better job abroad	1.7 (0.15)	1.7 (0.17)	2.2 (0.08)	15 (3.3)
Mean and SE for the combined score of Pull factors	26.27 (0.85)	22.70 (0.83)	21.71 (0.48)	
Mean and SE for the combined score of Push factors	7.48 (0.69)	7.89 (0.61)	10.08 (0.34)	
Mean and SE for the combined score of Pull and Push factors*	18.78 (0.92)	14.80 (0.90)	11.63 (0.49)	
Confidence interval for the combined score of Pull and Push factors	**16.96; 20.62**	**13.02; 16.59**	**10.66; 12.60**	

N o t e: *Combined score for Pull and Push factors was statistically significantly different in groups with different levels of intentions to migrate. Statistical significance was determined by using *t*-test.

Interestingly, the cumulative score of "pull" factors showed a bigger and statistically significant difference between groups of those who "leave KR" and "highly likely to leave," but the cumulative score of "pull" factors presented this pattern between "might be possible" and "highly likely to leave" groups. However, the combined score of push and pull factors showed a statistically significant difference among all three groups (Table 2).

We examined relationships between the socio-demographic characteristics of the participants and their migration intentions (Table 3) using regression analysis. As a result, we identified only three statistically significant covariates that might predict intention to migrate after adjusting for citizenship. Thus, students who rent apartments or dormitories had a more than two times higher chance of intent to migrate compared to those who live with parents (*OR* = 2.21 (95 % *CI*: 1.38–3.52). Married participants had lower chance of being willing to migrate compared to single respondents (*OR* = 0.43 (95 % *CI*: 0.23–0.80) and *OR* = 0.25 (95 % *CI*: 0.11–0.58), respectively). As a part of our sensitivity analysis, we examined all covariates in different subgroups of our research sample. We restricted it to only those who were citizens of KR, those who "leave KR" vs. "stay in KR" and other combinations of subgroups by intention to migrate. Marital status was the most reliable and statistically significant predictor in all our analysis models. "Parents' place of living" was another statistically significant factor in the full model. Participants who lived in a rural area had a 50 % lower chance of having an intention to migrate than those who lived in the capital city (*OR* = 0.51 (95 % *CI*: 0.3–0.89)) only after adjusting for citizenship and other statistically significant covariates in the model.

Table 3

Logistic regression analysis of the relationship between migration intentions and socio-demographic characteristics of participants

Analyzed factor	Odds Ratio and corresponding 95 % confidence interval	Adjusted Odds Ratio and 95 % confidence interval
Sex *(males are a reference group)*		
Females	0.787 (0.54–1.10)	
Place of living		
Living with parents	*reference group*	
Living with relatives	078 (0.42–1.45)	0.89 (0.46–1.73)
Renting apartment or dormitory	**2.18 (1.44–3.29)**	**2.21 (1.38–3.52)**
Living in one's own apartment / house	1.14 (0.70–1.84)	1.65 (0.99–2.76)
Marital status		
Single	*reference group*	
Married, no children	**0.42 (0.23–0.77)**	**0.43 (0.23–0.80)**
Married with children	0.63 (0.35–1.13)	0.60 (0.34–1.07)
Cohabitating with a partner	**0.29 (0.13–0.65)**	**0.25 (0.11–0.58)**
Financial status		
Poor	2.22 (0.42–11.61)	
Can't always afford the necessities	1.07 (0.76–1.54)	
Can afford everything necessary	*reference group*	
Can afford anything without limitations	0.50 (0.21–1.21)	
Future specialty		
Internal medicine	*reference group*	
Surgery / gynecology	1.05 (0.68–1.62)	
Haven't decided yet	0.83 (0.55–1.24)	
Citizenship *(KR citizenship is a reference group)*		
Non-KR	**4.06 (2.32–6.94)**	**4.85 (2.67–8.82)**
Missing data	**5.15 (3.01–8.80)**	**5.85 (3.25–10.5)**
Parents' place of living		

End of the Table 3

Analyzed factor	Odds Ratio and corresponding 95 % confidence interval	Adjusted Odds Ratio and 95 % confidence interval
Bishkek, the capital of KR	*reference group*	
Other city	1.36 (0.94–1.99)	0.66 (0.42–1.03)
Urban settlement	0.74 (0.45–1.23)	**0.51 (0.3–0.89)**
Parents' financial status		
Poor	0.93 (0.16–5.29)	
Can't always afford the necessities	1.07 (0.72–1.59)	
Can afford everything necessary	*reference group*	
Can afford anything without limitations	1.07 (0.58–1.98)	
Parents were born in Bishkek	*reference group*	
One parent was born in Bishkek	0.93 (0.37–2.31)	
Moved in Bishkek in the last 10 years	0.63 (0.28–1.43)	
Parents' education		
Secondary school	0.94 (0.46–1.90)	
Vocational education	*reference group*	
Higher education	1.11 (0.76–1.63)	
Work in the healthcare system (*YES is a reference group*)		
No	0.87 (0.61–1.24)	

Note: Cumulative logit-model using an ordinal result (Leave KR event). The ultimate model was adjusted for statistically significant covariates in the first model.

The most frequent country destinations for migration were Commonwealth of Independent States (CIS) such as Russia and Kazakhstan (48.1 % and 18.8 % of participants, respectively) followed by countries of the European Union (11.5 % of respondents) (Table 4).

Table 4

Country destination of students' migration intentions

Country destination	Students who decided to migrate, *N* (%)
Russian Federation	218 (48.1)
Kazakhstan	85 (18.8)
EU countries	52 (11.5)
North American countries	29 (6.4)
Turkey	22 (4.8)
Other countries	30 (6.6)
Missing N (%)	17 (3.8)
Total	453 (100)

Discussion. The prevalence of medical students' intention to migrate varies dramatically in literature by geographical region, methodology used in a study, and time when the study was conducted. Our study sample's percentage of students considering migration abroad was 86.1 %. We did not find any other research that examined medical students of physician migration in Central Asia. A high percentage of students intended to migrate was reported in Romania (84.7 %) and Ireland (88 %) [17, 21]. Similar studies from this region provided the prevalence of migration intentions as 50 % among Polish students [24]. Two studies in Lithuania 15 years apart estimated that 60 % and 39 % of medical students intended to migrate, respectively [20, 25]. This difference might be attributed to changes in a policy or an economic situation in the country as well as to different methodological approaches in the studies. High prevalence of migration intentions was also identified in Africa, Egypt (89 %) [18], and Asia, Turkey (46.3 %) [26] and Pakistan (33 %) [27].

The current situation with healthcare and medical education in KR shows many similarities with Romania and Ireland. These countries have universal health coverage, exporting model of medical education, and physician shortages in healthcare systems despite the high number of domestic and foreign medical graduates [17, 21, 22]. However, Romania and

Ireland are high-income countries, and their main migration tunnels for medical students are EU, UK, and North American countries [17, 21]. On the contrary, KR is LMIC and the main migration destination is the Russian Federation.

Students' intention to migrate by a country destination in our sample was almost similar to those patterns in KR general population. However, migration to the Russian Federation represents almost 80 % of migration flow in KR general population[4] but in our sample, only 48.1 % of participants intended to migrate. The third and fourth country destinations were the European Union and North American countries that jointly constituted about 17.9 % of our study sample, compared with 5 % of the KR general population[4].

We did not find publications investigating physicians' or medical students' migration in the Central Asian Region. However, historical similarities in healthcare systems' development and nowadays reorganizations in the region might suggest similar processes in neighboring countries.

The majority of studies that examined medical students' intention to migrate considered research samples as those who expressed willingness to migrate and those who did not ignoring the difference in the strength of the intentions. However, participants' heterogeneity by the strength of the intentions to migrate is difficult to overestimate. It partially explains the main drawback of studies that examined the intention of migration, namely, the gap between the high percentage of those who expressed willingness to migrate and the actual number of migrants. Thus, two groups, "leave KR" and "highly likely to leave KR", constitute only 27 % of the participants. They might be considered as those with a high probability that their intentions will transform into an actual decision to migrate in the nearest future.

Introducing the heterogeneity by the strength of intentions, we also provide valuable information for health authorities for future evidence-based migration policies. 'Might leave KR' is the most important and the largest group in our research sample (59.1 % of the participants). This group should be the primary target for future retention interventions accounting for their socio-demographic characteristics and Push-and-Pull factors. Moreover, the set of Push-and-Pull factors could be used as an express test for monitoring students' migration intentions using a combined score of Pull and Push factors that showed a statistically significant difference in the groups.

Thus, lack of professional opportunities was the major stimulating migration factor. This indicates that incentive programs should focus on non-monetary factors such as better academic infrastructure and increasing opportunities for professional development. Financial satisfaction definitely contributes to migration decisions but is not the primary driver.

We did not find strong differences in participants' characteristics by level of intention in our regression analysis. This could be explained by the effects of a "generational cohort" and a university's "catchment area". Universities enrolled students of the same age and from the same socio-economic pull that might mask possible differences. Thus, the strongest and most reliable characteristic was marital status which, along with another statistically significant covariate, students' place of living, cannot be helpful for planning university retention interventions in students' enrolment policies. The most practical characteristic of this type of policy is parents living in rural areas, but it was a statistically significant covariate only in the full model in our research sample. The weak effect of this characteristic might be explained by urbanization and intensive internal migration in KR [28]. Many families changed their place of living while students were attending university. 'Generation' effects can be eliminated by analyzing another cohort of final-year medical students and in

[4] Zdorov'e naseleniya i deyatel'nost' organizatsii zdravookhraneniya Kyrgyzskoi Respubliki za 2021 god: ezhegodnyi sbornik [Population health and work of healthcare organizations in the Kyrgyz Republic in 2021: annual digest]. Bishkek, The Ministry of Health of the Kyrgyz Republic, 2021. Available at: https://bit.ly/3BHDjbL (November 27, 2023) (in Russian).

this case the combined Pull and Push score can be used as an express-test to monitor students' intentions to migrate since it was statistically significantly different in all analyzed groups.

Major limitations of the study arose from the nature of the survey. Our cross-sectional study collected self-reported data that were not validated against any records and were prone to response and social desirability biases. Another limitation was 11.2 % of participants that refused to provide information about citizenship. However, conducted interview of the group and sensitivity analysis showed that it could not present any threats to our study results.

Conclusion. Physician migration, like any complex phenomenon, encompasses both positive and negative aspects that can vary depending on the country is a risk factor that can compromise the sustainability of a country's healthcare system. Our study serves as a pioneering evaluation of physician migration processes in Central Asia. The historical parallels in healthcare systems' development suggest comparable migration processes among neighboring countries. The study's results shed light on the potential scale of medical students' migration, the driving forces behind migration, and the specific circumstances prevalent in the region. A thorough examination of migration processes is vital for the region to provide an up-to-date understanding and effectively manage migration flows.

Despite differences in socio-economic factors, migration patterns, and geographical attributes, the shared characteristics among countries experiencing the "Irish paradox" indicate the existence of common underlying forces driving this phenomenon. The presence of the paradox seemingly amplifies the pressure on migration processes within the health sector, necessitating careful consideration when formulating countries' migration policies.

The study's primary findings are cause for concern regarding the future of the healthcare system in KR. A significant proportion of medical graduates have expressed intentions to migrate from the country. Developing evidence-based migration policies is of utmost importance, given the current state of healthcare. Continual monitoring of migration intentions among students from different generations is necessary to enhance retention programs. The combined score derived from our set of Pull and Push factors can serve as an express assessment tool for this purpose, aiding in decision-making and migration policy formulation.

Examining the migration intentions of medical graduates in Kyrgyzstan and formulating evidence-based decisions can effectively mitigate risks for the healthcare system associated with the shortage of qualified personnel and the outward flow of trained specialists from the country.

Retention programs targeting graduates should use strategies to enhance professional development and address pertinent concerns. Developing migration programs jointly with the Russian Federation as a primary destination for students offers an opportunity for mutual benefits and strategic alignment, ensuring the sustainability and effectiveness of healthcare systems while fostering international cooperation and exchange.

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Research article

PROGNOSIS OF SUICIDAL RISK AMONG LAW ENFORCEMENT OFFICIALS INCLUDING MILITARY PERSONNEL

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Suicide is a major medical and social concern for law enforcement, a contemporary army included, not only in Russia but abroad as well. In recent years, frequency of suicides and suicidal attempts has been growing among law enforcement officials (LEOs), military personnel included. Therefore, it seems relevant to develop a model for predicting suicide risk.

In this study, our aim was to develop a model for predicting suicide risk in LEOs based on express testing results. Our research object was represented by LEOs (n = 591), their average age being 23.71 ± 1.12 years.

To assess suicide risk, we used a questionnaire for suicide risk assessment 'SSR-2', which is a part of DAP-2 methodology for deviant behavior research, and a clinical-psychopathological method. LEOs' personality characteristics and their current psychophysiological state were identified by using vibration imaging, a technology for recording and mathematically analyzing micro-vibrations of the head and face. It has certain advantages over its analogues.

We determined psychophysiological characteristics, basic abilities (types of Gardner's multiple intelligence) and moral qualities that differed in people with elevated suicide risk against the control. We identified a difference between unconscious reactions of the examined people to stimuli and declared (conscious) ones, which indicates that LEOs tend to hide any signs of suicidal behavior in them. A mathematical model was built for predicting suicide risk: we developed an integral suicide risk assessment and created a probabilistic nomogram that makes it possible to establish likelihood of suicidal behavior signs with accuracy above 98 % relying on results obtained by a 5-minute express test.

Use of this predictive model helps identify those people among personnel who should undergo a profound check-up by a psychological support team. Our research results can serve as a basis for creating an objective concept for diagnostics of suicide risk factors in LEOs

Keywords: *suicide risk, suicide, law enforcement agencies, military personnel, prediction, vibration imaging, abilities, moral qualities.*

Suicide is a major serious social and medical concern for law enforcement, both in Russian and abroad, according to the contemporary analysis of the issue and long-term expert observations [1–6].

In recent years, frequency of suicides and suicidal attempts has been growing among law enforcement officials (LEOs) [1, 7]. As opposed to civil population, this dynamics is largely associated with drawbacks of draft and selection systems and insufficient attention paid to psychological and mental state of law enforcement personnel rather than with difficulties typical for a period of socioeconomic reforms [8].

Suicide destroys personnel's morale, weakens battle readiness, does great moral and psychological damage to the civil society, stimulates negative attitudes towards service in law enforcement agencies and creates a negative image in public consciousness. Thus, for example, conscripted soldiers are a vulnerable group of military personnel as regards suicide risk [9].

Today, serious attention is paid to suicide risk prediction. There are many scales and

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questionnaires aimed to diagnose suicide. However, in our opinion, they have a lot of considerable drawbacks: estimates are subjective in their essence; it is time-consuming and costly to conduct them and analyze the results; keys of many questionnaires are available in open access in the Internet. This leads to much greater difficulties in identifying real suicidal ideations of LEOs, makes preventive measures less effective and increases relevance of searching for reliable suicide risk indicators [10, 11]. The proper diagnosis and immediate treatment plan for those individuals exhibiting severe depressive traits could prevent up to 70 % casualties of suicide. Therefore, it is relevant to build models eligible for predicting suicide risk based on objective indicators of the human body [12].

Vibration imaging is a promising method for assessing suicide risk among LEOs [13, 14]. It involves detection and mathematical analysis of microvibrations of the head and face. The method has been used successfully to solve a wide range of applied tasks within medical-psychological research. It has certain advantages over its analogues: it is time-saving; it provides objective and precise estimates of a person's mental state; it allows estimating more people per one hour than any contact examinations; a person does not experience any physical impacts during an examination and this excludes any likelihood of distortions in its results [15–17].

The aim of this study was to develop a model for predicting suicide risk in law enforcement officials, military personnel included, based on express testing results.

Materials and methods. Our research object was represented by LEOs (n = 591), their average age being 23.71 ± 1.12 years. Examinations took place between 2021 and 2023. The following inclusion criteria were applied: male sex; a written consent to participate in the study. The exclusions criteria were female sex; absence of a written consent to participate in the study; testing conducted incorrectly; apparent sickness (high temperature, fever, etc.)

Groups of LEOs per presence / absence of suicidal risk were created by using a questionnaire for suicide risk assessment 'SSR-2', which is a part of DAP-2 methodology for deviant behavior research. Clinical-psychopathological methods were applied to identify suicide risk.

Psychophysiological state, abilities and moral qualities were estimated with Profiler+ software package, version 10.2.3.167, based on vibration imaging [18]. Military personnel were examined in conformity with all requirements to work with the technology recommended by the system developers.

Authenticity of differences between the study groups was estimated with Student's t-test; critical significance was taken at 0.05. We used discriminant analysis, onward step-by-step with inclusion (at F-enter = 2.0, F-remove = 1.9 and $p < 0.05$), and multiple regression to build classifications and decision rules. Mathematical analysis of the research data was performed in STATISTICA v.10.0.

Results and discussion. Two groups of participants were made following the examinations: SR0 group was made of people without suicide risk (n = 553; 93.6 %); SR group included people with suicide risk (n = 38; 6.4 %).

Table 1 provides the results of assessing differences in psychophysiological parameters obtained by using vibration imaging in two analyzed groups.

Obviously, we established authentic differences between the groups SR0 and SR only for variability of the 'Inhibition' parameter (V_E9 (inhibition)). Some apparent trends were also established for variability of the 'Stress' (V_E2 (stress), and E6 (charisma), E8 (self-regulation) and E10 (neuroticism) parameters.

It is quite interesting to analyze differences in variability of vibration imaging parameters. Changes in the structure of a vibration spectrum are a well-known sign of growing strain of body regulatory mechanisms regardless of an examined function [19, 20]. Activation of the parasympathetic nervous system leads to acetyl choline release, which makes the R–R interval longer and heart rate

lower. On the contrary, the sympathetic nervous system increases catecholamine expression by synapses, which increases heart rate and smooth muscle contractility [21]. Since quite a close relation has been established between mechanical microvibrations of the head and body and rhythmic activity of the central nervous system[1] [22], we can assume that people with suicide risk have higher strain of the regulatory systems, which manifests itself through growing variability of the 'stress' and 'inhibition' parameters. Deviations in the regulatory systems are known to occur long before any energy, metabolic, or functional disorders of different organs and systems in the body, let alone an actual disease; they are early prognostic signs of a developing pathology and are far ahead of any changes measurable by clinical, laboratory or instrumental tests [21]. Therefore, practical use of prognostic express-methods makes it possible to diagnose prenosological changes in LEOs' adjustment disorders as a predecessor of suicidal behavior at early stages [23].

Table 1

Assessment of differences between two groups of LEOs as per vibration imaging parameters

Parameter	SR0 group	SR group	*p*
	$M \pm \sigma$	$M \pm \sigma$	
Basic vibration imaging parameters			
E1 (aggression)	33.68 ± 7.43	33.33 ± 6.24	0.775
E2 (stress)	35.11 ± 4.36	34.76 ± 4.05	0.631
E3 (anxiety)	29.96 ± 7.77	29.94 ± 8.29	0.986
E4 (danger)	33.15 ± 3.14	32.91 ± 3.52	0.659
E5 (steadiness)	77.57 ± 4.50	77.77 ± 4.92	0.799
E6 (charisma)**	41.37 ± 16.26	36.56 ± 17.04	0.079
E7 (vitality)	16.15 ± 5.30	15.63 ± 4.33	0.553
E8 (self-regulation)**	59.26 ± 8.75	57.18 ± 9.39	0.160
E9 (inhibition)	20.93 ± 2.80	20.97 ± 3.05	0.933
E10 (neuroticism)**	47.15 ± 11.24	50.36 ± 14.39	0.096
E11 (depression)	33.42 ± 3.18	33.92 ± 3.08	0.355
E12 (happiness)	32.54 ± 6.68	31.64 ± 6.24	0.418
Variability of vibration imaging parameters			
V_E1 (aggression)	23.48 ± 5.45	23.91 ± 6.47	0.641
V_E2 (stress)**	18.26 ± 5.87	19.81 ± 8.11	0.126
V_E3 (anxiety)	34.90 ± 16.23	34.85 ± 17.01	0.986
V_E4 (danger)	13.56 ± 3.46	13.80 ± 3.40	0.681
V_E5 (steadiness)	12.26 ± 4.59	11.87 ± 5.40	0.615
V_E6 (charisma)	46.52 ± 33.18	51.91 ± 27.30	0.328
V_E7 (vitality)	35.81 ± 12.01	35.71 ± 11.62	0.960
V_E8 (self-regulation)	16.32 ± 5.67	16.71 ± 5.40	0.677
V_E9 (inhibition)*	22.59 ± 4.49	24.18 ± 6.40	0.042
V_E10 (neuroticism)	21.61 ± 1.60	21.84 ± 1.45	0.383
V_E11 (depression)	12.50 ± 3.25	12.41 ± 3.03	0.874
V_E12 (happiness)	18.92 ± 8.51	19.22 ± 8.58	0.831

N o t e: here and below in the text * points out indicators different with 95 % likelihood, and ** with 80 % likelihood as per Student's *t*-test. Names of vibration imaging parameters are given in brackets as they are interpreted by the technology developers.

[1] Rorakher G., Inanaga K. Microvibration: its biological function and significance for clinical diagnostics. Bern, Stuttgart, Wien, Hans Huber Publ., 1969, 160 p.

Table 2

Assessment of differences in abilities (as per multiple intelligence (MI) types) and moral qualities in different LEO groups

Characteristics	SR0	SR	*p*
Abilities (G. Gardner's MI types)			
Intrapersonal**	55.55 ± 30.52	62.90 ± 28.30	0.150
Philosophic-investigatory	52.51 ± 26.87	53.45 ± 29.04	0.835
Logical-mathematical	57.10 ± 29.79	52.83 ± 27.31	0.390
Business-selfish	23.97 ± 26.26	23.07 ± 24.05	0.838
Visual-spatial	57.02 ± 27.09	56.54 ± 28.02	0.916
Naturalistic	49.42 ± 29.22	53.49 ± 26.00	0.403
Locomotive	43.00 ± 27.48	42.86 ± 24.39	0.976
Musical-rhythmical*	34.49 ± 28.63	44.08 ± 28.84	0.046
Selfless	67.15 ± 24.79	62.43 ± 24.57	0.256
Verbal-linguistic	43.89 ± 30.05	49.55 ± 31.69	0.263
Creative	44.04 ± 29.69	38.00 ± 31.76	0.228
Interpersonal**	52.37 ± 29.93	43.10 ± 32.39	0.067
Moral qualities			
Wrath	25.29 ± 27.20	30.97 ± 29.61	0.216
Envy	24.43 ± 27.64	28.11 ± 22.86	0.424
Internet-addiction	19.45 ± 26.38	22.03 ± 23.71	0.557
Greed	32.01 ± 29.12	36.12 ± 27.19	0.398
Gluttony	40.03 ± 30.85	44.62 ± 36.56	0.381
Sloth*	23.53 ± 26.82	35.04 ± 30.18	0.011
Lust	21.37 ± 27.05	24.75 ± 23.61	0.453
Alcoholism, drug addition**	14.01 ± 21.50	19.45 ± 29.84	0.143
Egoism**	22.14 ± 27.47	29.78 ± 28.07	0.098
Suicide**	13.65 ± 20.95	19.75 ± 20.93	0.083
Theft, bribery*	14.86 ± 21.73	29.52 ± 22.47	0.000
Pride**	29.12 ± 27.24	35.42 ± 25.53	0.166

Direct differences in vibration imaging parameters manifest themselves in the symmetry of head and face micro-movements (parameter E6), in mean values of a sum of conditionally positive emotions (E8) and in the spread of measured values of inhibition over the measurement period (E10). Therefore, people with suicide risk have higher neuroticism and lower levels of positive emotions in general, which indicates that their psychophysiological state is unstable and their psychoemotional state has apparent sub-depression trends.

Data obtained during this study for different groups of LEOs that describe their key abilities (G. Gardner's multiple intelligence [24]) and moral qualities are of great interest.

Obviously, people with suicide risk tend to have the musical-rhythmical MI type more often as well as a more apparent intrapersonal type and less apparent interpersonal one. This indicates that LEOs with suicide risk are more often introverted, their psyche is turned inward, they focus on their internal world, do not have any need in communicating with others, and are more sensitive to sounds (their leading sensory organ is the hearing apparatus).

A significant advantage of vibration imaging is a provided possibility to estimate an unconscious response (IE) of a tested person to a presented stimulus (detection takes place at the moment when a stimulus has already appeared on the screen but a tested person has not yet given an answer by pressing 'yes/no' keys) and to compare it with an integral response (IE+YN). Mean values obtained for moral qualities by estimating unconscious responses are provided in Table 3.

Table 3

Assessment of differences in unconscious responses to stimuli associated with moral qualities in two LEO groups

Moral quality	SR0	SR	*p*
Wrath	33.75 ± 21.92	34.74 ± 21.89	0.787
Envy	33.48 ± 23.47	33.04 ± 23.18	0.911
Internet-addiction	34.93 ± 23.89	35.96 ± 16.39	0.794
Greed	34.33 ± 23.76	37.30 ± 20.17	0.453
Gluttony	35.25 ± 25.29	40.45 ± 22.25	0.218
Sloth	34.84 ± 22.99	38.15 ± 20.05	0.387
Lust	33.54 ± 24.40	30.10 ± 21.76	0.397
Alcoholism, drug addition	34.11 ± 23.58	36.99 ± 24.07	0.466
Egoism*	34.28 ± 25.32	45.29 ± 25.19	0.010
Suicide**	34.73 ± 22.69	40.89 ± 22.57	0.106
Theft, bribery	33.57 ± 21.67	34.40 ± 18.80	0.817
Pride**	33.57 ± 22.88	40.57 ± 21.90	0.068

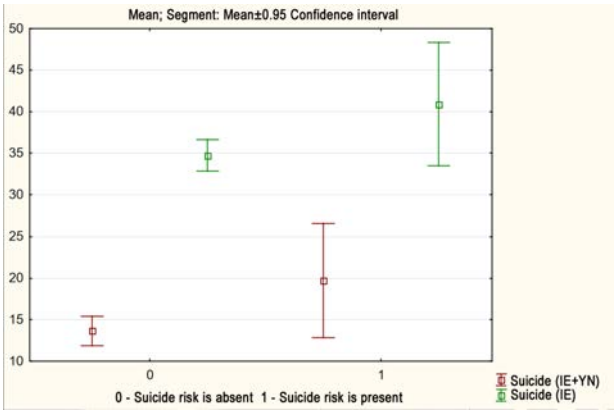

Figure 1. Differences between integral (IE+YN) and unconscious responses (IE) to stimuli associated with suicide in different LEO groups

Table 3 clearly shows that LEOs with suicide risks are more egoistic; put their interests above everything; have narcissism (not excluding auto-aggression). They also tend to have thoughts, concepts and feelings with suicidal ideation and readiness to realize them. Differences in unconscious and integral (Figure 1) responses to stimuli associated with identification of suicidal ideation indicate that people from the SR group tried to not declare their suicidal thoughts and ideations consciously.

A database was created to differentiate the analyzed LEO groups. It included 76 randomly selected observations (38 observations from the SR0 group and 38 observations from the SR group).

Discriminant analysis was applied to solve classification tasks. Assessment of informative value of characteristics revealed that 23 parameters were included into the model out of all vibration imaging parameters, their variability, abilities and moral qualities (integral and unconscious responses). They are provided in Table 4.

Table 4

Informative value of personality characteristics within the linear discriminant function

Personality characteristics based on the Profiler+ program	Wilkes (Lambda)	Partial (Lambda)	F-excl. (1.52)	*p*	Tolerance	1-toler. (R-sq.)
Musical-rhythmical MI type	0.33	0.56	41.11	0.000	0.32	0.68
E10 (Neuroticism)	0.30	0.61	33.50	0.000	0.32	0.68
E9 (Inhibition)	0.28	0.65	28.32	0.000	0.28	0.72
Suicide (unconscious response)	0.28	0.65	27.98	0.000	0.18	0.82
Theft, bribery (integral response)	0.26	0.71	21.07	0.000	0.46	0.54
Egoism (IE)	0.25	0.72	20.21	0.000	0.38	0.62
E6 (Charisma)	0.25	0.72	20.17	0.000	0.00	1.00
V_E5 (Variability of the Steadiness parameter)	0.25	0.74	18.36	0.000	0.18	0.82
Lust (IE)	0.24	0.76	16.40	0.000	0.47	0.53

End of the Table 4

Personality characteristics based on the Profiler+ program	Wilkes (Lambda)	Partial (Lambda)	F-excl. (1.52)	*p*	Tolerance	1-toler. (R-sq.)
E8 (Self-regulation)	0.24	0.78	14.84	0.000	0.00	1.00
Internet-addiction (IE)	0.23	0.79	14.04	0.000	0.18	0.82
Intrapersonal MI type	0.23	0.79	13.61	0.001	0.56	0.44
Internet-addiction (IE+YN)	0.23	0.80	12.88	0.001	0.26	0.74
Locomotive MI type	0.23	0.80	12.61	0.001	0.55	0.45
Visual-spatial MI type	0.22	0.82	11.08	0.002	0.66	0.34
Sloth (IE)	0.22	0.84	9.57	0.003	0.15	0.85
Wrath (IE+YN)	0.21	0.85	8.97	0.004	0.45	0.55
Gluttony, bulimia (IE+YN)	0.21	0.86	8.44	0.005	0.39	0.61
E5 (Steadiness)	0.20	0.91	5.12	0.028	0.03	0.97
E11 (Depression)	0.20	0.92	4.49	0.039	0.28	0.72
E1 (Aggression)	0.20	0.92	4.29	0.043	0.23	0.77
VSR, % (virtues to moral qualities ratio)	0.20	0.93	4.02	0.050	0.55	0.45
Alcoholism, drug addiction (IE+YN)	0.19	0.95	2.74	0.104	0.42	0.58

Use of conventional discriminant analysis made it possible to develop an integral suicide risk indicator in LEOs (*IIsr*), which is given by an equation based on coefficients provided in Table 5.

Table 5

Values of coefficients for calculating *IIsr* for law enforcement officers, including military personnel

Indicator	Coefficient
Absolute tern	-100.73
Theft, bribery (IE+YN)	0.17
Suicide (IE+YN)	0.33
Intrapersonal MI type	0.10
Musical-rhythmical MI type	0.19
Internet-addiction (IE+YN)	-0.17
E10 (Neuroticism)	3.19
E9 (Inhibition)	0.85
E5 (Steadiness)	-1.54
Wrath (IE+YN)	-0.09
Locomotive MI type	-0.11
Lust (IE+YN)	-0.18
Gluttony, bulimia (IE+YN)	-0.09
V_E5 (Variability of the Steadiness parameter)	1.12
E6 (Charisma)	-3.00
E8 (Self-regulation)	5.39
Visual-spatial MI type	0.10
VSR, % (virtues to moral qualities ratio)	-0.39
E11 (Depression)	-0.72
Sloth (IE+YN)	-0.28
Internet-addiction (IE)	0.27
Egoism (IE+YN)	0.18
E1 (Aggression)	0.35
Alcoholism, drug addiction (IE+YN)	0.06

The said indicator was represented by a conventional discriminant function, which separated the groups with and without suicide risk.

Group membership was estimated with using linear discriminant functions Z_0, Z_1:

$$Z_0 = -46{,}06 + 2{,}21 \times IIsr \text{ T-scores} \quad (1)$$

$$Z_1 = -94{,}48 + 3{,}18 \times IIsr, \text{ T-scores}, \quad (2)$$

where the index 0 is attributable to LEOs without suicide risk; the index 1, LEOs with suicide risk.

An estimation of membership in a group is performed as follows: the integral suicide risk indicator is calculated for each specific law enforcement official as per the above formula and on the basis of coefficient values provided in Table 5. An obtained *IIsr* value is substituted into the formulas (1) and (2), which are used to calculate Z_0 and Z_1 values. An ultimate conclusion on membership / not membership in a group with elevated suicide risk is made per the maximum Z_i value.

Predictive ability of decision rules equaled 100 % for the group without suicide risk; 97.37 %, the group with suicide risk; 98.68 % for the whole sample.

A probabilistic nomogram (Figure 2) was built to facilitate use of decision rules. It allows quick and visualized identification of suicide risk likelihood (%) in a LEO based on his

IIsr value. For example, if *IIsr* = 49 scores, suicide risk likelihood equals 30 % and likelihood of its absence equals 70 % for a LEO with this score estimate. If *IIsr* = 53 scores, suicide risk likelihood is 95 %.

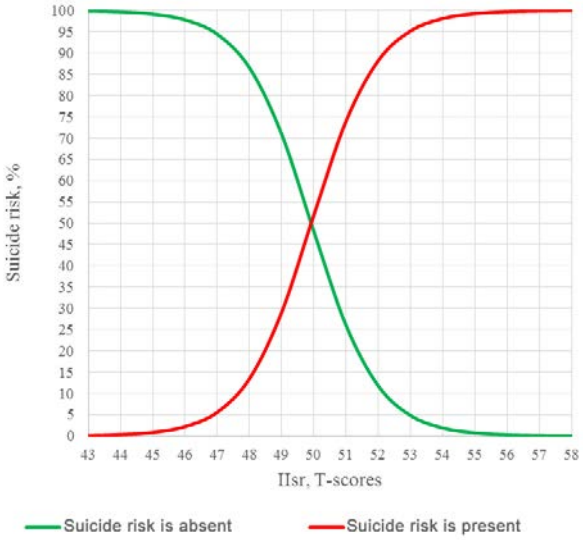

Figure 2. Probabilistic nomogram for suicide risk identification in law enforcement officers, including military personnel

The developed model can be implemented as an Excel macros; a result stating either presence or absence of suicide risk in a LEO can be received automatically upon completion of 5-minute testing. This is a considerable advantage for use within mass medical check-ups provided for law enforcement personnel.

Conclusion. Suicide risk prophylaxis in law enforcement officials, including military personnel, is accomplished not only to prevent accidents but also to protect personnel's physical and mental health. The developed model for suicide risk prediction makes it possible to obtain relevant data on likelihood of suicidal ideation, abilities and moral qualities of personnel after short-time testing. This allows developing personalized and optimized measures aimed at preventing suicidal behavior within medical and psychological support. A possibility to estimate both unconscious and integral responses given by examined LEOs to stimuli helps both a psychologist and commanders shape an opinion on as level of actual development of their moral qualities even if they would like to hide it. In our opinion, contactless express-methods, vibration imaging being among them, are quite promising in applied medical and psychological investigations conducted by various law enforcement agencies.

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Research article

POLYMORPHISM OF *TP53* (RS1042522) GENE AND PECULIARITIES OF THE IMMUNE PROFILE IN CHILDREN EXPOSED TO AIRBORNE BENZO(A)PYRENE

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Examining peculiarities of an immune profile and genetic polymorphisms is especially relevant when identifying markers of effect and sensitivity to exposure to benzo(a)pyrene in northern areas.

We examined 1253 children who lived in industrial centers and on conditionally clean territories in the north and south of Eastern Siberia. Levels of benzo(a)pyrene in ambient air and in children's blood were determined by using HPLC. TP53 (rs1042522) polymorphism was examined by using real-time PCR; p53 levels were identified with flow cytofluorometry; IgG to benzo(a)pyrene, by the radioallergosorbent tests.

Exposure of children in Northern Siberia to airborne benzo(a)pyrene at the dose of $7.11 \cdot 10^{-3}$ μg/(kg·day) causes benzo(a)pyrene contamination in blood, activates apoptosis (p53) and stimulates occurrence of specific sensitization (IgG to benzo(a)pyrene) ($p < 0.05$). Similar disorders were established in children in Southern Siberia under exposure to airborne benzo(a)pyrene at the dose of $86.46 \cdot 10^{-3}$ μg/(kg·day). The detected changes in immune profiles of children living in Northern Siberia are associated with G-allele and GG-genotype (rs1042522) of the TP53 gene (OR = 1.37–1.83, $p < 0.05$); children in Southern Siberia, C-allele and CC-genotype of the said gene (OR = 1.55–2.38, $p < 0.05$).

Therefore, the immune profile of children exposed to airborne benzo(a)pyrene at the dose of $7.11 \cdot 10^{-3}$ μg/(kg·day) in Northern Siberia bears some signs of activated apoptosis (p53) and specific sensitization (IgG to benzo(a)pyrene) associated with G-allele and GG-genotype of the TP53 gene (rs1042522) (OR = 1.37–1.83, $p < 0.05$). These identified changes in the immune profile are comparable with effects produced by exposure to airborne benzo(a)pyrene at the dose of $86.46 \cdot 10^{-3}$ μg/(kg·day) in Southern Siberia, which are associated with C-allele and CC-genotype of the same gene (OR = 1.55–2.38, $p < 0.05$). This confirms a hypothesis that effects of technogenic chemical factors can be modulated by specific climatic conditions in northern areas and a contribution made by genetic predisposition. Their combined effect creates a serious risk of developing impairments in an immune profile (OR = 1.37–1.83, $p < 0.05$; RR = 1.17; 95 % CI: 1.07–1.27) even under low-dose exposure to airborne benzo(a)pyrene.

Keywords: *benzo(a)pyrene, airborne exposure, children, immune profile, genetic polymorphism, apoptosis, p53, sensitization.*

Benzo(a)pyrene is a polycyclic aromatic hydrocarbon (PAH) of hazard degree I able to produce mutagenic, carcinogenic (IARC's group A carcinogen) and immunosuppressing effects [1, 2].

Impacts of technogenic chemical factors on human health in an actual industrially developed area are not isolated. A combination of climatic conditions and peculiar light regime typical for a given territory can modulate adverse effects produced by technogenic chemical exposures [3]. In particular, combined influence of subarctic climatic conditions and photoperiodic seasonal asymmetry in northern areas induces deadaptation-like changes in the immune regulation even under low-dose chemical exposures [4, 5].

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It should be noted that polymorphisms of candidate genes responsible for the immune regulation make a significant contribution to formation of a specific immune profile, which plays an important role in adaptation to changed environmental conditions [6, 7]. Changes in an immune profile associated with polymorphisms of the tumor suppressing gene p53 *TP53* (rs1042522) can be related to dysregulation of the cell cycle, DNA repair and apoptosis and growing risks of oncoproliferative states. This is especially relevant under exposure to benzo(a)pyrene as a well-known chemical carcinogen [8, 9].

Hence, it is quite relevant to accomplish a comparative assessment of peculiarities of an immune profile associated with the *TP53* (rs1042522) gene polymorphisms in children exposed to airborne benzo(a)pyrene in the south and north of Eastern Siberia for further development and substantiation of markers of effects and sensitivity to exposure to technogenic chemical factors in northern areas with specific climatic conditions and light regime.

In this study, we aimed to comparatively assess polymorphisms of the *TP53* (rs1042522) gene and peculiarities of an immune profile in preschoolers exposed to airborne benzo(a)pyrene in the north and south of Eastern Siberia.

Materials and methods. We comparatively assessed polymorphisms of the *TP53* (rs1042522) gene and immune profile indicators in preschoolers who lived in Eastern Siberia (n = 1253). The observation group 1 (n = 526) and the observation group 2 (n = 376) were made of children living in industrially developed areas in the north and south of the region respectively. The reference group 1 (n = 180) and the reference group 2 (n = 171) included children who lived on conditionally clean territories in the north and south of the region.

The study was accomplished in conformity with the fundamentals stated in the Declaration of Helsinki by the World Medical Association and approved by the Local Ethics Committee of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies (The meeting report No. 2 dated January 17, 2022).

Benzo(a)pyrene levels in ambient air and contamination with this PAH in the examined children's blood were identified by using high-performance liquid chromatography on an Agilent 1200 (USA) in conformity with the Methodical Guidelines MUK 4.1.3040-12[1] and MUK 4.1.1273-03[2].

The intracellular transcription factor p53 was determined by using flow-cytometric analysis on a FACSCalibur (USA). Production of IgG specific to benzo(a)pyrene was established by the radioallergosorbent tests.

SNP of the *TP53* (rs1042522) gene responsible for the transcription factor p53 were identified by real-time polymerase chain reaction (PCR-RT) on a CFX96 amplifier (Singapore). DNA was extracted from buccal epithelium by the sorbent method. A genotype of each participant was determined by allelic discrimination in TaqMan.

Data were statistically analyzed in StatSoft Statistica 10.0 by using ANOVA one-factor dispersion analysis. Data distribu-

[1] MUK 4.1.3040-12. Izmerenie massovoi kontsentratsii benz(a)pirena v krovi metodom vysokoeffektivnoi zhidkostnoi khromatografii [Measurements of mass concentration of benzo(a)pyrene in blood by high-performance liquid chromatography]: Methodical guidelines, approved by G.G. Onishchenko, the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, the RF Chief Sanitary Inspector on September 07, 2012. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200103098 (January 17, 2024) (in Russian).

[2] MUK 4.1.1273-03. Izmerenie massovoi kontsentratsii benz(a)pirena v atmosfernom vozdukhe i v vozdukhe rabochei zony metodom vysokoeffektivnoi zhidkostnoi khromatografii s fluorimetricheskim detektirovaniem [Measurements of mass concentration of benzo(a)pyrene in ambient air and workplace air by high-performance liquid chromatography with fluorometric detection]: Methodical guidelines, approved and enacted by G.G. Onishchenko, the RF Chief Sanitary Inspector and Deputy to the RF Minister of Health on April 01, 2003. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200034301 (January 17, 2024) (in Russian).

tion was checked for normality with the one-sample Kolmogorov – Smirnov test. The Tukey – Kramer test was applied to check authenticity of differences in multiple comparisons. The statistical significance for rejecting the null hypothesis (that is, absence of differences) was taken at $p < 0.05$. We calculated distribution of frequencies of the *TP53* (rs1042522) gene alleles and genotypes, odds ratio *OR*, relative risk *RR* and their 95 % confidence intervals (*CI*) for further analysis of relations between changes in immune regulation indicators and variant genotypes of this gene in Gen-Expert online calculator and Microsoft Office Excel 2010.

Results and discussion. Average annual benzo(a)pyrene levels equaled 0.62 average daily MPL in ambient air in an industrially developed area in the north and 0.014 average daily MPL in a conditionally clean area in the same region; they equaled 7.27 average daily MPL in ambient air in an industrially developed area in the south and 0.74 average daily MPL in a conditionally clean area in the same region[3].

An average daily exposure to airborne benzo(a)pyrene was 0.0071 μg/(kg·day) for children living in an industrially developed area in the north and was higher than that for children living in a conditionally clean northern area (0.0001 μg/(kg·day)) ($p = 0.001$). In its turn, an average daily exposure to airborne benzo(a)pyrene for children living in an industrially developed area in the south (0.0865 μg/(kg·day)) was not only authentically higher than that for children living in a conditionally clean southern area (0.0083 μg/(kg·day)) but also higher than that for children living in an industrially developed area in the north ($p = 0.001$).

Levels of contamination in blood of the children from the observation group in the north (0.00224 ± 0.00030 μg/dm^3) were higher than in the children from the reference group (0.00112 ± 0.00034 μg/dm^3) and the reference level ($p < 0.05$). Benzo(a)pyrene levels in blood of the children from the observation group in the south (0.00225 ± 0.00035 μg/dm^3) were also higher than those in blood of the children from the relevant reference group (0.00109 ± 0.00024 μg/dm^3) and the reference level ($p = 0.006$). However, benzo(a)pyrene levels did not differ authentically in blood of the children under low-dose exposure to airborne benzo(a)pyrene in an industrially developed area in the north and in blood of the children under high-dose exposure to airborne benzo(a)pyrene in the south ($p = 0.98$).

The immune profile of the examined children living in highly urbanized territories in the north and south of Eastern Siberia bears some signs of activated programmed cell death combined with developing specific hyper-sensitization to benzo(a)pyrene (Table 1).

Some signs of hyperexpression of the onco-suppressor protein p53 were identified in 43.9 % (231) of the children from the northern observation group against their peers in the corresponding reference group and the reference level as well ($p < 0.05$). Elevated p53 levels in the northern observation group were authentically associated with the G-allele and GG-genotype of the *TP53* gene (rs1042522) (*OR* = 1.37–1.83, $p < 0.05$) (Table 2).

[3] Ob utverzhdenii Programmy kompleksnogo razvitiya transportnoi infrastruktury munitsipal'nogo obrazovaniya «Gorod Dudinka»: reshenie Dudinskogo gorodskogo soveta deputatov ot 14.09.2017 № 10-0358 [On Approval of the program for complex development of the transport infrastructure in Dudinka municipal settlement: the Decision of the Dudinka Town Council of Deputies dated September 14, 2017 No. 10-0358]. *The official web-site with legal information on town Dudinka*. Available at: http://www.pravo-dudinka.ru/download/rgs/rgs_2017-09-14_10-0358.pdf (February 21, 2024) (in Russian); O sostoyanii i ob okhrane okruzhayushchei sredy Rossiiskoi Federatsii v 2018 godu [On the state and protection of the environment in the Russian Federation in 2018]: the state report. Moscow, Ministry of Natural Resources and Environment of the Russian Federation; NPP Kadastr, 2019 (in Russian); Sostoyanie zagryazneniya atmosfery v gorodakh na territorii Rossii za 2017 g. [Ambient air pollution in cities in Russia in 2017]: Annual data collection. St. Petersburg, 2018 (in Russian).

Table 1

Peculiarities of the immune profile of the children living in the north and south of Eastern Siberia under exposure to airborne benzo(a)pyrene

Reference level[4]	Observation group 1 – northern Siberia (n = 526)	Reference group 1 – northern Siberia (n = 180)	p_1	Observation group 2 – southern Siberia (n = 376)	Reference group 2 – southern Siberia (n = 171)	p_2
p53, % / p53,%						
1.2 –1.8	5.42 ± 0.47*	4.27 ± 0.29*	0.038	7.75 ± 0.89*	1.87 ± 0.10	0.001
IgG to benzo(a)pyrene, arb.un.						
0–0.3	0.208 ± 0.014	0.080 ± 0.02	0.001	0.212 ± 0.011	0.074 ± 0.009	0.001

N o t e: p_1 is authenticity of differences between the observation and reference group in the north; p_2 is authenticity of differences between the observation and reference group in the south; * means authentic difference from the reference level ($p < 0.05$).

Table 2

Frequencies of alleles and genotypes of the *TP53* (rs1042522) gene in the examined children in the north and south of Eastern Siberia, %

SNP	Genotype / allele	v_{obs}	v_{ref}	χ^2	p	*OR* (95 % *CI*)
TP53 (rs1042522)	Observation group 1 (n = 526) / Reference group 1 (n = 180)					
	CC	36.1	36.7	3.82	0.049	0.98 (0.69–1.39)
	CG	11.2	25.6			0.37 (0.24–0.57)
	GG	52.7	37.7			1.83 (1.30–2.59)
	C	41.7	49.4	6.49	0.01	0.73 (0.58–0.93)
	G	58.3	50.6			1.37 (1.07–1.74)
	Observation group 2 (n = 376) / Reference group 2 (n = 171)					
	CC	49.5	29.1	9.94	0.002	2.38 (1.59–3.57)
	CG	34.3	54.3			0.44 (0.30–0.65)
	GG	16.2	16.6			0.98 (0.59–1.62)
	C	66.6	56.3	8.76	0.003	1.55 (1.18–2.04)
	G	33.4	43.7			0.65 (0.49–0.85)

N o t e: v_{obs} is frequencies of alleles and genotypes in the observation groups 1 and 2; v_{ref} is frequencies of alleles and genotypes in the reference groups 1 and 2.

Levels of p53 were also higher in 54.5 % (205) of the children in the southern industrial area than in the children from the relevant reference group ($p < 0.05$), which, on the contrary, was associated with the C-allele and CC-genotype of the *TP53* (rs1042522) gene (*OR* = 2.17–2.83, $p < 0.05$).

Levels of the protein p53 expression in the children under high-dose exposure to airborne benzo(a)pyrene in the south were authentically 1.4 times higher than the same indicator in the children under low-dose exposure to airborne benzo(a)pyrene in the north ($p < 0.05$). Levels of the p53 protein were also higher in the children who lived in a conditionally clean northern area than in the children who lived in a conditionally clean area in the south ($p = 0.001$).

We established higher production of IgG specific to benzo(a)pyrene in 73.4 % (386) of

[4] Tietz' clinical guide to laboratory tests, 4th ed. In: A. Wu ed.; V.V. Menshikov translation. Moscow, Labora Publ., 2013, 1280 p. (in Russian).

the children from the observation group 1 and 63.1 % (237) of the children in the observation group 2 against the reference level and corresponding reference groups ($p < 0.05$). However, levels of this marker identified in the children under low-dose exposure to airborne benzo(a)pyrene in the north were comparable with those identified under high-dose exposure to airborne benzo(a)pyrene in the south ($p = 0.822$).

Benzo(a)pyrene is a highly toxic polycyclic aromatic hydrocarbon (PAH) able to produce strong cytotoxic, mutagenic, carcinogenic and neurotoxic effects [10]. Mutagenic and carcinogenic effects of benzo(a)pyrene occur due to covalent linking of its metabolite BaP-7,8-dihydrodiol-9,10-epoxide (BPDE) to nucleotide bases and the subsequent formation of cys- and trans-DNA adducts. This damages a nucleotide sequence, breaks DNA repair and replication and cell transformation and, consequently, results in cell death and / or carcinogenesis [11, 12].

Climatic and natural conditions in polar areas, in particular, in the north of Eastern Siberia are harsh and unstable as they are characterized with a long period of low temperatures, drastic changes in the atmospheric pressure, elevated electromagnetic activity and radiation as well as a changed light regime, namely, photoperiodic seasonal asymmetry. Extreme living conditions in northern areas make high demands of the immune and nervous systems as those maintaining homeostasis in the human body under unstable environmental conditions. Adaptation of the body to such harsh conditions becomes more complex and this leads to a decrease in adaptation potential and, consequently, facilitates occurrence of prenosological changes in an immune profile [13, 14].

The p53 protein is a transcription factor and tumor growth suppressor. It plays an important role in DNA repair, cell cycle regulation and apoptosis or programmed cell death. Activation of p53 by various DNA-damaging agents and carcinogens, benzo(a)pyrene included, stops the cell cycle in its G1 phase and induces Nucleotide Excision Repair (NER), an important pathway of DNA repair. It is put into effect by activating inhibitors of the cyclin-dependent kinase c21 (CDK-21) as well as the *GADD45* (Growth arrest and DNA damage) gene. However, a growing dose of a carcinogen as well as longer exposure to it creates higher risks of mutations of the tumor suppressor gene p53. DNA damage in a mutated cell does not stop the cell cycle or DNA repair due to disrupted p53-dpendent formation of the cyclin-dependent kinase inhibitor 1A p21, which results in its proliferation and transformation into a malignant neoplasm [15, 16].

In this study, elevated p53 levels were identified in children under isolated exposure to a technogenic factor (benzo(a)pyrene) (the observation group 2), in children living in harsh climatic conditions in a northern area (the reference group 1), and in children under combined exposure to both adverse factors, technogenic and climatic one (the observation group 1). This, probably, indicates that programmed cell death was activated for cells with DNA damage under exposure to various stress factors. We established that high-dose exposure to airborne benzo(a)pyrene, 0.0865 μg/(kg·day), associated with the C-allele and wild CC-genotype of the *TP53* (rs1042522) gene caused the greatest growth in the p53 expression, namely, by 4.1 times against the reference group 2. A less significant increase in p53 levels in the children who lived in an industrially developed area in the north of Eastern Siberia, namely, by 1.3 times, was probably associated with exposure to low doses of benzo(a)pyrene, 0.0071 μg/(kg·day), as well as such genetic determinants as a prevailing minor G-allele and GG-genotype of the *TP53* (rs1042522) gene. Frequency of the G-allele of the *TP53* (rs1042522) gene was 58.3 % in the children living in an industrially developed area in the north of Eastern Siberia. This is authentically higher than average frequencies in the global

(28.6 %), European (26.3 %) and Asian (41.5 %) populations[5]. According to literature data, the G-allele of the *TP53* (rs1042522) gene is associated with lower expression of the p53 protein, inhibited DNA repair and apoptosis [17]. It is also a known fact that isolated exposure to benzo(a)pyrene as well as combined exposure to benzo(a)pyrene and a vaccine SARS-CoV-2 antigen activates expression of the *TP53* (rs1042522) gene in CG-heterozygotes and, on the contrary, inhibits its expression in GG-homozygotes in *in vitro* experiments [18]. In addition to that, the GG-genotype of the *TP53* (rs1042522) gene might be associated with an elevated risk of developing oncoproliferative processes [19, 20], which is especially important under exposure to benzo(a)pyrene in the environment as an obvious carcinogen.

Conclusion. Benzo(a)pyrene levels identified in blood of children exposed to airborne benzo(a)pyrene at the dose of 0.0071 μg/(kg·day) were higher in an industrially developed area in the north of Eastern Siberia than in a conditionally clean area in the same region ($p < 0.05$) and did not differ from levels identified in blood of children exposed to airborne benzo(a)pyrene at the dose of 0.0865 μg/(kg·day) in the south of Eastern Siberia ($p > 0.05$). The same trend was revealed for immune regulation indicators. Thus, production of p53 and IgG specific to benzo(a)-pyrene was higher in children under low-dose exposure to benzo(a)pyrene in the north than in children living in a conditionally clean area in the north and was comparable with that identified in children under high-dose exposure to benzo(a)pyrene in the south of Eastern Siberia ($p < 0.05$). Changes in the immune regulation identified in children living in an urbanized area in the north were associated with the minor G-allele and GG-genotype of the *TP53* (rs1042522) gene (*OR* = 1.37–1.83, $p < 0.05$; *RR* = 1.17; 95 % *CI*: 1.07–1.27) and with the wild C-allele and CC-genotype of the same gene in children living in an industrially developed area in the south (*OR* = 1.55–2.38, $p < 0.05$). The phylogenetic aspect of the *TP53* (rs1042522) gene has an emphasis on the maximum duration of the cell cycle under 'northern stress' (limited functional of the tumor suppressor p53). An association between changes in immune profiles of children living in an industrially developed area in the north and the minor G-allele and GG-genotype of the said gene indicates that genetic predisposition makes an additional background contribution to occurrence of more intensive adverse effects produced by exposure to benzo(a)pyrene in a northern area with a specific climatic background and light regime. Therefore, these identified changes in the immune regulation in children living in an industrially developed area in the north (elevated levels of p53 and IgG specific to benzo(a)pyrene), which are associated with the G-allele and GG-genotype of the *TP53* (rs1042522) gene, describe peculiar adaptation reactions of the immune system under combined exposure to benzo(a)pyrene, sub-Arctic climatic conditions and photoperiodic asymmetry in the presence of relevant genetic determinants. Hence, they can be used as indicators of health risks (*OR* = 1.37–1.83, $p < 0.05$; *RR* = 1.17; 95 % *CI*: 1.07–1.27) for children exposed to airborne technogenic chemical factors in northern areas.

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[5] ALFA Allele Frequency of TP53 (rs1042522). *National Library of Medicine*. Available at: https://www.ncbi.nlm.nih.gov/snp/rs1042522#frequency_tab (February 11, 2024).

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Research article

IDENTIFYING THE FACTORS RELATED TO BODY FAT PERCENTAGE AMONG VIETNAMESE ADOLESCENTS USING MACHINE LEARNING TECHNIQUES

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The aim of this study was to investigate the factors influencing Body Fat Percentage (BFP) among Vietnamese adolescents aged 11 to 15 employing machine learning techniques for predictive analysis.

A total of 1,208 adolescents, comprising 598 boys and 610 girls, drawn from nine junior high schools in Vietnam's capital, were enrolled in the study. Body composition measurements were conducted using the HBF 375 (Omron) device by Bioelectrical Impedance Analysis method. The study questionnaire, initially validated by The National Institute of Nutrition, encompassed inquiries related to dietary behaviors, meal frequencies, physical activities, sedentary habits, and nutritional knowledge. A machine learning methodology employing a decision tree algorithm was employed to discern the primary determinants most significantly correlated with BFP.

This study successfully identified six distinct predictor groups associated with BFP among adolescents, leveraging the decision tree model, with Root Mean Squared Error (RMSE) and Mean Absolute Error (MAE) values of 4.80 and 3.80, respectively. Among these predictors, frequency of fruit consumption, snacking habits, mode of transportation to school, and screen time (computer and/or cell phone usage) emerged as the most influential factors linked to BFP in adolescents. The combination of these factors and interactions with gender and pubertal status can BFP in Vietnamese adolescents.

This research sheds light on the complex and diverse factors impacting BFP in Vietnamese adolescents. This study's results underscore the practical importance of promoting healthy eating and exercise habits among adolescents, offering valuable insights for parents and schools to enhance their childcare strategies.

Keywords: *machine learning, body fat percentage, predictability, influencing factors, eating habits, physical activity,Vietnamese adolescents, the decision tree.*

Body Fat Percentage (BFP) is widely accepted as an accurate and effective measurement of obesity status. Previous evidence has suggested that this index can provide additional insights into risks of cardiovascular health and other metabolic disorders as adipokines secreted by adipose tissue may affect many metabolic functions such as fat distribution, appetite, energy expenditure, insulin sensitivity and secretion, glucose and

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lipid metabolism [1]. The association between BFP and risk factors related to obesity is a subject of controversy when considering diverse ethnic populations. Additionally, there is limited information available regarding the effectiveness of these obesity assessment methods in Asian countries. In particular, in Asian populations, variations exist in the relative contributions of muscle mass, bone mass and bodily fluids to overall body weight when compared to Europeans. These differences are influenced by cultural subgroups, social and economic conditions, as well as nutritional characteristics [2]. While BFP plays a crucial role in evaluating the prevalence of overweight and obesity, there is a lack of comprehensive data regarding the distribution of body fat in adolescent populations, particularly in Asian regions.

Globally, urbanization significantly propels shifts in dietary patterns and levels of physical activity, with Vietnam standing as no exception to this trend [3]. Eating habits and physical activity levels have been recognized as a key player in changes in BFP [4]. Observations from a study in the city of Tehran showed that a comprehensive lifestyle intervention reduced BFP by 1.81 % in obese adolescents after 12 weeks of intervention [5]. In a study of 764 Indian schoolchildren aged 10–18 years, the authors showed that adolescents with healthy eating habits and regular physical activity had a lower BFP than that in adolescents with negative eating habits and and infrequent physical activity [6]. Besides, a study of 70 schoolchildren aged 14–15 also showed a significant relationship between physical activity and BFP [7]. The analysis of risk factors associated with eating habits and physical activity is the basis for making recommendations and proposing timely measures to reduce the increase in BFP at an early age as well as for proposing measures to prevent overweight and obesity in school age [8–10]. Machine learning is an application of artificial intelligence that helps systems automatically understand data from trained data without needing specific programming. Compared with classical statistics, the new point here is that a machine must efficiently perform inferences and learn from provided data using suitable algorithms and a massive data management facility of a computer. Hence, machine learning is regarded as a pioneering discipline within modern statistics and, more broadly, in the field of data science. Therefore, with the development of big data, use of machine learning algorithms to extract information to produce intelligent data is a necessary task. Research on 7162 Chinese people, using 11 algorithms of machine learning has shown that the random space classification algorithm achieves high overall accuracy and area under the curve. The study, using the evaluation criterion BMI, showed that duration of vigorous intensity activity per week and duration of moderate intensity activity per week were strongly associated with obesity [11]. The study by Babajide et al. (2020) investigated the applicability of machine learning to improve body mass prediction in a dietary intervention program [12]. A study of 40,032 Britons found that machine learning models based on two-dimensional projection allow near-perfect estimation of the volume of adipose tissue [13].

However, at present, studies applying machine learning in analyzing the relationship between eating habits and physical activity to BFP are still very limited. The purpose of this study was to identify risk factors and protective factors for BFP as well as their predictability in the representative population of 11 to 15-year-old students using machine learning techniques. The results of this study are the basis for making recommendations on daily food consumption and physical activity habits as well as developing policies and adjusting intervention programs to control an increase in obesity rates in this population.

Materials and methods. A total of 1208 adolescents (598 boys and 610 girls), aged

11–15 years, originating from nine junior high schools in the capital of Vietnam, were included in the study. Nine schools were selected from 583 junior high schools in Hanoi by simple random sampling method. Students at each school were selected using Epi info 6 software. Healthy students would be eligible for inclusion, if they were free of known chronic disease and were not taking any medication influencing body composition (e.g. β-blockers or diuretics).

The study protocol was approved by the local ethics committee at the Department of Human and Animal Physiology, Faculty of Biology, Hanoi National University of Education. The data collection and storage comply with ethical guidelines and protect individuals' confidentiality. The investigators informed all the school principals, teachers, the participants and their parents for the potential benefits and risks in relation to the study. Parents or guardians provided written informed consent for their child's participation in the study. Throughout the investigation, children had the right to decline answering any questions or to discontinue their participation in the study at any time.

Anthropometric measurements, which included weight, height, waist circumference (WC), and hip circumference (HC), were conducted in accordance with the standardized method developed by National Institute of Nutrition. These measurements were taken with the children wearing minimal clothing, after their shoes and hair ornaments were removed. Height, WC, and HC were measured to the nearest 0.1 cm, while body weight was measured to the nearest 0.1 kg using standardized medical scales. WC was measured at the midpoint between the iliac crest and the lowest rib, and HC was measured at the widest part of the buttocks using an inelastic tape measure. Each of these measurements was performed twice for each child, and the average value was utilized for subsequent analysis. Body Mass Index (BMI) was calculated by dividing the child's weight in kilograms by the square of height in meters. Students' nutritional status was assessed using the criteria established by the International Obesity Task Force (IOTF).

Bioelectrical Impedance Analysis (BIA): participants in this study underwent measurements of body composition using the HBF 375 (Omron) device. Body fat percentage (BFP) was in the focus of this analysis. Prior to these measurements, participants refrained from intense physical activity for at least 12 hours, abstained from consuming food or beverages for at least 3 hours, and ensured they had urinated and defecated within the last 30 minutes. Female participants were excluded from testing during their menstrual period. All BIA measurements were conducted in the morning.

The validation of the survey questionnaire was initially carried out by The National Institute of Nutrition. The questionnaire included questions about food behaviors, main meal frequencies, physical activity, sedentary behaviors, and nutrition knowledge. General information included age, gender, and residence area. Characteristics for eating habits (18 items) included frequencies of eating breakfast; eating speed; number of meals per day; snacking habits; type of food consumed in the snack; time to eat snacks of the day; sensory liking for vegetables / fruits / fatty food / sweet food / carbonated beverage / fast food / animal organs; frequency of consumption of vegetables / fruits / fatty food / sweet food / carbonated beverage / fast food / animal organs. Physical activity was measured based on 27 items: activity preferences, modes of transportation to school, frequency of walking or riding a bicycle, playing or not playing sport games, frequency of exercise, time spent being sedentary, sleep duration, frequency of vigorous, light, or moderate exercise. Nutrition knowledge was collected based on 9 items regarding a general nutrition concept as consuming good food for health or not and obesity-related knowledge

as definition of obesity and adequate methods of weight control.

Machine learning algorithms. The decision tree algorithm was used to make predictions for target values in regression tasks or target classes in classification tasks. Our primary emphasis was on solving regression problems, wherein the decision tree's terminal nodes, also known as leaf nodes, can accommodate continuous values, typically in the form of real numbers.

The process of constructing a regression tree involves iteratively dividing the dataset into increasingly smaller subsets while progressively expanding the decision tree structure. The final result is a fully grown tree, comprising decision nodes and leaf nodes. Decision nodes (for example, 'Gender') bifurcate into two or more branches (such as 'Male' and 'Female'), each representing possible attribute values. On the other hand, leaf nodes (for instance, 'BFP value') signify the ultimate decision pertaining to the numerical target value. The topmost decision node in the tree, which corresponds to the most informative predictor, is referred to as the root node. Throughout this experimental investigation, we harnessed the power of the Scikit-learn library, a Python-based machine learning toolkit [14].

Model evaluation. In assessing a Regression Model, we utilize two essential metrics: Root Mean Squared Error (RMSE) and Mean Absolute Error (MAE) [15]. These metrics serve as indicators of the model's precision and the magnitude of deviation from the actual values. Technically, RMSE is the square root of the mean of the squared errors, whereas MAE is the mean of the absolute errors. In this context, an error represents the disparity between the predicted values (values estimated by our regression model) and the genuine values of a variable. Concretely, the formulas are as follows:

$$RMSE = \sqrt{\frac{\sum (y_i - y_p)^2}{n}}, \qquad (1)$$

$$MAE = \frac{\left|(y_i - y_p)\right|}{n}, \qquad (2)$$

where y_i = actual value; y_p = predicted value, n = number of observations.

Results and discussion. Table 1 shows the characteristics of the study subjects by gender. Boys and girls had similar age, 13.0 and 12.9 years, respectively. However, boys, compared with girls, had a significantly greater weight, height, waist circumference, waist-to-hip

Table 1

General characteristics of the participants

Parameter	Boys (N = 598)	Girls (N = 610)	P-value
Age (years)[b]	13.0 (12.1–13.8)	12.9 (11.9–13.7)	0.406
Weight (kg)[b]	44.8 (37.3–52.2)	43.6 (37.8–49.0)	**0.03**
Height (cm)[a]	154.9 ± 10.3	153.1 ± 6.6	**< 0.0001**
BMI (kg/m^2)[b]	18.5 (16.6–20.8)	18.4 (16.5–20.2)	0.097
Waist circumference (cm)[b]	67.0 (62.5–73.1)	65.3 (62.0–69.6)	**< 0.0001**
Waist to hip ratio[b]	0.81 (0.78–0.86)	0.78 (0.75–0.81)	**< 0.0001**
Nutritional status			
+ Obesity (%)	4.5	0.8	**0.001**
+ Overweight (%)	13.5	11.4	
+ Normal weight (%)	67.6	73.9	
+ Underweight (%)	14.4	13.9	
BFP (%)[b]	18.0 (13.3–22.6)	21.1 (18.4–23.5)	**< 0.0001**
Subcutaneous fat percentage (%)[a]	12.5 ± 4.3	17.9 ± 4.0	**< 0.0001**
Muscle mass percentage (%)[b]	36.3 (33.5–38.7)	29.5 (28.1–31.0)	**< 0.0001**

N o t e: BMI is body mass index; BFP is body fat percentage; [a] data are mean ± SD; [b] data are median (interquartile range). P-values obtained by Student T test or Mann – Whitney U test or Chi-square test. Bold values indicate significant difference between cases and controls.

ratio, and muscle mass percentage ($P < 0.001$). In contrast, the BFP and the subcutaneous fat percentage of boys was lower than that of girls. In boy, BFP was 18.0 %, and subcutaneous fat percentage was 12.5 % meanwhile, in girls, the corresponding values were 21.1 % and 17.9 %, respectively. There was also a difference in nutritional status between male and female adolescents ($P = 0.001$) detected by using the IOTF criteria. Specifically, the rate of overweight and obesity in boys was much higher than in girls (18 % versus 12.2 %).

When investigating the correlations between body fat percentage and some certain anthropometric variables in Vietnamese adolescents, the findings revealed several significant associations. Body fat percentage exhibited strong positive correlations with Body Mass Index ($r = 0.51$), Waist Circumference ($r = 0.42$), and Hip Circumference ($r = 0.31$). Conversely, a negative correlation was observed between body fat percentage and height ($r = -0.30$) (Figure 1).

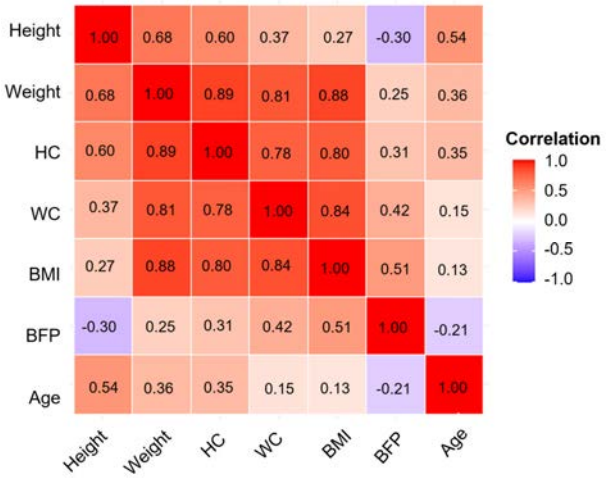

Figure 1. The correlations between body fat percentage and some anthropometric variables

The development of predictive model for adolescents aged between 11 and 15. ***Decision Tree Analysis.*** In assessing a regression model, we utilized two essential metrics: Root Mean Squared Error (RMSE) and Mean Absolute Error (MAE). These metrics serve as indicators of the model's precision and the magnitude of deviation from the actual values. Technically, RMSE is the square root of the mean of the squared errors, whereas MAE is the mean of the absolute errors. In this context, an error represents the disparity between the predicted values (values estimated by our regression model) and the genuine values of a variable.

The experimental results, evaluated using the decision tree model shown in Table 2, indicate RMSE and MAE values of 4.20 and 3.29 for the training dataset, and 4.80 and 3.80 for the validation dataset, respectively. The square root of the average of the squared errors and the average of the absolute errors between the two datasets are relatively small. Therefore, the predictive model developed in this study can be considered highly capable and stable.

Table 2

Decision tree model evaluation ($N = 1208$)

Category	Training (80 %: 966)	Validation (20 %: 242)
RMSE	4.20	4.80
MAE	3.29	3.80

Note: RMSE: Root Mean Squared Error; MAE: Mean Absolute Error.

The decision tree predicted the value of BFP in adolescents from the interaction of environmental factors including gender, pubertal status, and lifestyle-related factors. The decision tree model comprises seven terminal nodes. Notably, among these nodes, four lifestyle-related factors that contribute to an increase in BFP (excluding gender and pubertal status) were as follows: girls who did not consume snacks (predicted BFP was 22.85); girls who both did not consume snacks and had screen time exceeding 2 hours per day (predicted BFP was 21.815); boys who consumed fruit less than three times per week (predicted BFP was 20.749); boys who both consumed fruit less than three times per week and used sedentary mode of transport to schools (predicted BFP was 26.641) (Figure 2).

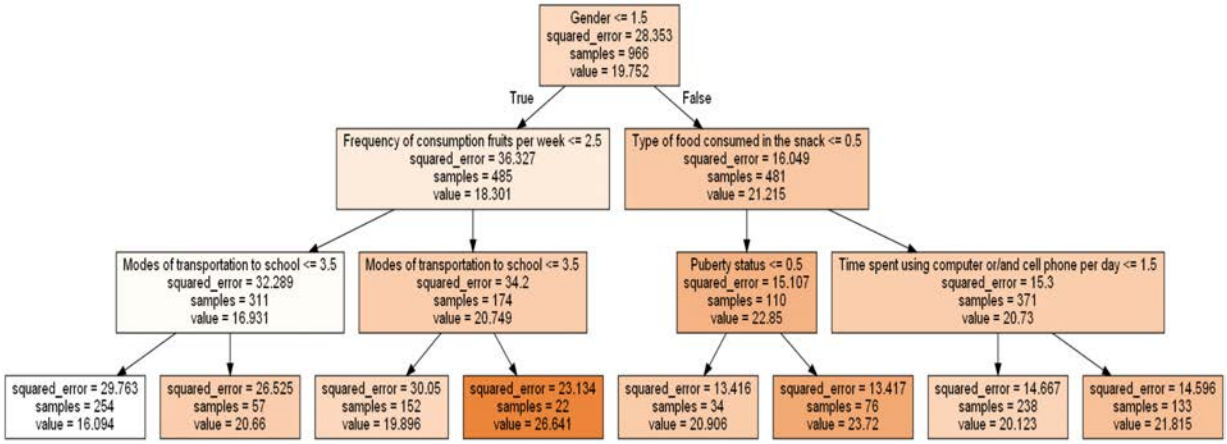

Figure 2. The decision tree model identifies risk groups with high BMI among adolescents aged between 11 and 15: Value is predicted BFP; Gender: 1 = male; 2 = female; Frequency of consumption fruits per week: 1 = > 5 times/week; 2 = 3–5 times/week; 3 = < 3 times/week; Types of food consumed in the snack: 0 = nothing; 1 = milk and dairy products; 2 = high-carb foods; 3 = fast food; Modes of transportation to school: 1 = walking; 2 = cycling; 3 = bus; 4 = motorbike; 5 = car; Puberty status: 0 = Tanner stage 1, 2, 3; 1 = Tanner stage 4, 5; Time spent using computer or / and cell phone per day: 1 = < 2 hours/day; 2 = ≥ 2 hours/day)

Evaluation of the model. Furthermore, to assess the effectiveness of the Decision Tree method more comprehensively, we conducted a comparison with another method, linear regression.

The results on the test data in Figure 1 also reveal that the Decision Tree method exhibits relatively low errors, with RMSE and MAE values of 4.80 and 3.80, respectively. In contrast, linear regression yields higher values of 5.12 for RMSE and 4.20 for MAE (Table 3). Consequently, it can be observed that the Decision Tree method provides more reliable results compared to linear regression.

Table 3

Performance indicators of the machine learning algorithms

Method	RMSE	MAE
Linear regression	5.12	4.20
Decision tree	4.80	3.80

Note: RMSE: Root Mean Squared Error; MAE: Mean Absolute Error.

In this research, a machine learning-centered methodology was employed to predict BFP based on the dietary patterns and physical activity of adolescents aged 11–15 years. The results revealed that within this age group, several lifestyle-related factors exerted the most substantial influence on BFP. These influential factors encompassed the frequency of fruit consumption, snacking behaviors, the mode of transportation to school, and the duration of computer and/or cell phone usage.

Within the context of this research, BIA was employed to measure BFP. BIA finds widespread application within epidemiological and clinical contexts for the assessment of body composition [16]. BIA stands out for its high level of safety, particularly when employed with adolescents and its suitability for widespread use. Despite the inherent margin of error, certain studies indicate that the error of the BIA method remains comparatively minimal [17, 18]. A study conducted on 200 healthy volunteers showed that the correlation coefficient between BIA (using HBF 359) and DXA measurement of BFP was 0.89 ($P < 0.001$) [19].

Our results showed that the Decision Tree method provides more reliable results compared to linear regression. Decision trees represent one of the most widely adopted machine learning algorithms that can effectively

address both regression and classification challenges. Decision Tree method stands as a potent instrument for forecasting overweight and obesity, drawing from a diverse array of factors including lifestyle, dietary habits, genetics etc. [20, 21]. Numerous research studies employ a range of machine learning algorithms to attain remarkable accuracy in predicting obesity [22]. Studies using machine learning in the assessment of BFP offer promising insights and have the potential to improve accuracy and efficiency in predicting body fat levels. On the other hand, using decision trees can predict BFP from the aggregate interaction of multiple risk or protective factors instead of just evaluating each factor individually. Accurate BFP assessment through machine learning has significant population health implications [22]. However, prediction of BFP from environmental factors in adolescents is still very limited.

In our study, frequency of fruit consumption and snacking turned out to be the best predictors. Numerous studies have investigated the correlation between diets and BMI, overweight, and obesity among adolescents in various countries. However, the findings from these research endeavors have not been consistently aligned. In a prior study encompassing 34 countries, it was reported that there was no significant association between overweight status and the consumption of fruits or vegetables [23]. Conversely, in a prospective cohort study conducted in the United States involving 14,900 children, it was revealed that intake of fruit and fruit juice did not serve as a predictor for changes in BMI [24]. According to the data from the International Study of Asthma and Allergies in Childhood, encompassing 201,871 adolescents, it was observed that adolescents who consumed fruits, vegetables, pulses, and nuts three or more times per week exhibited a lower BMI in comparison to those who rarely or occasionally consumed these foods [25].

The results of our study also showed that adolescent girls who did not eat snacks had higher BFP than those who did. Numerous research studies indicate that consumption of snacks may lead to an elevation in daily calorie intake instead of diminishing it. Nonetheless, snacking remains an integral component of a wholesome weight loss strategy. Optimal choices for weight loss include snacks that are abundant in complex carbohydrates, protein, and fiber, as they contribute to prolonged satiety [26]. An analysis conducted using data from the China Health and Nutrition Survey, covering the years 2006, 2009, and 2011, indicated that being in the highest snacking tertile was linked to the most substantial reduction in BMI z scores (-2.1) ($P < 0.05$) in overweight children aged between 7 and 13 years [27].

In this study, it was found that time spent using computer or/and cell phones was important in predicting BFP in adolescents. Some studies have demonstrated that the disproportionate utilization of electronic devices, particularly by adolescents, exerts a significant impact on the physical, psychological, and social well-being of this cohort [28]. An evaluation was conducted on a population-based sample of Finnish twins ($N = 4{,}098$); the results indicated that increased time spent using a home computer was linked to a heightened risk of overweight. Moreover, a positive linear trend was observed between cell phone usage and BMI, with a beta coefficient of 0.18 (95 % CI: 0.06–0.30) [29]. The outcomes of the dual-class meta-analysis encompassing 44 studies also revealed that adolescents categorized within the highest range of screen time demonstrated a 1.27-fold increased likelihood of developing overweight or obesity ($P < 0.001$) [30].

Over the past few decades in Vietnam, the nature of school commuting has shifted towards a more sedentary trend. The existing literature is still inconsistent regarding any associations between school commuting and body composition. The meta-analysis, which encompassed 13 research papers, exclusively concentrated on the connection between active

school commuting and the body mass index of children and adolescents. Among the final selection of 13 studies, three studies established definitive associations, three studies indicated partial associations confined to certain subgroups or constrained by societal/geographical factors, while seven studies exhibited no discernible correlations [31].

Strengths and limitations. Some factors associated with BFP in adolescents, as established in prior research, such as physical activity level, were not included in the decision tree model. It's essential to approach these results with caution because the absence of these variables in the model does not necessarily imply that they are unrelated to BFP. Several limitations should be considered in interpreting our findings. Firstly, the generalizability of the results to other ethnic regions may be challenging, as the database used for analysis was specific to adolescents in Hanoi. Secondly, while machine learning can reveal associations, it may not establish causality. Nevertheless, this study boasts several strengths. Firstly, it endeavors to unravel complex relationships among predictor variables using a decision tree analysis approach. Secondly, the application of machine learning techniques allows for more nuanced and data-driven exploration of factors linked to BFP, potentially uncovering non-linear relationships that conventional statistical methods might overlook.

Implications for practice. The findings of this study carry significant practical implications, primarily highlighting the importance of encouraging healthy eating and exercise habits among adolescents. Moreover, parents and schools can incorporate these findings into their childcare strategies. In order to maintain a healthy BFP in children, it is recommended that they consume a minimum of three servings of whole fruits per week and consider incorporating additional healthy snacks alongside their three main meals each day. Additionally, children should prioritize engaging in active modes of transportation while limiting their screen time.

Conclusion. In conclusion, it is noteworthy that this study has successfully identified six distinct groups of predictors related to BFP among adolescents using the decision tree model. Importantly, it took into account multiple variables simultaneously, enhancing the predictive accuracy of the model. Among these predictors, the most significant factors associated with BFP in adolescents include frequency of fruit consumption, snacking habits, mode of transportation to school, and the screen time. This study illuminates some intricate and diverse factors that impact BFP in Vietnamese adolescents. The combination of these factors and interactions with gender and pubertal status can determine BFP in Vietnamese adolescents. However, it's essential to acknowledge that there may still be unclear relationships among these predictors. Therefore, future studies should aim to delve deeper into these associations and further explore the underlying complexities within this multifaceted field of research.

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Research article

ROLE OF CELLULAR IMMUNITY IN MALIGNANT TUMORS DEVELOPMENT IN INDIVIDUALS CHRONICALLY EXPOSED TO IONISING RADIATION

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Some long-term effects of radiation could be related to changes in the immune system resulting from radiation exposure. Immunity disorders caused by radiation can influence carcinogenesis.

Cellular immunity factors were investigated in peripheral blood of workers chronically exposed to occupational combined radiation (external gamma-rays and internal alpha-particles), with malignant neoplasms diagnosed after blood samples were taken or without them, and in the control group.

The aim of this study was to examine effects of radiation on the cellular immunity status in individuals chronically exposed to ionizing radiation who had malignant neoplasms developed after blood sampling.

The relative and absolute number of lymphocyte subpopulations (total T-cells, T-helpers, T-cytotoxic, total B-cells, NK-cells, NKT-cells and activated T-cells) was detected by flow cytofluorometry.

The absolute number of T-cells was significantly reduced in workers chronically exposed to occupational combined irradiation, with or without malignancies, compared to the control, which may contribute to tumor progression at an early stage of its onset. At the same time, workers without malignancies had a significant increase in the relative number of T-cytotoxic lymphocytes, which may be a factor preventing tumor development. A significant increase in the relative number of natural killer cells (NK cells) was detected in individuals with malignant neoplasms chronically exposed to occupational combined irradiation, compared with the control, which may indicate enhanced antitumor defense that developed in response to exposure to tumor antigens. In addition, a significant decrease in the absolute and relative number of T- and B-lymphocytes was found in the group of workers with malignant neoplasm, compared with the control. A significant increase in the relative number of T-helpers was found in both groups of workers. Since the role of T-helpers in the antitumor response is ambiguous, additional research on types of T-helpers is planned to clarify the results of the present study.

Keywords: *occupational exposure, ionizing radiation, malignant neoplasms, innate immunity, adaptive immunity, antitumor immunity, T- and B-lymphocytes, T-helpers.*

People who have been exposed to ionizing radiation are known to have elevated risks of malignant neoplasms (MNs) [1–4]. Ionizing radiation can produce mutagenic effects and promote cancerous cell transformation by damaging their genetic apparatus and inducing epigenetic changes in organs and tissues [5]. A close relationship has been established between the state of the immune system and MNs progression [6–8]. The immune system is responsible for genetic stability of the body internal environment. It removes both alien and own mutated molecules and cells thereby providing body resistance to MN progression.

Ionizing radiation can modulate carcinogenesis by inducing changes in the immune system. At present, the opinions about the interaction between ionizing radiation and the immune system under exposure to it are largely controversial. High-dose radiation has been shown to induce immunosuppression. At the same time, various cellular components of

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the immune system give rather ambiguous quantitative and functional responses under exposure to low and medium doses [7].

Some radiation-induced late effects are considered to be caused by changes in the immune system induced by the radiation exposure [9]. Thus, liquidators examined in the preclinical MN period were compared with liquidators without MN or any pre-tumor states. In the former group, some changes were observed in the T-cell sub-population (lower CD3+ and CD4+-T-lymphocytes percentage, lower CD4+/CD8+ immune regulation index, elevated relative and absolute levels of cytotoxic CD8+-T-lymphocytes) and there was also an increase in relative and absolute levels of NK-cells and elevated levels of total IgE [10]. Also individuals with pre-cancer diseases tended to have activated absorbing and lysosomal functions of the phagocytic section in the immunity, a moderate decrease in levels of CD4+ (T-helpers), CD8+ (T-killers) and CD5+ lymphocytes[1].

Findings of the studies focusing on the role of the immune system in MN progression and on radiation-induced carcinogenesis are plentiful in research literature. Despite that, the state of the immune system in people with MNs who were earlier exposed to ionizing radiation, especially chronically, has not been studied enough yet.

The aim of this study was to examine effects of ionizing radiation on the cellular immunity status in chronically exposed individuals with MNs developed after blood sampling.

Materials and methods. Three groups were examined to estimate the cellular immunity status. The first group included nuclear workers chronically exposed to combined (external gamma-ray and internal alpha-particle) radiation without MNs in pre- and post-morbid medical histories (workers without MNs). The second group comprised nuclear workers chronically exposed to combined radiation and diagnosed with MNs one year after blood sampling or later (workers with MNs). The third (control) group comprised individuals never exposed to ionizing radiation in occupational activities and without a MN reported in either pre- or post-morbid medical histories. The following exclusion criteria were applicable for these three groups: radiotherapy; living in areas contaminated with radionuclides; diseases of the circulatory system (DCSs); acute or exacerbated chronic diseases at the moment of examination within this study,

Basic description of the analyzed groups is provided in Table 1.

Table 1

Description of the analyzed groups

Parameter		Workers without MNs; *M*; *SD* [*CI* 95 %] (*Median*; min–max)	Workers with MNs; *M*; *SD* [*CI* 95 %] (*Median*; min–max)	Control; *M*; *SD* [*CI* 95 %] (*Median*; min–max)
The number of people		72	22	72
Sex	Women (%)	37 (51.4)	4 (18.2)	38 (52,8)
	Men (%)	35 (48.6)	18 (81.8)	34 (47,2)
Age, years		72.1; 10.9 [69.6–74.7] (73.0; 49.0–89.0)	78.2; 3.2* [76.8–79.6] (79.0; 71.0–84.0)	70.7; 9.2 [68.6–72.9] (72.0; 51.0–87.0)
Total dose of external gamma-ray exposure absorbed in the BM, Gy		0.750; 0.699 [0.585–0.914] (0.630; 0.018–2.293)	1.573; 0.600 [1.307–1.839] (1.533; 0.491–3.065)	–
Total dose of internal alpha-particle exposure absorbed in the BM, Gy		0.072; 0.092 [0.050–0.094] (0.051; 0.000–0.521)	0.090; 0.074 [0.057–0.123] (0.075; 0.003–0.298)	–

N o t e: BM is for bone marrow.

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The lymphocyte subpopulation structure was identified with flow cytometry [11]. Blood samples were taken between 7 and 9 a.m. on empty stomach from the basilic or cephalic vein into 2-ml vacutainers for venous blood with lithium-heparin. After sampling, the samples were mixed gently by not less than 8 stirs.

Relative and absolute counts of lymphocyte subpopulations (total T-cells, T-helpers, T-cytotoxic lymphocytes, total B-cells, NK-cells, NKT-cells and activated T-cells) were established by using the panel of monoclonal antibodies with the two-color combination of fluorochromes (Beckman Coulter, USA) in accordance with the user instruction provided by the manufacturer. Obtained samples were analyzed on Fc 500 flow cytometer (Beckman Coulter, USA).

The resulting data were statistically analyzed in Statistica 10 software package (StatSoft. Inc., USA). Validity of the zero hypothesis was estimated by using the non-parametric Mann – Whitney test. Correlations were estimated by using the Spearman non-parametric rank correlation coefficient[2].

Results and discussion. Comparative analysis of cellular immunity indicators revealed that workers without malignancies chronically exposed to combined radiation had significantly lower absolute T-lymphocyte levels and significantly elevated relative levels of T-helpers and T-cytotoxic lymphocytes compared to the control (Table 2).

No significant differences were found in the cellular immunity indicators between nuclear workers with MNs diagnosed after blood sampling and without MNs; only a descending trend in relative levels of T- and B-lymphocytes was observed (Table 3).

Relative levels of natural killers and T-helpers were significantly higher in radiation-exposed workers with MNs than in the control group. In addition to that, we observed a significant decrease in absolute and relative levels of T- and B-lymphocytes in workers with malignancies compared to the control group (Table 4).

Therefore, our findings indicate that workers with MNs developed after blood sampling, who were chronically exposed to combined radiation, had a significantly lower absolute T-lymphocyte level compared to the control. This is consistent with the results obtained by other researchers [12–14]. T-cells are components of the adaptive immunity system and can adopt either a regulatory or effector phenotype producing both pro- and anti-inflammatory effects [15]. Tumor-specific T-cells (TSTs) are actively investigated for different tumor types [16]. At an early stage in tumor development, immunogenic antigens are produced in sufficient quantities and naïve T-cells are primed in drainage lymph nodes. Then they are activated and migrate into a developing tumor where they perform a protective effector immune response by eliminating immunogenic cancer cells. Hence, an observed decrease in T-lymphocyte levels in workers with malignancies developed after blood sampling might promote tumor progression at its early stage.

Workers chronically exposed to combined radiation, both with and without MNs, had elevated relative T-helper levels compared to the control, which is in line with literature data [17]. CD4+ T-helpers 1 (Th-1), which determine anti-tumor response by secreting large quantities of pro-inflammatory cytokines, such as IL-2, TNF-α and IFN-γ, promote not only priming and activation of cytotoxic T-lymphocytes but also anti-tumor activity of macrophages and natural killers (NK) and enhanced presentation of anti-tumor antigens in general [18]. However, T-helper activation as per Th2-type has a negative effect since Th2-cytokines (IL-4 in particular) can activate both myeloid cells and macrophages as per an alternative type, which does not promote tumor rejection [19]. Some studies report a direct cytotoxic effect of CD4+-T-lymphocytes on a tumor [20]. As can be seen from the foregoing data, T-helpers play a rather controversial role in anti-tumor responses; therefore, this study needs to be supplemented by investigating T-helper types to clarify its findings.

[2] Zar J.H. Biostatistical analysis. New Jersey, Prentice Hall Publ., 1999, 663 p.

Table 2

Lymphocyte subpopulations in the examined groups

Indicator	Workers without MNs; ($n = 72$) *M*; *SD* [*CI* 95 %] (*Median*; min–max)	Control; ($n = 72$) *M*; *SD* [*CI* 95 %] (*Median*; min–max)	*p*-value*
NK-cells, × 10^6/l (CD3-CD16+CD56+) Reference range: 123–369	293.7; 207.1 [245.0–342.4] (232.2; 35.0 –1054.0)	299; 237.3 [243.3–354.8] (227.2; 37–1448)	0.9300
NK-cells, % (CD3-CD16+CD56+) Reference range: 9–21	13.2; 8.1 [11.3–15.1] (10.0; 1.7–38.3)	14; 25.9 [7.9–20.1] (9.3; 2.1–224.7)	0.2806
T–NK-cells, × 10^6/l (CD3+CD16+CD56+) Reference range: 7–165	100.1; 132.4 [69.0–131.2] (64.5; 6.0–780.0)	77.3; 103.7 [52.9–101.6] (50.5; 7–838)	0.5745
T–NK-cells, % (CD3+CD16+CD56+) Reference range: 1–6	4.4; 5.5 [3.1–5.6] (2.8; 0.2–32.5)	2.7; 1.9 [2.3–3.1] (2.2; 0.5–8.8)	0.1542
B-lymphocytes, × 10^6/l (CD3-CD19+) Reference range: 111–376	191.1; 98.3 [168.0–214.2] (170.0; 29.0–472.5)	292.9; 536 [167–418.9] (211; 12–4610)	0.0751
B-lymphocytes, % (CD3-CD19+) Reference range: 7–17	8.5; 3.7 [7.6–9.4] (8.4; 1.0– 18.1)	9.8; 5.2 [8.6–11] (8.9; 0.6–36.3)	0.1555
T-lymphocytes, × 10^6/l (CD3+CD19-) Reference range: 946–2079	1658.8; 694.3 [1495.6–1822.0] (1504.0; 756.0–4250.0)	1988.4; 1045.4 [1742.7–2234.1] (1846; 836–9398)	0.0028*
T-lymphocytes, % (CD3+CD19-) Reference range: 61–85	74.7; 11.2 [72.1–77.4] (76.5; 42.9–95.2)	76; 8.6 [74–78.1] (75.8; 47.9–91.7)	0.5664
T–h (helpers), × 10^6/l (CD3+CD4+) Reference range: 576–1336	931.0; 358.8 [846.7–1015.3] (895.5; 407.0–2278.7)	903.2; 402.3 [808.7–997.7] (877; 260–3378)	0.6821
T–h (helpers), % (CD3+CD4+) Reference range: 35–55	42.4; 8.8 [40.3–44.5] (44.0; 24.8–60.2)	35.3; 8.7 [33.3–37.4] (34.2; 14.8–57.5)	0.0000*
T–c (cytotoxic), × 10^6/l (CD3+CD8+) Reference range: 372–974	626.4; 376.9 [537.8–714.9] (558.5; 188.0–2597.0)	638.8; 467 [529.1–748.6] (560.5; 167–3874)	0.8542
T–c (cytotoxic), % (CD3+CD8+) Reference range: 19–35	27.6; 9.5 [25.4–29.9] (27.0; 8.2–49.8)	23.3; 6.5 [21.7–24.8] (23.9; 8.7–41.7)	0.0046*

N o t e: * means estimated as per the Mann – Whitney test.

Table 3

Lymphocyte subpopulations in the examined groups

Indicator	Workers with MNs; (*n* = 22) *M*; *SD* [*CI* 95 %] (*Median*; min–max)	Workers without MNs; (*n* = 72) *M*; *SD* [*CI* 95 %] (*Median*; min–max)	*p*-value*
NK-cells, × 10^6/l (CD3-CD16+CD56+) Reference range: 123–369	359.6; 228.5 [258.3–460.9] (294.0; 57.0–1006.0)	293.7; 207.1 [245.0–342.4] (232.2; 35.0–1054.0)	0.1467
NK-cells, % (CD3-CD16+CD56+) Reference range: 9–21	16.4; 9.4 [12.3–20.6] (16.3; 3.7–34.9)	13.2; 8.1 [11.3–15.1] (10.0; 1.7–38.3)	0.1556
T–NK-cells, × 10^6/l (CD3+CD16+CD56+) Reference range: 7–165	105.2; 119.8 [52.1–158.4] (50.5; 4.0–411.0)	100.1; 132.4 [69.0–131.2] (64.5; 6.0–780.0)	0.8095
T–NK-cells, % (CD3+CD16+CD56+) Reference range: 1–6	4.7; 5.0 [2.5–7.0] (2.8; 0.2–14.8)	4.4; 5.5 [3.1–5.6] (2.8; 0.2–32.5)	0.8372
B-lymphocytes, × 10^6/l (CD3-CD19+) Reference range: 111–376	162.1; 100.8 [117.4–206.8] (139.5; 51.0–451.0)	191.1; 98.3 [168.0–214.2] (170.0; 29.0–472.5)	0.1312
B-lymphocytes, % (CD3-CD19+) Reference range: 7–17	7.6; 6.1 [4.9–10.3] (5.7; 2.0–31.5)	8.5; 3.7 [7.6–9.4] (8.4; 1.0–18.1)	0.0548
T-lymphocytes, × 10^6/l (CD3+CD19-) Reference range: 946–2079	1565.2; 618.2 [1291.1–1839.3] (1370.5; 788.0–3501.0)	1658.8; 694.3 [1495.6–1822.0] (1504.0; 756.0–4250.0)	0.6552
T-lymphocytes, % (CD3+CD19-) Reference range: 61–85	69.5; 11.8 [64.2–74.7] (69.8; 49.5–88.5)	74.7; 11.2 [72.1–77.4] (76.5; 42.9–95.2)	0.0699
T–h (helpers), × 10^6/l (CD3+CD4+) Reference range: 576–1336	888.1; 320.2 [746.1–1030.1] (847.5; 450.0–1814.0)	931.0; 358.8 [846.7–1015.3] (895.5; 407.0–2278.7)	0.6360
T–h (helpers), % (CD3+CD4+) Reference range: 35–55	40.1; 8.5 [36.3–43.8] (37.9; 26.4–54.3)	42.4; 8.8 [40.3–44.5] (44.0; 24.8–60.2)	0.3172
T–c (cytotoxic), × 10^6/l (CD3+CD8+) Reference range: 372–974	598.5; 286.1 [471.6–725.3] (573.5; 166.0–1114.0)	626.4; 376.9 [537.8–714.9] (558.5; 188.0–2597.0)	0.8583
T–c (cytotoxic), % (CD3+CD8+) Reference range: 19–35	26.8; 10.9 [22.0–31.7] (28.4; 8.1–45.1)	27.6; 9.5 [25.4–29.9] (27.0; 8.2–49.8)	0.9005

N o t e: * means estimated as per the Mann – Whitney test.

Table 4

Lymphocyte subpopulation in radiation-exposed workers with MNs diagnosed after blood sampling and in individuals non-exposed to radiation and free of MNs (control)

Indicator	Workers with MNs, (n = 22) *M*; *SD* [*CI* 95 %] (*Median*; min–max)	Control, (n = 72) *M*; *SD* [*CI* 95 %] (*Median*; min–max)	*p*-value*
NK-cells, × 10^6/l (CD3-CD16+CD56+) Reference range: 123–369	359.6; 228.5 [258.3–460.9] (294.0; 57.0–1006.0)	299; 237.3 [243.3–354.8] (227.2; 37–1448)	0.1129
NK-cells, % (CD3-CD16+CD56+) Reference range: 9–21	16.4; 9.4 [12.3–20.6] (16.3; 3.7–34.9)	14; 25.9 [7.9–20.1] (9.3; 2.1–224.7)	0.0241*
T–NK-cells, × 10^6/l (CD3+CD16+CD56+) Reference range: 7–165	105.2; 119.8 [52.1–158.4] (50.5; 4.0–411.0)	77.3; 103.7 [52.9–101.6] (50.5; 7–838)	0.8582
T–NK-cells, % (CD3+CD16+CD56+) Reference range: 1–6	4.7; 5.0 [2.5–7.0] (2.8; 0.2–14.8)	2.7; 1.9 [2.3–3.1] (2.2; 0.5–8.8)	0.6423
B-lymphocytes, × 10^6/l (CD3-CD19+) Reference range: 111–376	162.1; 100.8 [117.4–206.8] (139.5; 51.0–451.0)	292.9; 536 [167–418.9] (211; 12–4610)	0.0265*
B- lymphocytes, % (CD3-CD19+) Reference range: 7–17	7.6; 6.1 [4.9–10.3] (5.7; 2.0–31.5)	9.8; 5.2 [8.6–11] (8.9; 0.6–36.3)	0.0061*
T- lymphocytes, × 10^6/l (CD3+CD19-) Reference range: 946–2079	1565.2; 618.2 [1291.1–1839.3] (1370.5; 788.0–3501.0)	1988.4; 1045.4 [1742.7–2234.1] (1846; 836–9398)	0.0075*
T- lymphocytes, % (CD3+CD19-) Reference range: 61–85	69.5; 11.8 [64.2–74.7] (69.8; 49.5–88.5)	76; 8.6 [74–78.1] (75.8; 47.9–91.7)	0.0199*
T–h (helpers), × 10^6/l (CD3+CD4+) Reference range: 576–1336	888.1; 320.2 [746.1–1030.1] (847.5; 450.0–1814.0)	903.2; 402.3 [808.7–997.7] (877; 260–3378)	0.6045
T–h (helpers), % (CD3+CD4+) Reference range: 35–55	40.1; 8.5 [36.3–43.8] (37.9; 26.4–54.3)	35.3; 8.7 [33.3–37.4] (34.2; 14.8–57.5)	0.0290*
T–c (cytotoxic), × 10^6/l (CD3+CD8+) Reference range: 372–974	598.5; 286.1 [471.6–725.3] (573.5; 166.0–1114.0)	638.8; 467 [529.1–748.6] (560.5; 167–3874)	0.9644
T–c (cytotoxic), % (CD3+CD8+) Reference range: 19–35	26.8; 10.9 [22.0–31.7] (28.4; 8.1–45.1)	23.3; 6.5 [21.7–24.8] (23.9; 8.7–41.7)	0.1181

N o t e: * means estimated as per the Mann – Whitney test.

Workers chronically exposed to combined radiation and free of MNs in pre- and postmorbid medical histories had elevated relative T-cytotoxic lymphocyte levels compared to the control. This is also consistent with findings reported in other studies[3] [10, 21]. Cytotoxic CD8+ T-cells are basic anti-tumor ones. During priming and activation by antigen-representing cells, CD8+ T-cells are differentiated into cytotoxic T-lymphocytes. They perform an effective attack of a tumor, which usually ends in direct destruction of tumor cells by exocytosis of perforin- and granzyme-containing granules [22]. Occurrence of infiltrating CD8+ T-cells and Th-1 cytokines in a tumor correlates with a favorable prognosis for many tumors [23]. Elevated levels of cytotoxic T-lymphocytes in exposed workers without malignancies in their case history can, therefore, be considered a factor preventing tumor progression.

A role that belongs to B-lymphocytes in tumor progression is less clear than that of T-cells. Literature data indicate that B-lymphocytes promote carcinogenesis [24]. Different pathways were described to explain this tumor-promoting role of B-lymphocytes, from immunosuppression through secretion of IL-10 [25] and TGFβ [26] to direct stimulation of proliferation of tumor cells by IL-35 produced by B-cells in pancreatic neoplasia [27]. Also, B-cells stimulate angiogenesis and chronic inflammation by depositing immunoglobulins in a tumor [28]. A decrease in relative B-cell levels in workers chronically exposed to combined radiation with later developed MNs can be considered a favorable sign since these cells promote carcinogenesis.

Comparative analysis of cellular immunity indicators between workers chronically exposed to combined radiation with MNs and the control individuals revealed a higher relative level of natural killers, which might be a sign of intensified anti-tumor protection as a response to effects produced by tumor antigens.

Therefore, our findings indicate that radiation exposure modifies various components of the cellular immunity. Effects of the ionizing radiation on lymphocyte subpopulations are controversial since changes in their counts and rates have both stimulating and inhibiting impacts on MNs. However, given the fact that T-lymphocytes are considered the main anti-tumor effector by most researchers and that their level goes down due to the exposure to ionizing radiation, we can conclude that ionising radiation has a negative impact on the cellular immunity of nuclear workers due to chronic occupational exposure to ionizing radiation.

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Review

UNCERTAINTIES IN RISK ANALYSIS AND MODERN APPROACHES TO THEIR REDUCTION

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The article analyzes the most common approaches to the risk assessment procedure and focuses on uncertainties at each stage of risk analysis. These uncertainties not only impede risk analysis but are also able to skew its results. The greatest impact on reliability of final risk assessments is caused by uncertainties associated with assessment of exposure, in particular, with establishing toxicological parameters in experiments and their extrapolation onto assessed population groups. An effect of a selected toxicant on a test animal sample is identified with an expected negative effect produced by it on a real human population. In addition, in laboratory experiments, in contrast to natural conditions, a population is affected only by controlled factors in small amounts.

Next, the article describes some uncertainties that arise at the stage of assessing the dose-effect relationship; in studies aimed at reducing uncertainties at this stage, it is almost impossible to detect a link between pollution and diseases not declared for research purposes. The problem of toxicological assessment of mixtures is described; the article highlights that at the moment there are no data on effects produced by most known mixtures on human health or any data on possible interactions between different chemicals either. The concept of exposome is described, which is an analysis of impacts of all environmental factors on an individual throughout his lifetime.

It is concluded that the existing concepts of risk assessment are applicable mainly for comparing hypothetical benefits and hypothetical damage at the population level. Given that, it seems quite relevant to develop such a concept of risk assessment that can be additionally used in planning preventive measures aimed at reducing morbidity and mortality and increasing life expectancy. At the same time, this concept should include a comprehensive assessment of mixtures affecting the body, considering the influence of natural and climatic conditions and non-specific reactions of the body.

Keywords: *risk analysis, risk assessment, uncertainty, exposure, "dose – effect", influence of natural conditions, mixtures of chemicals, the exposome concept.*

Research literature provides us with several basic definitions of "public health risk". Risk is described as a set of adverse outcomes for people's life and health due to various exposures or as likelihood of adverse effects on people's life or health considering their severity, or as likelihood of outcomes caused by a certain hazardous event[1] [1–3]. The WHO (World Health Organization) World Health Report 2002 defines a risk as "a probability of an adverse outcome, or a factor that raises this probability". In the Russian Federation,

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the legislation has the following definition of risk: "Risk is likelihood of harm to citizens' lives or health, property of physical or juridical persons, state or municipal property, the environment, lives or health of animals and plants considering severity of this harm" (the Federal Law 'On Technical Regulation' issued on December 27, 2002 No. 184-FZ[2]).

Conventionally, the health risk assessment methodology applied to assess risks caused by chemical exposures consists of four main stages[1] [1, 2]: 1) hazard identification (screening investigation of all possible exposure sources, identification of key pollutants), 2) exposure assessment (establishing what quantities of a chemical entered the body by various introduction ways due to contacts with various environmental factors), 3) detection of a 'dose-effect' relationship (a relationship between a dose and intensity of harm caused by exposure to a chemical), 4) risk characteristics (risk quantification, risk analysis and description of uncertainties, and data generalization). The risk assessment procedure has been repeatedly described in literature in a similar way [1, 2, 4].

The aim of this review was to analyze approaches to reducing uncertainties that occur in risk analysis as well as the existing concepts of health risk assessment.

Many authors have noted that uncertainties can occur at any stage in risk analysis. They not only impede risk analysis but are also able to skew research results [1, 5, 6]. Uncertainties associated with exposure assessment have the greatest influence on validity of ultimate risk assessment [1]. There are several major sources of uncertainties that can occur at this stage in risk analysis. For example, some ways through which pollutants affect the human body can be excluded from analysis; monitoring results might be incomplete; a selected mathematical model does not characterize an exposure comprehensively. One more source is mistakes made by researchers such as descriptive mistakes, mistakes in choosing an expected exposure scenario, mistakes at any stage in quantitative analysis including sampling and sample preparation. Reduction in some of these uncertainties can be achieved by using models of pollutants distribution and by estimating a structure of various social population groups.

Mathematical methods, in particular, regression models, cluster analysis, and fuzzy set theory, are actively employed in contemporary studies that concentrate on health risk assessment [5, 7–9]. For example, J.P. Fabisiak with colleagues [10] rely on land use regression (LUR) to describe distribution of black carbon and nitrogen dioxides, their major sources being diesel exhausts, point industrial sources, as well as residential wood burning. The authors estimate increased mortality and hospitalization from coronary heart disease as a specific health endpoint of interest. They examine a linear dose-effect relationship over the range of pollutant concentrations expressed in the study, although they assume there may be significant departure from linearity at extremes of exposures. Still, the authors mention some limitations in employing LUR. It is noteworthy that these limitations can be extrapolated onto use of any other model for health risk assessment. In particular, the exposure estimates reflect projections of long-term average exposure concentrations; hence they ignore short-term fluctuations in concentrations that may also play a role in initiating untoward cardiovascular events. Besides, the LUR model described by J.P. Fabisiak with colleagues [10] incorporates mobile source plume analysis but may underestimate the contribution from fixed point sources.

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[2] O tekhnicheskom regulirovanii: Federal'nyi zakon № 184-FZ ot 27.12.2002, prinyat Gosdumoi 15.12.2002 [On Technical Regulation: the Federal Law No 184-FZ issued on December 27, 2002, approved by the State Duma on December 15, 2002]. *KonsultantPlus*. Available at: https://www.consultant.ru/document/cons_doc_LAW_40241/ (April 02, 2023) (in Russian).

Also, when building any mathematical model for health risk analysis, we should consider previously diagnosed diseases in research participants as well as a stage of a disease they have at the moment a research is conducted. It is necessary for identifying any possible impacts exerted by these factors on an effect of environmental pollution.

Many researchers point out that high uncertainty at the exposure assessment stage might be caused by toxicological parameters being established predominantly in experiments [11–13]. In particular, a reference dose, which is considered safe, is calculated based on results of various animal experiments performed on rats, mice, or rabbits [14–18] and then recalculated for the human body using some coefficients [19–22]. However, the US Food and Drug Administration (US FDA) conducted some studies to compare results of experimental pre-clinical and clinical investigations. As a result, it was established that approximately 90 % of analyzed chemicals, which had been declared safe in pre-clinical investigations, turned out to be highly toxic in clinical ones. Toxic effects on the human body were identified for 20 % of these chemicals [11, 23, 24]. There are several basic reasons for this inefficiency in transferring experimental results onto actual conditions. First, an effect produced by an analyzed toxicant on an animal test sample is identified with an expected negative effect produced by it on a real human population. Second, a test population is affected by a controlled factor in laboratory conditions whereas several factors affect a population simultaneously in natural ones and not all of them can be controlled. In addition, it is noteworthy that toxicological studies make it possible to derive a dose-effect relationship primarily for determined effects (radiation sickness, chemical burns, poisoning, etc.). The most reliable data for stochastic effects (cancer, cardiovascular diseases, etc.) can be derived by epidemiological studies[3]. At the same time, transferring results of epidemiological studies on an analyzed exposed population can be a considerable source of uncertainties at the stage when a dose-effect relationship is assessed.

Epidemiological studies usually concentrate on finding a relationship between pollution and specific diseases, for example, cardiovascular diseases [25], cancer [26], or non-communicable diseases in general [27]. However, it is almost impossible to detect a link between pollution and diseases not declared for research purposes in such studies. For example, J.P. Fabisiak with colleagues [10] chose increased mortality and hospitalization from coronary heart disease as a specific health endpoint of interest. In their study, the authors did not analyze any relationships with other diseases, for example, respiratory ones.

In addition to that, uncertainties occur at the stage of assessing a dose-effect relationship from such sources as identification of critical organs / systems; lack of knowledge on mechanisms of interactions between different components in chemical mixtures or peculiar kinetics and dynamics under different ways by which a chemical enters the body and under its simultaneous introduction by various ways; difference in the risk assessment methodology in Russian and foreign studies [1].

Numerous studies focus on reducing uncertainties at the stage of assessing a dose-effect relationship. Their actual aim is to predict a number of new disease cases due to an analyzed exposure [5, 10, 28, 29]. In particular, we should mention The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) as one of the most extensive studies aimed at systematizing and assessing

[3] Demin V.F. Analiz riska v obespechenii bezopasnosti cheloveka v chrezvychainykh situatsiyakh [Risk analysis in providing safety for people in emergencies]: Dissertation … for the Doctor of Technical Sciences Degree. Moscow, 2016, 221 p. (in Russian).

health risks (including those caused by environmental pollution). The authors make the following conclusion: ambient air pollution causes respiratory infections and tuberculosis, neoplasms, maternal and neonatal disorders, diabetes and kidney diseases, chronic respiratory diseases, and cardiovascular diseases (which are prevalent) [30]. However, the GBD researchers face certain difficulties since some countries are often unable to provide them with sufficient necessary data for analysis [31]. It is due to this reason that the methodology developers tried to consider many factors to compare a burden of various diseases using mathematic modeling. These factors are prevalence of some diseases and their symptoms, age at death, etc. However, this modeling is still not optimal and this can be illustrated by such an example as assessment of the DALY (disability-adjusted life year) parameter in Russia where it has the same value for the whole country [30]. But we should remember that Russia is the largest country in the world located across three different climatic zones and with apparent differences both in living standards and healthcare availability.

Conventionally employed health risk assessment methodologies that deal with chemical exposures are predominantly based on assessing exposure to some specific chemicals (and their maximum permissible levels); however, at present, some existing rules in the European Union include requirements that cover chemical mixtures as well [32]. The main problem of toxicological assessment of mixtures is absence of any data on effects produced by most known mixtures on human health [33–39]. Another serious issue is possible interactions between chemicals (that is, synergetic or antagonistic effects) and influence produced by these effects on hazards posed by a chemical mixture. Separate chemicals in a mixture can interact with each other thereby influencing each other's absorption, metabolism, excretion, or toxic dynamics. This may change a scope or sometimes even essence of a toxic effect [40, 41]. Several authors developed the Adverse Outcome Pathway (AOP) model [42–45]. It is a conceptual construct that portrays existing knowledge concerning the linkage between a direct molecular initiating event and an adverse outcome at a biological level of organization relevant to risk assessment. This model provides substantiation for mapping relevant data on toxicity of specific chemicals thus making it possible to identify which chemicals can produce combined effects. In case no data are available, the model demonstrates the necessity to conduct further research. Therefore, AOP helps integrate data derived by different testing methods (in vitro, in silico and in vivo) at different levels of biological organization and thereby facilitates elimination of gaps in data on toxicity [43].

The well-known phrase "genetics loads the gun environment pulls the trigger" illustrates a complex relationship between human diseases and the environment. This famous analogy by Dr. Judith Stern, Distinguished Professor of Nutrition and Internal Medicine at the University of California, Davis, conveys the message that disease phenotypes are not only a result of interaction between different genes within the host but also between genes and the environment [46]. An attempt to integrate environmental parameters when calculating an individual risk of diseases was made when the exposome concept was developed. According to the definition by C.P. Wild [47], the exposome encompasses life-course environmental exposures (including lifestyle factors), from the prenatal period onwards. The exposome concept is similar to the genome concept and was developed to quantify environmental exposures. The exposome model includes three broad categories of environmental exposures: internal, specific external and general external [48, 49]. The internal environment is considered an internal chemical environment of the body; that is, exposure partici-

pants are biologically active substances in the body formed due to usual vital activities, physical activity, gut microflora activity, inflammation, and oxidative stress. Specific external exposures are caused by, in particular, infectious agents, smoking, and alcohol abuse. Finally, general external exposures in the exposome include a socioeconomic status, mental exposures, and climate [50]. However, despite some promising postulates, the exposome model has not yet brought about any specific methods for health risk assessment. Nevertheless, many researchers share the opinion that adverse effects are often produced by a whole variety of heterogeneous factors and by each separate factor [5]. Typically, many people are simultaneously under exposure and they tend to have different responses to effects of negative factors [51–55].

To sum up all the aforementioned, we can conclude that all the existing studies strive not to create a new scheme for risk assessment but rather to reduce uncertainties. A considerable part of uncertainties occurring within health risk assessment is not given enough attention in the available studies and even within research trends in general. It is noteworthy that the existing methodologies for assessing health risks caused by chemical exposures are predominantly based on assessing exposure to specific chemicals. Any data on an exposure to the entire mixture are available for a limited number of them; any information on a dose-effect relationship and a mechanism of action typical for a specific component is often absent for many chemical classes. Conventional methods of health risk assessment practically never consider additional influence exerted by weather and climate (for example, cold temperatures). These methods are also unable to estimate nonspecific body reactions induced by pollutants (in particular, oxidative stress). All the abovementioned methods do not allow establishing clear relationships between pollution and morbidity / mortality. Approaches that are suggested for assessing effectiveness of population health risk mitigation make it possible to estimate whether planned or implemented protection activities are sufficient or relevant. But these approaches do not involve developing methods of adaptation to living in a polluted environment for population.

In our opinion, as well as in some other authors' opinion [11], at present, the risk assessment methodology in Russia should be updated to guarantee relevant health risk assessment; it is also necessary to perform a comprehensive analysis of foreign experience in the sphere including establishment of DNEL (Derived No-Effect Level and DMEL (Derived Minimal Effect Levels) in the REACH (Registration Evaluation Authorization and Restriction of Chemicals) international system [56], to revise maximum permissible levels (MPLs), and to revise identification of target organs and systems. It is worth noting that in Russia, just as in any other large country, it is necessary to consider substantial differences in effects produced by natural factors on population living in different climatic conditions. Different annual mean temperatures, wind rose, precipitations and other meteorological conditions have substantial influence on morbidity and mortality [57–60].

Most epidemiological criteria that have been developed so far and are actively used in health risk assessment reflect an expected growth in frequency of health disorders per a unit of influencing concentration. Although these criteria are, as a rule, based on results derived by several independent epidemiological investigations, it is still wrong to use them to predict changes in mortality or morbidity rates of a specific population living in a specific area. Just as any other risk assessments, they are only relative values, which describe comparative priority of these or those pollutants, their sources in the environment, etc. To sum up all the aforementioned, we can conclude that the existing risk assessment concepts are applicable mostly for comparing

hypothetic benefits and hypothetic damage at the population level. Given that, it seems quite relevant to develop such a concept of risk assessment that can be additionally used in planning preventive measures aimed at reducing morbidity and mortality and increasing life expectancy. At the same time, this concept should include a comprehensive assessment of chemical mixtures affecting the body, considering the influence of natural and climatic conditions and non-specific reactions of the body.

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