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CONTENTS

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QUESTIONING THE EARLY EVENTS LEADING TO THE COVID-19 PANDEMIC

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Sixteen months after the January 30, 2020 declaration by the World Health Organization of a Public Health Emergency of International Concern regarding the spread of COVID-19, SARS-CoV-2 had infected ~ 170 million humans worldwide of which > 3.5 million had died. We critically examine information on the virus origin, when and where the first human cases occurred, and point to differences between Chinese and later clinical presentations. The official patient Zero was hospitalized in Wuhan, Hubei province, China, on December 8, 2019, but retrospective analyses demonstrate prior viral circulation. Coronaviruses are present in mammals and birds, but whether a wild animal (e.g. bat, pangolin) was the source of the human pandemic remains disputed. We present two contamination models, the spillover versus the circulation model; the latter brings some interesting hypotheses about previous SARS-CoV-2 virus circulation in the human population. The age distribution of hospitalized COVID-19 patients at the start of the epidemic differed between China and the USA–EU; Chinese hospitalized patients were notably younger. The first Chinese publications did not describe anosmia-dysgeusia, a cardinal symptom of COVID-19 in Europe and USA. The prominent endothelial involvement linked with thrombotic complications was discovered later. These clinical discrepancies might suggest an evolution of the virus.

Key words: *SARS-CoV-2 diagnostics, patient zero, zoonotic disease, autopsies, clinical presentation, dysgeusia / anosmia.*

Sixteen months after the World Health Organization (WHO) declared a Public Health Emergency of International Concern (PHEIC) on January 30, 2020, the novel SARS-CoV-2 betacoronavirus had infected approximately 170 million people worldwide of which > 3.5 million had died. The scientific community's response has been prolific,

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with more than 147,000 articles referenced in PubMed as of May-end, 2021, but several scientific issues remain unresolved.

We critically examine available information on the origin of the virus, when and where the first human cases occurred, and point to differences between Chinese and later clinical presentations of COVID-19 that affected choice of treatment. Our objective is to present the current state of knowledge regarding three major questions: What triggered this pandemic? When did the patient/cluster zero occur? How to explain differences in age of onset and clinical presentation of COVID-19 patients in China and, subsequently, those in Europe and the USA? This first part of our research considers and is based on facts established by the World Health Organization (WHO) reports and extracted (in-extenso citations) from selected published papers, mostly Chinese, but without any pretension of completeness.

The quest for patient zero and the pandemic's early Chinese phase. Biomedical scientists faced with emerging zoonoses and infectious diseases search for the first to fall ill on the assumption this will reveal or illuminate disease acquisition and perhaps even aetiology. The search for Patient Zero and for index cases is a priority for epidemiologists and infectologists. Obviously, the primary case, "*the person who first brings a disease into a group of people*" must be distinguished from the index case which *"is the patient in an outbreak who is first noticed by the health authorities, and who makes them aware that an outbreak might be emerging*". Giesecke [1] cautions that "*For many outbreaks, the primary case will never be known*" adding "*for all outbreaks that are discovered, there will always be one (or more) index cases*". Patient Zero, or more precisely the first, primary case, is almost impossible to find as other cases probably existed concurrently at the beginning of the disease and either sought no medical assistance (asymptomatic or only with mild symptoms) or were diagnosed incorrectly. The official story of the COVID-19 pandemic based on declarations of Chinese national health authorities transmitted to the WHO [2, 3]. Key dates and content of those transmissions are:

♦ December 31, 2019: Declaration of a pneumonia cluster by the Wuhan Municipal Health Commission, Hubei, China;

♦ January 7, 2020: Chinese authorities issue the identification of the causative agent, a novel coronavirus;

♦ January 10, 2020: WHO issues comprehensive technical guidance on how to detect, test and manage cases;

♦ January 12, 2020: Chinese publication of the RNA sequence of the coronavirus genome;

♦ January 30, 2020: WHO publishes evidence of 7,818 confirmed cases of COVID-19 worldwide, of which 82 were present in 18 countries other than China;

♦ February 24, 2020: Report of the WHO–China Joint Mission on Coronavirus Disease 2019;

♦ March 11, 2020: WHO declares COVID-19 to be a pandemic.

Chinese preparedness. As a consequence of the 2002–2003 Severe Acute Respiratory Syndrome (SARS) outbreak in Guangdong Province (south of Hubei Province), Chinese authorities had built a medical detection system for new viruses associated with respiratory infections. This surveillance system of influenza-like illness (ILI) and severe acute respiratory infection (SARI) is detailed in the 2021 WHO report [4]. This system gave excellent results for the 2013–2017 Asian-lineage avian H7N9 Influenza epidemics and led to an article co-authored with a U.S. Centers for Disease Control & Prevention (CDC) CDC scientist [5]. The close cooperation between the Chinese CDC and American CDC must be underlined; it started in the nineteen eighties and "*played a crucial role in China's responses to emerging infectious diseases, such as SARS-CoV, avian influenza, and COVID-19"* [6].

The backdrop for the outbreak of COVID-19 in Wuhan, Hubei Province, was

Chinese expertise and experience with zoonotic coronaviruses, not only in regard to human Severe Acute Respiratory Syndrome (SARS) in 2002–2004 but also to Swine Acute Diarrheal Syndrome (SADS), a fatal disease of piglets in 2017, both of which originated in Guangdong Province. Given the apparent rise of bat coronaviruses (CoVs) in China, with potential to induce severe diseases in humans and animals, the Chinese Academy of Sciences Key Laboratory of Special Pathogens and Biosafety of the Wuhan Institute of Virology (WIV) warned of the threat in a paper submitted on January 29, 2019 to the journal *Viruses*, which published the article on March 2, 2019; this was approximately one year before the WHO declared the SARS-CoV-2-related COVID-19 pandemic. In their 2019 paper, Yi Fan and colleagues stated: "*It is generally believed that bat-borne CoVs will re-emerge to cause the next disease outbreak. In this regard, China is a likely hotspot. The challenge is to predict when and where, so that we can try our best to prevent such outbreaks". "These studies, revealed that various SARS-CoVs capable of using human ACE2 [angiotensin converting enzyme-2] are still circulating among bats in China, highlighting the possibility of another SARS-like disease outbreak"* [7]. No doubt, the Chinese medico-scientific community was aware of the hazards and well prepared.

The outbreak management. What happened in China when the SARS-CoV-2-related disease outbreak occurred and when patients came to Wuhan's hospitals diagnosed as "*pneumonia of unknown cause*" or "*atypical pneumonia*"? Standardized medical diagnosis procedures were used in accord with proper medical practice anywhere in the world. "*Since the cause was unknown at the onset of these emerging infections, the diagnosis of pneumonia of unknown cause in Wuhan was based on clinical characteristics, chest imaging, and the ruling out of common bacterial and viral pathogens that cause pneumonia*" [8]. At first, the atypical pneumonia might have been attributed to the usual winter seasonal flu, both by medical teams and by patients. In this regard, it is noteworthy to highlight the statement of Mrs. Wei Guixian, considered to be one of the first index cases: "*Every winter, I always suffer from the flu. So, I thought it was the flu."*[1]. This impression is underlined by a team from the Wuhan Center for Disease Prevention and Control that stated: *"The time period in concern coincided with the winter peak of influenza and other respiratory illnesses. The number of ILI (influenza-like illness) cases in all age groups increased dramatically starting in early December 2019 and reached the peak by the New Year"* [9]. Assessment of the etiologic diagnosis proved to be challenging: "*Notably, in the early stage, nucleic acid detection kits for SARS-CoV and other coronaviruses were used for COVID-19 diagnosis, with varying specificity and sensitivity. Meanwhile, when detection kits were not available, imaging examinations, especially chest computed tomography (CT), played an important role in the diagnosis of COVID-19, although these examinations are not specific to COVID-19*" [10].

Chinese publications, notably the *China CDC Weekly*, documented subsequent events [11–14]. Usual techniques were used to culture and isolate the virus. Thereafter, extraction and sequencing of the virus's RNA allowed the realization of PCR testing tools and serological detection of SARS-CoV-2 antibodies. RT-PCR methods were then assessed for their sensitivity and specificity. Reports unfolded as shown chronologically below:

♦ December 21, 2019: Cluster of pneumonia cases in Wuhan Jinyintan Hospital (public hospital in Wuhan's Dongxihu District). RNA extraction, sequencing and culture to assess the virus in three cases [11, 13];

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[1] Woods A. Shrimp vendor at Wuhan market may be coronavirus «patient zero». *New York Post*. Available at: https://nypost.com/2020/03/27/shrimp-vendor-at-wuhan-market-may-be-coronavirus-patient-zero/ (June 15, 2021).

♦ December 29, 2019: Report to the Wuhan health authorities of a cluster of cases of viral pneumonia of unknown aetiology (VPUE) (i.e., four individuals working in the Jianghan District Huanan Seafood Wholesale Market (HSWM) hospitalized with pneumonia);

♦ December 30, 2019: Wuhan CDC investigations revealed additional patients linked to the seafood market; health authorities from Hubei Province reported this cluster to China CDC Beijing;

♦ December 31, 2019: China CDC experts sent to Wuhan to support the investigation and to provide samples from patients for laboratory analyses;

♦ January 3, 2020: China National Institute for Viral Disease Control and Prevention (IVDC) sequenced a novel β-genus coronavirus (2019-nCoV, later named SARS-CoV-2) with three distinct strains identified in a patient's sample of bronchoalveolar lavage fluid [11];

♦ January 6, 2020: China National Pathogen Resource Center reported electron microscope findings that the new virus showed the typical morphology of a coronavirus [14];

♦ January 9, 2020: "*Chinese CDC announce that a novel coronavirus (2019-nCoV) had been detected as the causative agent of 15 of the 59 pneumonia cases*" [15];

♦ January 11, 2020: "*A team led by Prof. Yong-Zhen Zhang of Fudan University in Shanghai posts the genetic sequence of the virus on an open-access platform, sharing it with the world. China CDC and two other Chinese teams subsequently also post genetic sequences of the virus on an open-access platform. China shares the virus' genomic sequence with WHO*" [16];

♦ January 11, 2020: PCR tests for 2019-nCoV provided to Wuhan hospitals [11];

♦ January 21, 2020: A German led team publishes an in-silico real-time PCR test for the new coronavirus, research that was "*enabled by the willingness of scientists from China to share genome information before formal publication, as well as the availability of broad sequence knowledge from ca 15 years of investigation of SARS-related viruses in animal reservoirs*" [17]. This test served to diagnose the early cases across Europe.

Early in January 2020, three research teams, each working independently (Shanghai, Wuhan, Beijing), successfully sequenced the new virus and published their results. Metagenomic RNA sequencing of a sample of bronchoalveolar lavage fluid (BALF), obtained from a Wuhan Central Hospital patient hospitalized on 26 December 2019, allowed identification of the complete viral genome of a new RNA virus strain of 29,903 nucleotides, which was designated as "WH-Human 1" [18]. Analysing samples from seven patients with severe pneumonia who had been admitted to Wuhan Jinyintan Hospital, the WIV laboratory found five samples to be PCR-positive for CoVs. Metagenomics analysis using next-generation sequencing identified a 29,891 base-pair CoV genome using one patient's BALF [19]. The third team identified ten genome sequences of 2019-nCoV obtained from nine patients that showed 99.98 % sequence identity, with base pairs ranging from 29,829 to 29,844 [20]. This breakthrough allowed the construction of RT-PCR tests in China [14] and assessment of their sensitivity and specificity.

Early cohort reviews. In mid-January 2020, the Chinese teams began to publish on the new coronavirus infection in international journals, several weeks before WHO would declare the disease pandemic. The major Chinese publications [8, 21–23], plus the 2021 WHO–China report [24], described the timing of the start of the Wuhan pandemic, yet with certain discrepancies. At the start of the outbreak, all reports distinguished Huanan Seafood Wholesale Market (HSWM) workers or visitors from those with no HSWM contact. All agreed that Patient Zero had been hospitalized in early December 2019 in Wuhan. However, depending on the individual articles, it seems that several index cases were identified, since the hospitalization dates were recorded as December 1, December 8 and December 12. The *South China Morning Post* even reported

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(from their examination of government data) that "*a 55-year-old from Hubei province could have been the first person to have contracted COVID-19 on November 17*" [10, 25]. An interesting article that tries to detangle the aetiology of influenza-like illness cases in Wuhan by retrospective analysis of 640 throat swabs collected between October 6, 2019 and January 21, 2020 found only 9 swabs in the period January 4 and 20, 2020 to be positive for SARS-CoV-2 RNA by quantitative PCR. The authors suggested that "*COVID-19 was gradually expanding among the ILI cases during January*" [9].

Evidence of human-to-human transmission among close contacts was established in mid-December 2019 [21]. This interhuman contamination was also assessed in a family cluster in Shenzhen, Guangdong, after two members had visited a relative in a Wuhan hospital: "*We report here a familial cluster of unexplained pneumonia due to 2019-nCoV. These findings suggested that person-to-person transmission and intercity spread of 2019-nCoV by air travel are possible, supporting reports of infected Chinese travellers from Wuhan being detected in other geographical regions*" [26].

Limitations have been evoked by the Chinese scientists and mathematical models have provided better estimations of the epidemic. Thus, a Beijing study estimated a total of 3,933 cases of novel coronavirus-infected pneumonia in Wuhan (95 % confidence interval (CI): 3,454–4,450) with onset of symptoms by January 19, 2020 [27]. Li and colleagues pointed to the limitations of their cohort of 425 cases: "*Confirmed cases could more easily be identified after the PCR diagnostic reagents were made available to Wuhan on January 11, which helped us shorten the time for case confirmation*", "*Early infections with atypical presentations may have been missed, and it is likely that infections of mild clinical severity have been under-ascertained among the confirmed cases*" *[21].*

Index cases outside China. Examination of peer-reviewed papers published between December 1, 2019 and July 9, 2020 and listed in *PubMed*, the *China National Knowledge Infrastructure*, *Web of Science*, and the WHO database of publications on COVID-1, revealed the identification of index cases in 16 different countries / regions from Asia, Europe, North America and South America. Twelve first cases occurred in January 2020, all from China or in contact with Chinese patients, while four additional cases in February and March reported travel histories in Italy (Bolivian, Brazilian), Iran (Afghan) and UK (American) [28]. Additional information, shown below, has since become available regarding the citizenship and travel origin of the index cases from China:

♦ January 3, 2020: Index case in Nepal [28];

♦ January 13, 2020: Index case in Thailand [29];

♦ January 16, 2020: Index case in Japan [29];

♦ January 16, 2020: Index cases in France, two Chinese tourists and a traveller returning from Wuhan [28, 30];

♦ January 19, 2020: Index cases in Washington State, USA [31] and in South Korea [28, 29];

♦ January 23, 2020: Index cases in Italy: two Chinese tourists [32], Toronto (Canada) and Vietnam [28];

♦ January 24, 2020: Index case in Germany (infected by a Chinese woman on professional travel) [28, 33];

♦ January 26, 2020: Index cases in UK and Finland [28];

♦ January 31, 2020: Index cases in Russia. Chinese tourists in Siberia, who needed medical assistance [34].

Based on this information, it would appear that, by the end of January 2020, WHO would have been justified in declaring a pandemic, which is defined as "*a worldwide spread of a new disease*" [35]. Perhaps WHO waited for the certainty of "*an epidemic over a very wide area, crossing international boundaries and usually affecting a large number of people*" [36], an unequivocal fact by March 11, when the pandemic was declared?

Quickly, the quest for the primary patient native to their respective country interested teams in France, UK, Italy and the USA. This search was also one of the 2021 Joint WHO – China study [4], which concluded that "*studies from different countries suggest SARS-CoV-2 circulation preceded initial detection of cases by several weeks*." This statement was based on the discovery of neutralizing antibodies in a few participants in an Italian cancer screening program (October, 2019), PCR analysis of a throat swab from a child with suspected measles (early December, 2019), and PCR-based sewage sample analysis in northern Italy (mid-December, 2019). Additional data from France included the isolation of neutralizing antibodies in blood samples from mid-December and PCR-based detection of oropharyngeal SARS-CoV-2 in a patient hospitalized at the end of December. In Brazil, RT-PCR testing of sewage detected SARS-CoV-2 (November 27, 2019), and serological testing of 7,389 donated blood samples collected in the USA between December 13, 2019 and January 17, 2020 yielded 106 positive samples.

Unsolved mysteries about the origin of SARS-CoV-2. The origin of SARS-CoV-2 and routes of human infection are subjects of intense debate shadowed by political concerns. Lack of data on index cases, assessment difficulties, other uncertainties and the complexity of interactions, which are taken into account by the scientific community, are the characteristics of such an inquiry. Metagenomics and specific molecular genetic tools such as phylodynamic and phylogeographic analysis, and Bayesian phylogeographic reconstruction, are tools that have been used to clarify these concerns. Since these complex analyses are incomplete and beyond the scope of this article, the following assumes SARS-CoV-2 had a primary zoonotic origin and the outbreak is Wuhan can be explained by one of two lines of hypotheses.

The 2021 WHO – China report. On March 29, 2021, the WHO experts proposed four hypotheses that could account for the emergence of the SARS-CoV-2 in the section of their report entitled "*Zoonotic Origins of SARS-CoV-2"* [4]. These four hypotheses were discussed and rated according to their probability: a direct transmission from bats to humans, transmission via an intermediate host, the consumption of frozen meat infected by the virus, and a laboratory accident. Doubt was expressed that the Wuhan Huanan market represented a major source of contamination, where 38 wild and wild-caught and farmed non-domesticated terrestrial species were sold between May 2017 and November 2019 [37]. The 2021 WHO Report triggered many comments, notably in prestigious journals, e.g. *Science* [38] and *The Lancet* [39]. On April 1, 2021, *Nature* stated: "*A World Health Organization report makes a reasonable start, scientists say, but there are many questions yet to be answered. The report concludes that the chances of COVID-19 having originated in a lab accident are slim. But there is growing pressure, including some from researchers, for a more comprehensive inquiry into this possible route. The question of the pandemic's origins has been politically fraught from the start*" [40]. By June 2021, it was clear that the origin of COVID-19 was under renewed examination beyond WHO.

A novel approach, the "viral circulation model". The current paradigm for the emergence of zoonotic diseases is the "spillover" model. According to this model, a zoonotic virus capable of infecting humans is already present in a reservoir species and transmitted to humans by an intermediate species. However, this was never observed. The spillover model is an intellectual construction that failed to confront reality when it was created. While seemingly sound when first advanced, SARS, MERS and COVID-19 has shown that none of the predictions of the spillover model has been realized. No reservoir, no intermediate species and no human-adapted viruses were found in the wild.

Given the apparent failure of the spillover concept, a new evidence-based model – the "circulation model" – was developed to explain the emergence and transmission of

SARS-CoV-2 infectious diseases [41–43]. Based on field observations, the "circulation model" hypothesizes that viruses circulate among various hosts simply upon contact and compatibility. These viruses evolve differently in each host. The human pandemic viruses exist only in humans, which explains why they are not found in the wild. Only related viruses of the same group can be found.

The virus circulation model describes a process of emergence of naturally occurring viruses in the human population but does not pinpoint the exact origin of SARS-CoV-2. Two different steps must be considered: 1) the original infection of humans with a virus circulating in the wild, and 2) the undetected inter-human transmission of the virus prior to any recognition of the disease. The former is very likely to occur in anthropogenic rural areas. The emergence is directly linked to human behaviour, mobility and societal factors, when the epidemic threshold is overridden. As stated by Frutos and colleagues, "*The danger, i.e., the presence of CoVs potentially capable of emerging as an epidemic or a pandemic is recognized. It requires human activity to amplify the frequency of virus encounters and thus create amplification loops to reach the threshold necessary to trigger an epidemic. This is where the risk lies, in the anthropogenic amplification loop*s" [42]. This model is consistent with early virus circulation in Wuhan: "*However, the virus had probably already been circulating since early October 2019*" [42]. Plato and colleagues [44, 45] support this model and name the early phase "*the pre-Wuhan period*", which they suggest started in the first half of 2019.

Data from COVID-19 clinical presentations and autopsies: comparison between China and Western countries. Comparison of the first Chinese clinical descriptions issued from study of a small series of hospitalized patients with those originating from Western countries reveals discrepancies that merit examination. Below we consider the difference in the age distribution of the first hospitalized patients, the quasi absence of smell and taste alterations in Chinese patients, and the practice of autopsies.

The age distribution of the early cases. Review of 278 hospitalized patients with COVID-19 pneumonia in Wuhan gave insight into the early demographic data of Chinese persons with the disease [46]. Chinese publications of early cases [8, 21–23] reported a predominance of males and a median age at diagnosis under 60 years. *"As of 10 February 2020, only three relatively large-scale case studies have thoroughly demonstrated the clinical features of patients with pneumonia caused by SARS-CoV-2 pneumonia in Wuhan"* [47]. However, significant differences are noticed in reports originating from medical authors in Wuhan. In the Wuhan Jinyintan Hospital, the average age was 55.5 years, and the patients' percentage over 60 years was 37 % [22], while the China CDC data show, respectively, an average age of 49 years, with 13.8 % over 65 [23]. These data differ from those from Western countries (USA, Europe), where older patients were most heavily affected. The U.S. CDC consistently reported throughout the pandemic that hospitalization risk was linked with older age [48]. In Italy, the average age ranged between 60 and 67 years [47] and, in New York City, USA, an average patient age of 63 is found in one cohort of 5,700 hospitalized patients [47]. However, the age group distribution varies markedly among different published series. In Australia, the median age was 58 years [49] while two case series from Iraq showed a very large variability ranging from 12 % to 40 % for COVID-19 patients over 60 [50, 51]. Interpretation of the typical age distribution of the first cases of COVID-19 is challenging because in must consider many variables, including general demographic data, national population age distribution, patient recruitment from urban/rural areas and patient behaviours.

Anosmia and dysgeusia. Posted on February 25, 2020 at medRxiv, Mao and colleagues [52] were the first to describe hyposmia and hypogeusia in the 214-person cohort of Wuhan hospitalized patients. They noted a small percentage of patients with disorders of smell and taste but noted the difficulty of capturing such subjective symptoms in their cohort. *"In patients with PNS symptoms, the most common reported symptoms were taste impairment (12 (5.6 %)) and smell impairment (11 (5.1 %)"* [52]. Smell and taste alterations are now considered as pathognomonic symptoms of COVID-19, occurring early and sometimes as the only symptom in mild and moderate clinical forms of the disease in 65–70 % of patients [53]. In March 2020, several warning calls regarding this phenomenon were issued from different countries, including Korea, Italy, Germany and Iran [54, 55]. This Iranian study [55] used an unusual methodology with self-reporting of anosmia and an online auto-questionnaire available on the social networks that attracted 15,228 persons but all with an unknown COVID-19 status. This study found that 76.2 % (10,069) of presumably COVID-19 patients had reported the sudden onset of anosmia or hyposmia. These alerts prompted Ears, Nose and Throat specialty organizations in France, UK and the USA to inform their members in March 2020 [56–58]. Publications followed on-line from a Belgian-French team on April 2 [59] and from an Italian team [60] on April 15. The latter had observed chemosensory dysfunction in 19.4 % of their 320 cases. This symptom elicited great interest and led to publications in April–May from Korea [61], Italy [62], France [63], and Iran [64]. A European collaborative group started follow-up of a European cohort that increased in size over time [65]. *"A total of 1,754 patients (87 %) reported loss of smell, whereas 1,136 (56 %) reported taste dysfunction"* [66]. Interest in the chemosensory dysfunction of COVID-19 grew rapidly [67], with assessment and therapeutic proposals [68], follow-up and evolution [69–71].

The clinical evolution of hyposmia/ anosmia and dysgeusia is an important issue for patients because, for example, reduction or loss of smell perception raises the possibility of early central nervous system SARS-CoV-2 involvement, notably of the olfactory bulb [63, 64, 69, 70]. Complete clinical screening of COVID-19, as with any disease, not only appropriately engages the patient but also provides information critical for accurate diagnosis. Indeed, the strikingly common chemosensory symptoms have helped to differentiate clinically a nose-ears and throat COVID-19 presentation from symptoms associated with influenza. Meng and colleagues [71] have addressed why the apparent prevalence of chemosensory dysfunction was lower in China than elsewhere. Among their hypotheses is their proposal of a differential susceptibility among populations to SARS-CoV-2 mutants, citing Forster and colleagues who found different clades of the virus in Europe compared to China [72]. That SARS-Cov-2 mutated during its spreading phase from China to abroad is legitimate, as the further evolution of the pandemic showed the emergence of multiple variants in several countries across the world.

Autopsies and SARS-CoV-2 targets. To our knowledge and as noted in a review [73], only a few autopsy reports and no series were published by Chinese teams in the early months of the pandemic. Among the first autopsies cited in the WHO–China report [24], is one dedicated to the lung. Another, cited by Mao and colleagues [52], also examined the brain; the report issued in Chinese by the *"National Health Commission of the People's Republic of China. Diagnosis and treatment of the novel coronavirus pneumonia (Trial version 7)"*, *"Autopsy results of patients with COVID-19 showed that the brain tissue was hyperaemic and oedematous and some neurons degenerated"* [52]. Later (in April 2020), a histopathological analysis of 26 autopsies showed endothelium involvement in the kidneys [74]. Autopsies are considered risky since COVID-19 and specific protective equipment was mandatory [75].

Several autopsies were undertaken in the USA [76, 77] and in European laboratories [78–80]. The results of these post-mortem studies explained the multiple tissue targets of

COVID-19 and, as a result, dramatically changed the therapeutic approach in severe cases of COVID-19. A key finding was the suggestion of vascular dysfunction, severe capillary congestion, widespread Endothelitis and microthrombi [78, 79], notably: *"we demonstrate endothelial cell involvement across vascular beds of different organs in a series of patients with COVID-19"* [78]. This explained why COVID-19 could induce, along with an intravascular disseminated coagulopathy, thrombosis of arterial vessels in the brain (ischemic stroke) as well as in the lung (embolism).

Final comments. Despite the tremendous efforts of the medico-scientific community in documenting many aspects of COVID-19, uncertainties and grey zones persist about the origin and early stages of the pandemic. The disease clearly first exploded in Wuhan, but the timing and causes are still unclear. Was it in January 2020 in association with the Chinese New Year holiday period? Retrospective analyses have established early viral circulation beyond China, notably in Brazil, France, Italy and the USA. Answers to these critically important questions will likely assist in anticipating, detecting and monitoring future outbreaks of highly infective viruses, whether of coronavirus pedigree or otherwise.

The COVID-19 pandemic has demonstrated the difficulties of detecting an outbreak of a new disease, whether represented by a unique patient and/or by small clusters of index cases. If these difficulties are to be surmounted, it may be possible to restrict virus spread using public health methods that, in the case of COVID-19, were successfully utilized in countries such as Australia, New Zealand and Taiwan, where testing, tracing, isolation and communication were practiced effectively. However, no matter the effectiveness of public health responses, control of the medical phase caused by a rapidly spreading infectious agent is far too late to detect avert the threat of a looming pandemic from an environmental agent [81]. Consistent with the precautionary principle, as applied to environmental disease, humanity needs a far greater degree of global cooperation for the effective detection and monitoring of circulating viruses that pose a threat to human or animal health. Embracing the "One Health" approach of simultaneous attention to animal and human disease should be helpful in addressing virus detection and transmission. Additionally, timely reporting with complete transparency and universal access to supporting data is mandatory for the prevention and, if necessary, tracking and containment, of future outbreaks of infectious diseases with pandemic potential. Notwithstanding collective human responsibilities, we must find ways to surmount the usual "I" trilogy, ignorance, ideology, inertia, that has been identified in another context [82].

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Research article

SCORE ESTIMATE OF COVID-19 RISKS AS PER SOCIO-HYGIENIC AND BEHAVIORAL INDICATORS

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Epidemiologic situation remains a serious concern all over the world due to the coronavirus infection spread. It is vital to adhere to measure of non-specific COVID-19 prevention. According to literature data, the highest risks of the infection spread occur in public transport, retail outlets where foods and nonfoods are sold, medical organizations, and chemists' shops.

Our research objects were socio-hygienic and behavioral indicators that were risk factors of the coronavirus infection. Our research aim was to substantiate a score estimate of the COVID-19 contagion risk based on socio-hygienic and behavioral indicators.

Questioning was applied to determine frequency of visiting public places and adherence to basic measurements of non-specific COVID-19 prevention; overall, 400 respondents took part in it. A questionnaire was developed by experts of the Department of General Hygiene at Sechenov University and contained questions aimed at revealing informative signs (risk factors) of the coronavirus infection spread. Cluster analysis was applied to group respondents' questions and to identify informative signs for further development of a scale showing risk categories. Factor analysis in a form of principal component analysis was applied to questions that had the highest number of statistically significant indicators of Spearman's correlation coefficient.

We developed a procedure for assessing risks of COVID-19 contagion according to socio-hygienic and behavioral indicators and substantiated risk categories. The most significant risk factors were indicators related to mandatory mask wearing when visiting specific social objects (risk objects); when taking trips by various means of public transport and duration of such trips; keeping social distance when visiting social objects. We performed score estimate of risk categories regarding COVID-19 contagion.

Key words: *pandemic, COVID-19, coronavirus infection, risk factors, risk objects, risk categories, non-specific prevention, social distancing, obligatory mask wearing.*

The pandemic of new coronavirus infection (SARS-CoV-2) is a serious threat for the global society regarding many aspects. According to data provided by the WHO, on April 21, 2021 more than 140.0 million confirmed cases of the disease were registered all over the world including 4.6 million cases in the Russian Federation (RF for short) [1]. Studies established that it was possible to determine whether a person was infected with SARS-CoV-2 virus 1–3 days prior to occurring symptoms ("pre-symptoms" period) [2–4]. A share of symptomless carriers varies significantly across the population and is assumed to be from 18 to 81 % [5].

We should note that at present there is a descending trend in incidence with the coronavirus infection due to activities aimed at COVID-19 prevention being implemented everywhere [6]. But the existing epidemiologic situation is still rather unfavorable [7].

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Research works accomplished in 2020–2021 concentrated on assessing risks of the coronavirus infection spread among various occupational groups [8] assessing and managing COVID-19-related risks at a workplace [9], and examining SARS-CoV-2 transmission in public transport in China [10].

These and some other publications [11, 12] are based on using risk assessment methodology which is highly informative and efficient given the existing conditions of the COVID-19 pandemic.

Authors of a study that involved visualizing occupations with the highest risks of COVID-19 occurrence applied several risk assessment criteria, notably a number of people in occupational groups under exposure, exposure value (dose), and some others [8].

Chinese experts accomplished a study on "SARS-CoV-2 transmission in public transport in Hunan Province, China" that involved assessing risks of contagion through building up routes of an imaginary infected person who used public transport. The research showed that SARS-CoV-2 was transmitted quite effectively in closed overcrowded spaces.

In October 2020 in Great Britain a scientific research project was initiated that focused on assessing risks of COVID-19 transmission in public transport and determining optimal measures aimed at controlling the virus spread. The participating researchers have been developing a model showing potential virus spread through airflows. This research known as a project on assessing COVID-19-related transport risks is going to be accomplished in buses and trains including light railways [13].

A study by British scientists on coronavirus (COVID-19) involved developing a guide on safe transport for operators and also used such criteria as a number of exposed population, duration and value (dose) of exposure [12].

In Russia several measures have been implemented to reduce risks of COVID-19 spread; they involved imposing certain limitations on passenger flows in public transport (a number of passengers in transport per a unit of time), making passenger flows less dynamic (shortening duration of trips using public transport), as well as improving ventilation systems[1].

According to data provided by Rosstat more than 3.4 billion people use metro in Russia[2]. In

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[1] O dopolnitel'nykh merakh po nedopushcheniyu rasprostraneniya COVID-2019: Postanovlenie Glavnogo gosudarstvennogo sanitarnogo vracha RF ot 30.03.2020 № 9 [On additional measures aimed at preventing COVID-2019 spread: The Order by the RF Chief Sanitary Inspector dated March 30, 2020, No 9]. Available at: http://publication.pravo.gov.ru/Document/View/0001202004010005?index=3&rangeSize=1 (March 05, 2021) (in Russian); Vremennye rekomendatsii po profilakticheskim meram dlya obespecheniya protivoepidemicheskoi bezopasnosti passazhirskikh perevozok zheleznodorozhnym transportom, napravlennye na snizhenie riska vozniknoveniya i rasprostraneniya koronavirusnoi infektsii (COVID-19) (utv. Ministrom transporta RF 25.05.2020) [Temporary recommendations on prevention measures for providing anti-epidemic safety of passenger trips by railways transport, aimed at reducing risks of COVID-19 infection occurrence and spread (approved by the RF Minister of Transport on may 25, 2020)]. Available at: https://mintrans.gov.ru/documents/10/10628 (March 09, 2021) (in Russian); Vremennye metodicheskie rekomendatsii po organizatsii raboty predpriyatii avtomobil'nogo transporta, gorodskogo nazemnogo elektricheskogo transporta i vneulichnogo transporta v tselyakh zashchity passazhirov i personala v usloviyakh neblagopriyatnoi epidemiologicheskoi obstanovki i poetapnogo snyatiya ogranichenii, svyazannykh s rasprostraneniem novoi koronavirusnoi infektsii (COVID-19) (utv. Ministrom transporta RF 25.05.2020) [Temporary methodical recommendations on organizing motor transport activities, city surface electrical transport and off-road transport in order to protect passengers and personnel given the unfavorable epidemiologic situation and step-by-step removal of limitations elated to spread of the new coronavirus infection (COVID-19) (approved by the RF Minister of Transport on may 25, 2020)]. Available at: https://mintrans.gov.ru/search?value=Временные+методические+рекомендации+по+организации+работы+предприятий+автомобильного+транспорта (March 09, 2021) (in Russian); O dopolnitel'nykh merakh po snizheniyu riskov rasprostraneniya COVID-2019 pri organizatsii zimnikh passazhirskikh perevozok zheleznodorozhnym transportom v period sezonnogo pod"ema zabolevaemosti ostrymi respiratornymi virusnymi infektsiyami 2020–2021 gg.: Postanovlenie Glavnogo gosudarstvennogo sanitarnogo vracha po zheleznodorozhnomu transportu RF ot 30.10.2020 N 10 (red. ot 16.11.2020) [On additional measures aimed at reducing risks of COVID-19 spread when organizing passenger trips by railway transport in winter during a seasonal rise in indigence with acute respiratory viral infections in 2020–2021: The Order by the RF Chief Sanitary Inspector on Railway Transport issued on October 30, 2020 No. 10 (last edited on November 16, 2020)]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_366742/ (March 12, 2021) (in Russian).

[2] Osnovnye itogi raboty transporta [Basic results of transport activities]. *The Federal State Statistic Service*, 2020. Available at: https://rosstat.gov.ru/folder/23455 (March 20, 2021) (in Russian).

Moscow the overall passenger flow taken in different periods of time amounts to 8.5 million people a day or up to 163 thousand people a day at one station [14].

Dynamism of passenger flow is a substantial factor influencing spread of the coronavirus infection. A great number of stations (332) and lines (14) in Moscow underground railways makes for dynamic overlapping of passenger flows and this can cause a potential epidemiologic threat since such flows can include symptomless SARS-CoV-2 carriers and people who are reaching the end of the incubation period [15].

A number of passengers in public transport and duration of their trips can be quite high thus making for more rapid spread of the infectious agent. It is rather difficult or almost next to impossible to keep social distance under such conditions.

We should note that heat emission by passengers in underground carriages leads to temperature rise inside them and it makes for better spread of the infectious agent in this medium [16]. In this situation it is advisable to provide efficient ventilation. It was established that open windows and high air circulation speed always resulted in slower infection spread under any conditions [17].

In Russian a number of passengers who use land public transport (buses, trams, trolleybuses, electrical buses etc.) amounts to more than 10 billion people per year[2] or 4 million people a day [18].

Air ventilation in a bus can rely on inside air recirculation; in this case a probability of the infectious agents spread and, consequently, of passengers getting infected with it grows by several times [19].

At the very beginning of the pandemic Chinese researchers performed a retrospect subject study on SARS-CoV-2 transmission from a "primary" patient in public transport in Hunan province. They revealed 12 cases confirmed by laboratory tests that were directly related to one person infected with COVID-19 and spreading the diseases during bus trips [10].

We should bear in mind that risks of the infection spread grow in case we assume that people use both underground and surface transport. E.A. Starodumova built a mathematical model that involved using six different means of public transport: fixed-run taxi, bus, tram, electrical train (in-city and suburban), and metro during both rush and calm hours [20]. An imaginary infected person who was not wearing a face mask was "placed" inside different means of transport and then the model was used to determine in which transport the greatest number of people would be in a zone where contagion was the most probable. The results revealed that a probability to find oneself at a hazardous distance from the infections sources amounted to 100.0 % in a fixed-run taxi; 69.7 % in a bus; 36.7 % in a suburban electrical train; 34.0 % in an in-city electrical train on the Moscow Central Ring; 31.0 % in a tram; 29.6 % in a metro carriage. The said model was built based on an assumption that passengers were 4.5 meters away from a supposed source of the infection.

Suburban passenger trains are an important component of a transport system in a city agglomeration. And we should note that suburban transport is an object with risks of COVID-19 spread since duration of contacts between passengers together with dynamism of transport flows is only growing at present. A carriage of a suburban electric train may carry up to 260 passengers during rush hours and 116 passengers beyond them. It was established that on average 42 people were within a possible contagion zone in a suburban electric train during calm hours and the number grew to 95 people during rush hours.

According to the Order by Moscow mayor[3] (March 2020) respiratory personal pro-

[3] O vvedenii rezhima povyshennoi gotovnosti: Ukaz mera Moskvy ot 5 marta 2020 goda N 12-UM (v red. 06 oktyabrya 2020) [On introducing red alert regime: The Order by Moscow mayor issued on March 05, 2020 No. 12-UM (last edited on October 06, 2020)]. Available at: http://docs.cntd.ru/document/564377628 (March 09, 2021) (in Russian).

tective equipment (face masks or respirators) and personal protective equipment for hands (gloves) became obligatory in public transport and in retail outlets. Since the Order by the RF Chief Sanitary Inspector came into force[4] (October 2020) face masks that protected respiratory organs became obligatory in all public places in the country.

Visits to food-selling outlets create certain risks of contagion for population. Moscow Urbanism Center accomplished a study together with Habidatum analytical company with its aim to determine the most epidemiologically unfavorable districts in the capital according to economic activities that were allowed when quarantine measures were valid [21]. Three basic indicators were used: a number of people who used the same elevator (a risk to get infected from neighbors taking into account how close person-to-person interactions were) a number of people per outlets selling essential goods and items, notably, per 1 chemist's within a 10-minute distance and per 1 square meter in a retail outlet within a 5–20-minute distance.

Each of these indicators was standardized via linear scaling and summated. Minimal values were established for central and western districts in Moscow. It was due to Moscow downtown being quite different from dormitory areas in various aspects, notably, lower population density, a small number of people per one elevator (apartment blocks are different in these two types of city districts) and well-developed infrastructure.

A number of people visiting retail outlets that sell non-food goods and dynamism of such buyer flows are less apparent in comparison with public transport. However we should note that elevated number of factors that can lead to transmission makes such objects rather hazardous when it comes down to risks of COVID-19 spread. It is well known that viability of any infectious agent depends on a surface type, air temperature and some other factors [22–24].

Certain limitations were imposed in medical organizations to mitigate risks of COVID-19 spread[5].

Data taken form literature, accomplished studies, and issued regulatory documents on restricting COVID-19 spread give grounds for preliminary conclusion that the highest risks related to the infection spread occur in public

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[4] O dopolnitel'nykh merakh po snizheniyu riskov rasprostraneniya COVID-19 v period sezonnogo pod"ema zabolevaemosti ostrymi respiratornymi virusnymi infektsiyami i grippom: Postanovlenie Glavnogo gosudarstvennogo sanitarnogo vracha RF ot 16 oktyabrya 2020 goda № 31 (v red. 13.11.2020) [On additional measures aimed at mitigating risks of COVID-19 spread during seasonal rise in incidence with acute respiratory viral infections and influenza: The Order by the RF Chief Sanitary Inspector issued on October 16, 2020 No. 31 (last edited on November 13, 2020)]. Available at: http://docs.cntd.ru/document/566108530 (March 09, 2021) (in Russian).

[5] O vremennom poryadke organizatsii raboty meditsinskikh organizatsii v tselyakh realizatsii mer po profilaktike i snizheniyu riskov rasprostraneniya novoi koronavirusnoi infektsii COVID-19: Prikaz Ministerstva zdravookhraneniya RF ot 19 marta 2020 № 198n (v red. 04.12.2020) [On temporary organization of activities performed by medical organizations to implement measures aimed at preventing and reducing risks of the new coronavirus infection COVID-19: The Order by the RF Public Healthcare Ministry dated March 19, 2020 No. 198n (last edited on December 04, 2020)]. Available at: http://www.consultant.ru/document/cons_doc_LAW_348101/2ff7a8c72de3994f30496a0ccbb1ddafdaddf518/ (March 09, 2021) (in Russian); MR 3.1.0209-20. Rekomendatsii po organizatsii protivoepidemicheskogo rezhima v meditsinskikh organizatsiyakh pri okazanii meditsinskoi pomoshchi naseleniyu v period sezonnogo pod"ema zabolevaemosti ostrymi respiratornymi infektsiyami i grippom v usloviyakh sokhraneniya riskov infitsirovaniya novoi koronavirusnoi infektsiei (COVID-19): Metodicheskie rekomendatsii (utv. Federal'noi sluzhboi po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka 20.08.2020) [MR 3.1.0209-20. Guideline on organizing anti-epidemic regime in medical organizations when rendering medical aid to population during seasonal rise in incidence with acute respiratory viral infections and influenza given persisting risks of contagion with the new coronavirus infection (COVID-19): Methodical guidelines (approved by the Federal Service for Surveillance over Consumer Rights protection and Human Wellbeing on August 20, 2020)]. Available at: https://www.garant.ru/products/ipo/prime/doc/74541600/#review (March 22, 2021) (in Russian); Vremennye metodicheskie rekomendatsii. Profilaktika, diagnostika i lechenie novoi koronavirusnoi infektsii (COVID-19) (utv. Zamestitelem Ministra zdravookhraneniya RF) (versiya 10 ot 08.02.2021) [Temporary methodical recommendations. Prevention, diagnostics and treatment of the new coronavirus infection (COVID-19) (approved by the Deputy to the RF Public Healthcare Minister) (Version 10 issued on February 08, 2021)]. Available at: https://static-0.minzdrav.gov.ru/system/attachments/attaches/000/054/804/original/Временные_MP_COVID-19_%28v.10%29-08.02.2021-2.1_%28003%29.pdf (March 22, 2021) (in Russian).

transport, retail outlets selling both foods and non-food products, as well as medical organizations and chemists'.

Research aim and tasks. The research aim was to substantiate a score estimate of the COVID-19 contagion risk based on socio-hygienic and behavioral indicators.

To do that, the following tasks were set:

1. To establish informative signs (risk factors) of the coronavirus infection spread;

2. To develop a scale showing risk categories for COVID-19 contagion;

3. To suggest a score estimate of risk categories for COVID-19 contagion.

Materials and methods. We relied on questioning to determine how frequently people visited public places and whether they adhered to basic non-specific measures aimed at preventing the coronavirus infection spread. A questionnaire was developed by experts of the Department of General Hygiene at Sechenov University and contained questions that were aimed at revealing the most significant risk factors that could cause contagion with COVID-19 at various social objects. Risk-oriented approach became the methodological grounds for determining objects with elevated risks of the coronavirus infection spread [25, 26]. 400 people took part in the questioning. 11.0 % out of them stated they had already had COVID-19 (75.0 % had mild symptoms and didn't need hospitalization and 25.0 % had to be hospitalized).

Research results were statistically analyzed with STATISTICA Base software package. A correlation between signs was statistically examined using Spearman's non-parametric correlation coefficient (*r*) with Fisher's z-transformation (*z*) applied to approximate the exact distribution of the correlation coefficient. Cluster analysis was applied to group respondents' answers and to identify informative signs for further development of a scale showing risk categories. Principal component analysis (at a level being > 0.70) was applied to the questions that had the highest number of statistically significant indicators of Spearman's correlation coefficient. Overall dispersion share was equal to 60.43 %.

Critical significance (*p*) was taken $p \leq 0.01$ when statistical hypotheses were tested.

Results and discussion. Spearman's correlation analysis revealed that 20 questions out of 51 had the highest number of statistically significant values of the correlation coefficient. Next, we applied principal component analysis to these 20 signs thus identifying the following three factors (Table 1).

Table 1

Factor analysis results applied to identify significant factors

Signs (N = 400)	Significant factors		
	Factor 1	Factor 2	Factor 3
8			0.859833
9			
10			0.856364
13		0.731499	
14		0.786084	
15		0.781985	
17		0.838199	
18		0.816375	
24			
25			
26			
28	0.816092		
29	0.75684		
30	0.750926		
31			
33	0.747646		
34			
37			
38	0.776322		
39			
Expl. Var (dispersion)	5.507479	3.416335	2.090956
Prp. Totl (a share of dispersion)	0.262261	0.162682	0.099569
Cumulative (a share of dispersion)	0.2812	0.2344	0.0887

Factor 1 is the most informative (28.12 %). Its structure is determined by values of positive variables in an answer to a question "What do you do to protect yourself from the coronavirus?" This factor can be identified as "Behavioral strategy". During

the pandemic respondents tried to avoid going to out-patient clinics, food-selling outlets, street vendors, kiosks, retail outlets selling non-foods; they also kept social distance.

Factor 2 has informative value equal to 23.44 % and is represented by positive responses given by participants who mentioned several city objects where risks of COVID-19 contagion were higher such as public land transport, suburban electric trains, chemists' and non-foods shops. This factor can be identified as "Outer conditions for contagion". Most respondents mentioned exactly these city objects when selecting those with high risks of COVID-19 contagion.

Factor 3 has informative value equal to 8.87 % and includes only positive variables regarding obligatory face masks wearing. Respondents mentioned wearing a face mask in public transport, at a workplace, in shop and a chemist's as a more important factor that could prevent COVID-19 contagion. This factor can be identified as "obligatory mask wearing".

Hierarchical cluster analysis aimed at grouping respondents' answers allowed identifying clusters of indicators that can later be applied to distribute questioned people into several groups as per estimated signs and to test differences between these groups including those related to risks of COVID-19 contagion (Figure).

Risk factors were selected according to nearest neighbor algorithm as per consequent agglomeration table. It provided an opportunity to trace dynamics of growing differences as per clusterization steps and determine a step at which a drastic increase in differences took place. 16 factors were selected out of total 46. Having calculated hierarchy of the informative signs, we obtained data given in Table 2 (a threshold for selecting leading factors for clusterization is the hierarchy coefficient equal to 0.7).

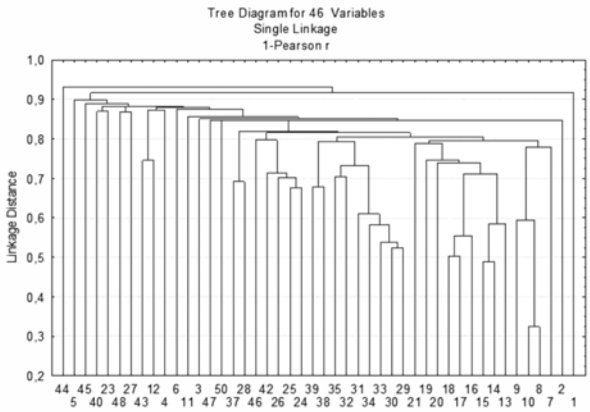

Figure. Results of cluster analysis

Table 2

Hierarchy of informative signs (risk factors)

No.	Risk factor	1-*r*	Score
1	Wearing face masks in public land transport	0.324156	1.5
2	Wearing face masks in a shop, chemist's etc.	0.324156	1.5
3	Taking underground trips	0.487818	3.5
4	Taking a suburban electric train	0.487818	3.5
5	Going to a chemist's	0.503621	5.5
6	Going to retail outlets selling non-foods	0.503621	5.5
7	Going to food shops	0.524694	7.5
8	Going to street vendors or kiosks	0.524694	7.5
9	Going to food shops	0.554532	10
10	Going to hairdresser's or beauty shops	0.581808	11
11	Using public land transport	0.583966	12
12	Not wearing a face mask at a workplace	0.594983	13
13	Going to an out-patient clinic	0.678507	14.5
14	Going to a usual in-patient clinic (not for COVID-19-infecte patients)	0.678507	14.5
15	Social distancing	0.691358	16.5
16	Social distancing when visiting medical organizations	0.691358	16.5

Table 3

Score estimates as per risk factors scales (according to data taken form respondents' answers)

No.	Risk factor	Scale	Score	Average
1	Wearing face masks in public land transport	Yes No	0.5 2	1.25
2	Wearing face masks in a shop, chemist's etc.	Yes No	0.5 2	1.25
3	Taking underground trips	Up to 1 hour 1 hour–1.5 hours 2 and more hours	0.5 1 2	1.75
4	Taking a suburban electric train	Up to 1 hour 1 hour–1.5 hours 2 and more hours	0.5 1 2	1.75
5	Going to a chemist's	Yes No	1 0	0.5
6	Going to retail outlets selling non-foods	Yes No	1 0	0.5
7	Going to food shops	Yes No	1 0	0.5
8	Going to street vendors or kiosks	Yes No	1 0	0.5
9	Going to food shops	Yes No	1 0	0.5
10	Going to hairdresser's or beauty shops	Yes No	1 0	0.5
11	Using public land transport	Up to 1 hour 1 hour–1.5 hours 2 and more hours	0.5 1 2	1.75
12	Not wearing a face mask at a workplace	Yes No	1 0	0.5
13	Going to an out-patient clinic	Yes No	3.5 0	1.75
14	Going to a usual in-patient clinic (not for COVID-19-infecte patients)	Yes No	3.5 0	1.75
15	Social distancing	Yes No	0.5 3	1.75
16	Social distancing when visiting medical organizations	Yes No	1 3	2.0

Therefore, we established the most significant risk factors. They are socio-hygienic and behavioral indicators that are related to visiting various social objects and trips (and their duration) on different kinds of public transport, wearing face masks and keeping social distance when visiting various objects (risk objects). Next, score estimates were given as per scales of informative signs based on data taken from respondents' answers (Table 3).

At this stage in our research we gave score estimates as per scales of informative signs which would later allow calculating odds ratio (*OR*) between groups included into a study with a greater number of respondents, first of all, those who have already had COVID-19.

To assign a respondent into a risk category, it is necessary to give a score estimate as per each informative sign (Table 4). An average identification value (a range from 16.1 to 20.0) and higher calculated for a respondent indicates that non-specific preventive measures are required to reduce risks of contagion.

Conclusions:

1. The most significant "factors" that can protect from the coronavirus infection include indicators that characterize the following: respondents' "behavioral strategy"

Table 4

Risk categories (score estimates)

Risk category	Scores (summated)
Low	< 8.0
Below average	8.1–16.0
Average	16.1–20.0
Above average	21.1–26.0
High	> 26.1

(avoiding public places); “outer conditions for contagion” at various objects; obligatory face mask wearing. Risk factors of contagion with the coronavirus infection are indicators that characterize visits to various social objects and trips (and their duration) on various kinds of public transport, wearing face masks and keeping social distance at various objects (risk objects).

2. We developed a procedure for assessing risks of contagion with the coronavirus infection as per risk factors. This procedure can be used to examine distribution and to assess socio-hygienic and behavioral risk factors among population; it can also be used to include people into a study, first of all, those with COVID-19 in their case history, and for further calculation of *OR* between groups of respondents as well as analyzing risks of COVID-19 contagion.

3. We performed score estimates of risks categories for contagion with the coronavirus infection.

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

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Research article

ON ISSUES RELATED TO NATIONAL RISK-BASED SYSTEM FOR CONTROL OVER FOOD PRODUCTS DISTRIBUTED ON THE MARKET

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This research is vital given great significance of food safety for population and bearing in mind that food products are an independent object of sanitary-epidemiologic control as it is stipulated by the legislation.

We suggest approaches to creating a risk-based model for control over food products distributed on the market. These approaches involve categorizing food products as per potential health risks for consumers; building up risk profiles of food products; optimizing laboratory support provided for control and surveillance activities taking into account food products safety management.

When categorizing food products, risk is assessed as a combination of probable violation of obligatory requirements to safety and severity of consequences these violations might have. Food products that are assigned into extremely high, high and considerable risk categories are subject to systemic control once a year, every two years or every three years accordingly. In case a surveillance object seems "law-abiding', its category and intensity of control procedures may be changed. Programs for laboratory control over food products are suggested to be based on risk profiles, spotting out priority indicators that make major contributions into risks. Also the approach involves using-mathematical models that describe a relation between a number of observations and an expected answer (as a reduction in quantities of deviating samples at the next stage in the control cycle). This model determines how many samples of priority indicators should be tested in order to achieve a target risk level. It also allows predict an expected number of violations and health risk rates at the next stage in the control cycle given the present number of observations.

85 regional registers of food products were created and categories were determined as per health risks for all groups of food products under surveillance. It was shown that in some cases it was necessary to increase a number of observations over priority ("risky") indicators in order to detect hazardous products and withdraw them from the market. Certain examinations seem redundant as they don't play any role in making control procedures more efficient.

The suggested approaches are universal and dynamic. Basic trends in the model development may include more targeted selection of products for control; risk profiles creations and systemic actualization; further development of laboratory support for control (surveillance) given that the food products market is changing dynamically in the country.

Key words: *food products distributed on the market, risk-oriented control, laboratory control, product safety management.*

Control over safety and quality of products (goods), especially food products that are distributed on the consumer market is among the most important tasks to be solved by authorities in any country and the Russian Federation is no exception[1] [1–5]. On one hand, this is vital due to population being less satisfied with food products when they are not safe and / or do not conform to quality standards [6, 7]; on the other hand, unsafe or low quality food products may cause various diseases, even grave ones in some cases, and this results

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[1] Ob utverzhdenii Doktriny prodovol'stvennoi bezopasnosti Rossiiskoi Federatsii: Ukaz Prezidenta RF ot 21 yanvarya 2020 g. № 20 [On Approval of the Doctrine on the food safety in the Russian Federation: The Order by the RF President dated January 21, 2020 No. 20]. *Garant: the information and legal portal*. Available at: https://www.garant.ru/products/ipo/prime/doc/73338425/ (October 04, 2021) (in Russian).

in poorer medical and demographical indicators [8–11]. Thus, Dubois-Brisonnert [8] showed in their research that approximately 1.5 million cases of food poisoning were annually registered in France only and they caused about 250 deaths. Food-borne diseases include various allergic reactions, communicable diseases with new properties or with more severe clinical course [8, 9], resistance to antibiotics, gastrointestinal disorders, diseases of the nervous system, etc. [10, 11].

According to the documents issued by the World Health Organization, "food safety" is "*assurance that food will not cause adverse health effects to the consumer when it is prepared and/or eaten according to its intended use*". This safety is provided by "*preventing and eliminating hazards caused by contaminants, admixtures, natural toxins or any other substances, whether chronic or acute, that may make food injurious to the health of the consumer or reducing them to acceptable and safe levels*"[2].

Without doubt, application of HACCP (Hazard Analysis and Critical Control Point) principles in food manufacturing is the primary and key component in providing its quality and safety [12]. HACCP system is the internationally tested and accepted efficient tool for managing production processes in order to minimize microbiological, biological, physical, chemical and other risks that products might get contaminated when being manufactured. Its primary advantage is its capability to not only reveal technical, technological, behavioral and any other mistakes at each stage in food production but also prevent them [13]. The system is oriented at maximum assured provision of food safety and quality and this is the primary task that has to be tackled by food industry in its overall operations [14, 15].

We do not intend to lessen the importance of the preventive role played by the system for analyzing risks and critical points and management quality in food manufacturing; still, we should note that the state sanitary control over products (goods) that are already distributed on the market is among the most significant components in the system aimed at protecting health (and sometimes even lives) of food consumers [16, 17]. Control over goods on shelves in retail outlets, in workshops and kitchens of catering facilities etc. is the last and the most direct barrier between potentially unsafe food and people who consume it.

Many countries use risk-based model of food control and surveillance activities [18–21]. The same model started to be developed and implemented by Rospotrebnadzor at the very beginning of the administrative reforms in the Russian Federation. In 2017 the RF Chief Sanitary Inspector approved the methodical recommendations on assigning economic entities into specific categories as per potential health risks[3]. This document ensures spotting out objects under surveillance that create the greatest risks of damage to protected social values.

The Federal Law "On the state control (surveillance) and municipal control in the Russian Federation" that came into force on June 01, 2021[4] stipulates that products (goods) are an

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[2] Codex Alimentarius. General Principles of Food Hygiene CXC 1-1969. *FAO, WHO*. Available at: https://www.fao.org/fao-who-codexalimentarius/sh-proxy/fr/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCXC%2B1-1969%252FCXC_001e.pdf (December 04, 2021).

[3] MR 5.1.0116-17. Risk-orientirovannaya model' kontrol'no-nadzornoi deyatel'nosti v sfere obespecheniya sanitarno-epidemiologicheskogo blagopoluchiya. Klassifikatsiya khozyaistvuyushchikh sub"ektov, vidov deyatel'nosti i ob"ektov nadzora po potentsial'nomu risku prichineniya vreda zdorov'yu cheloveka dlya organizatsii planovykh kontrol'no-nadzornykh meropriyatii: utv. Federal'noi sluzhboi po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka 11 avgusta 2017 g. [MR 5.1.0116-17. The risk-based model of control and surveillance activities in the sphere of providing sanitary-epidemiologic welfare. Classification of economic entities, types of activity and objects under surveillance as per potential human health risks for organization of scheduled control and surveillance activities: methodical guidelines (approved by the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing on August 11, 2017)]. *The Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing*. Available at: https://www.rospotrebnadzor.ru/documents/details.php?ELEMENT_ID=9037 (December 07, 2021) (in Russian).

[4] O gosudarstvennom kontrole (nadzore) i munitsipal'nom kontrole v Rossiiskoi Federatsii: Federal'nyi zakon ot 31.07.2020 № 248-FZ [On the state control (surveillance) and municipal control in the Russian Federation: The Federal Law issued on July 31, 2020 No 248-FZ]. *KonsultantPlus: the reference system for legal documentation*. Available at: http://www.consultant.ru/document/cons_doc_LAW_358750/ (September 30, 2021) (in Russian).

independent object under control (Clause 16). Before that products were controlled only as a component of economic entities activities.

Accordingly, just as any other objects that are subject to control, products are to be assigned into specific categories as per potential health risks and intensity of surveillance activities should be relevant to these risks. Passage of this law required developing science-based approaches to planning control and surveillance activities in regard to products (goods). And since it is chemical and biological contamination of food that is the primary hazard factor, laboratory control is seen to be the most significant component in any surveillance activity.

Control over products distributed on the market aims to detect, remove and completely eliminate (withdraw) unsafe products from distribution. Simultaneously there should be signal to all participants on the market that surveillance will reliably provide this elimination.

Bearing all this in mind, we can see two primary tasks in planning control procedures:

– to determine types of food that are subject to the most intense control (but still, all food products distributed on the market should be under control);

– to substantiate optimal volumes of laboratory analyses of specific products taking their risk category into account.

Solution to the first task (spotting out priority food products) can be found in the methodical document approved by the RF Chief Sanitary Inspector in 2016[5]. The document stipulates how to assess a specific food product as per risk criteria. Health risk is examined in full conformity with its definition as a combination of a probable undesirable event (violated requirement to product safety) and severity of consequences.

The document also allows assigning food products into specific categories as per health risks taking into account frequency of violations of mandatory requirements to safety and severity of probable health disorders among consumers given the current consumption of a specific food product, both values being statistically established at a given moment (period) of time. The document is widely used in practice by Rospotrebnadzor regional offices [22, 23].

At present this methodical document is to be brought into line with the provisions stipulated by the 248-FZ since it should provide a solution to the second task, namely minimal sufficient or optimal numbers of laboratory analyses performed on products with different health risk levels.

A classic solution to the task how to determine a sufficient number of instrumental measurements can be derived with a formula used to calculate an error of mean for a binary random variable. The aim is to determine a number of measurements that provide detection of deviations from a standard (criterion) with preset precision and level of significance). To do that, Koichubekov [24], for example, suggested performing sampling studies of products during a year with a sampling volume calculated as per the following ratio:

$$n = \frac{Z^2 p(1-p)}{\Delta^2}, \qquad (1)$$

where n is a number of sampling studies (a sampling volume); p is estimated frequency of violations of hygienic standards; Δ is permissible error in frequency of violations of hygienic standards; Z is a quantile of standard normal distribution of the order 0.975.

A volume of sampling studies determined as per the ratio (1) allows quite certain determination how frequently violations are detected. Any increase in a sampling volume will result in a smaller error but, accordingly, a decrease in it will lead to a greater one. Such ap-

[5] Klassifikatsiya pishchevoi produktsii, obrashchaemoi na rynke, po risku prichineniya vreda zdorov'yu i imushchestvennykh poter' potrebitelei dlya organizatsii planovykh kontrol'no-nadzornykh meropriyatii: Metodicheskie rekomendatsii (utv. Prikazom Rospotrebnadzora ot 18.01.2016 g. № 16) [Classification of food products distributed on the market as per potential health risks and property losses by consumers for organizing scheduled control and surveillance activities: Methodical guidelines (approved by the Order by Rospotrebnadzor issued on January 18, 2016 No. 16)]. Moscow, The Federal Center for Hygiene and Epidemiology of Rospotrebnadzor, 2016, 38 p.

proach to organizing control and surveillance activities involves greater numbers of measurements for products with low frequency of violations than for those with high frequency. This situation contradicts to principles of the risk-based approach that involves stricter control over objects with more frequent violations of sanitary requirements and lower burden on objects that comply with them.

An issue related to substantiating a relevant sampling volume when surveillance over products is organized within the risk-based approach requires taking into account cause-effects relations between frequency of detected violations and a number of accomplished studies.

If we accept a hypothesis that a reduction in frequency of violations results from an increase in intensity of surveillance, then we face another task which is how to determine a volume of sampling and accomplished studies that provide achieving the preset level of detected violations or risk.

Therefore, instead of solving a task how to assess product quality with preset reliability, it seems advisable to set a management task a solution to which can provide results with greater significance for sanitary services and food consumers. That is, we have to answer a question: how many samples and of what product should be taken and examined during control and surveillance activities to ensure reduction in a number of deviating samples to a certain (preset or target) level bearing in mind that resources are limited.

It is very important to answer this question since efficiency of instrumental research differs as per product groups, specific indicators, and regions [25–27].

Since the research results give grounds for making decisions on elimination of discrepancies, administrative measures, etc., it is essential to develop unified and science-based approaches to the content and volumes of analyses performed in control over food distributed on the market.

Our research aim was to develop approaches to optimizing the risk-based sanitary-epidemiological control (surveillance), including laboratory support, as a tool for managing food safety.

We should bear in mind that the research focuses only on food safety. Aspects related to risk-based assessments whether product marking or quality conform to mandatory requirements, including falsification, require separate investigation.

Materials and methods. Products (goods) for which violations of mandatory sanitary requirements were detected were considered unsafe food.

Potential health risk was determined as a combination of probable violation of requirements to a specific product, severity of health disorders caused by this violation, and an exposure scope taken as a number of people consuming unsafe food.

Health risks for consumers were assessed as per the algorithm stated in the approved methodical recommendations[5] taking into account that generally products distributed on the consumer market were characterized with violations of mandatory requirements with frequency established by control and surveillance activities.

A probability that obligatory requirements would be violated was described by the frequency of detected violation in all regions in the Russian Federation. Bearing the precautionary principle in mind, we took 95 % percentile in the distribution of a regional relative indicator (a number of violations per 1 inspection) over the last three years as frequency of violations.

Severity of consequences for consumers' health caused by unsafe food was taken as a combination of severity of health disorders for a specific consumer caused by unsafe food (values close to zero meant that health disorders were mild and values close to 0.95 meant they were severe) and a scope of these disorders. The scopes were determined by estimating volumes of food consumption, regional peculiarities taken into account[6].

[6] Potreblenie osnovnykh produktov pitaniya naseleniem Rossiiskoi Federatsii [Consumption of basic food products by population in the Russian Federation]. *The Federal State Statistic Service*. Available at: https://rosstat.gov.ru/compendium/document/13278?print=1 (September 27, 2021) (in Russian).

Food products were categorized as per potential health risk according to the criteria stipulated in the Provisions on the Federal State Sanitary Surveillance[7]).

Objects were assigned into the following risk categories: extremely high risk, high risk, considerable risk, average risk, moderate risk, and low risk.

We analyzed the following data to determine necessary scope of laboratory support for control and surveillance activities (a number of analyses and food samples):

– data on a number of taken samples as per specific food products in a given region and in all the RF regions over the last few years (the Statistical Report Form “Data on the results of the federal state surveillance accomplished by Rospotrebnadzor regional offices” issued in 2010–2020);

– data on a number of detected violations as per specific indicators for the same food products on a regional and country level;

– data on probable adverse effects on consumers’ health that may be caused by violated requirements to a specific indictors and severity of these effects;

– volumes in which specific foodstuffs are consumed in a given region (according to statistical reports provided by Rosstat and sampling studies of household spending);

– population in a given regions including its age structure (children and adults).

We assumed there was the following functional link:

$$n \sim puM , \qquad (2)$$

where n is a number of analyses; p is frequency of detected violations of a hygienic standard; u is specific severity of health disorders; M is an exposure scope (practical calculations involved using a number of consumers or population related to 100,000 as a scale factor); the sign “~” means there is a certain functional link.

The formula (2) is general in it essence and reflects the basic hypothesis that covers all safety indicators and all food products; therefore, indices that identify specific food products and safety indicators are omitted.

When a specific safety indicator is considered for a given food product, specific severity of health disorders is the constant; therefore, we can derive the equation (3) with its precision up to the constant:

$$\frac{n}{M} = v \sim p , \qquad (3)$$

where v is a specific volume of analyses regarding a standardized indicator (hygienic standard) for a specific food product.

A specific volume of analyses v was taken as a number of food product analyses per 100,000 people in a RF region that were accomplished or planned to be accomplished during control and surveillance activities over a calendar year.

Within system analysis a specific volume of analyses is a vector that describes a number of analyses for a system of safety indicators $V^T = \{v_i\}, i = 1...I$, where I is a number of standardized indicators for an examined food product. The whole system of indicators or its part can be determined from just one food sample.

The functional link between a number of accomplished analyses aiming to determine whether food conforms to hygienic standards and frequency of detected violations (3) is the basis for management tasks.

Food safety in a region is an object to be managed. This safety is determined by a system of indicators reflecting how often hygienic standards are violated and creating a space with different states of an object to be managed given by the phase vector:

$$P^T = \{p_i\}, i = 1...I. \qquad (4)$$

[7] O federal'nom gosudarstvennom sanitarno-epidemiologicheskom kontrole (nadzore) (vmeste s «Polozheniem o federal'nom gosudarstvennom sanitarno-epidemiologicheskom kontrole (nadzore)»): Postanovlenie Pravitel'stva RF ot 30.06.2021 N 1100 [On the federal state sanitary-epidemiologic control (surveillance) (together with “The Provisions on federal state sanitary-epidemiologic control (surveillance)”): The RF Governmental Order issued on June 30, 2021 No. 1100]. *KonsultantPlus: the reference system for legal documentation*. Available at: http://www.consultant.ru/document/cons_doc_LAW_389344/c3ec9aec7f786991ebd558c3002ea5caa6a22c1a/ (September 27, 2021) (in Russian).

Given that health is influenced by a whole set of all standardized safety indicators, we can establish that management aims to control the functional that describes health risk and can be given as the following equation:

$$Risk = \left(\sum_i p_i u_i\right) M = \\ = \left(\sum_i p_i \sum_j \alpha_{ij} g_j\right) M \to \min, \quad (5)$$

where α_{ij} is a coefficient describing a *j*-th health disorder caused by violated *i*-th safety indicator; g_j is a severity of consequences when the *j*-th health disorder is detected.

Finding a solution to the task (5) requires identifying hazard for each indicator of specific food products. Probable negative health responses caused by violated hygienic food standards were established based on literature data. Coefficients describing severity of health disorders were taken in accordance with the recommendations issued by the WHO[8] and data of the meta-analysis provided by Minsu Osk with colleagues [28].

Bearing probable responses to violations in mind, we believe that the system should involve creating "risk profiles" for food products, that is, determining indicators that make the greatest contribution to overall risks caused by food and are subject to the priority and strictest control.

And the task here was to determine a desirable frequency of control over priority (risk) factors so that frequency of detected violations could reach a desirable (target) level in the next control cycle. Therefore, contents and scopes of laboratory analyses become an instrument for managing food safety.

A functional link between actual frequency of detected violations (a state of food as an object to be managed) and management vector is determined through statistical modeling of relationships based on departmental statistic data. Attention is paid to intensity of laboratory control over food safety and frequency of detected violations.

We assumed that frequency of control and surveillance activities and analyses influenced frequency of violations of mandatory requirements in the next year.

A type of this functional relation was determined by an exponential model corresponding to the argument that it was possible to make food fully conforming to safety criteria by a significant increase in intensity of control and that total absence of control results in food safety going down to its critical values.

All the aforementioned hypotheses borne in mind, we searched for relationships between management indicators and a state of food in accordance with the following regression model:

$$p_i^{t+1} = a1_i \left(v_i^t\right)^{a2_i}, \quad (6)$$

where p_i^{t+1} is a frequency of violation of *i*-th standardized food indicator detected in the year *t*+1; m_i^t is a number of accomplished analyses regarding the *i*-th indicator in the year *t*; M^t is a number of consumers; $a1_i$, $a2_i$ are parameters of the regression model and the parameter *b* is conditioned with $a2_i < 0$.

There are certain limitations imposed on management indicators and food indicators in the management task (5)–(6):

– limitations on achievement of target values (target safety) by indicators describing food safety:

$$p \le p^* \text{ or } p_i \le p_i^{Цел}, i = 1...I. \quad (7)$$

We should note that it is advisable to take into account provision of surveillance authorities with necessary resources ($\sum_i n_i \le W$) when solving the task. But it requires a separate study bearing in mind other criteria related to optimization of control systems. It is also vital to determine target food safety, that is, to

[8] Global burden of disease 2004 update: disability weights for diseases and conditions. *WHO*. Available at: https://www.who.int/healthinfo/global_burden_disease/GBD2004_DisabilityWeights.pdf (September 01, 2021).

determine acceptable risk level and, accordingly, acceptable frequency of detected violations of specific indicators. We should remember that detecting all probable violations of mandatory requirements involves total control over food which seems too expensive and rather inefficient. The issue is a task to be solved within strategic planning and requires participation by experts and decision-makers. In the present research a target safety level p_i^* was given by average country frequencies of detected violations as of the end of 2020 or by a specifically preset parameter being 1 % of samples with detected violations.

Finding solutions to the management task (5)–(7) in regard to a specific food product determines a number of analyses corresponding to preset target safety levels.

$$v_i^* = \left(\frac{p_i^*}{a1_i} \right)^{1/a2_i} . \qquad (8)$$

A number of analyses accomplished in a specific region is determined by a specific number of analyses multiplied by a number of consumers (population): $n_i^* = v_i^* M$. The necessary number of analyses is determined as a maximum component of the vector $N^T = \{n_i\}, i = 1...I$.

Essentially a solution to the task (5)–(7) regarding a system of indicators and specific food products helps determine a certain common federal standard of laboratory support for control and surveillance activities; this standard will allow developing an analysis program for a given region. And if we want to satisfy the boundary condition (8), we should set and solve the optimization task (5) with the target function.

When this optimization task is set for a given region, it results in occurring contradictions associated with the established model (6) not being consistent with actual ratio between a number of analyses and frequencies of detected violations. It means that a different number of analyses is required in different regions to provide the same frequency of detected violations.

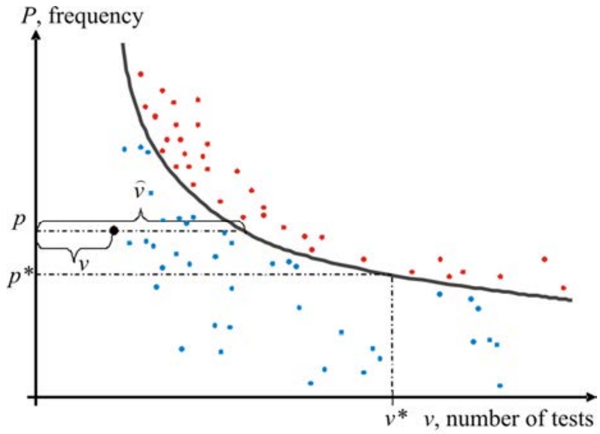

Figure 1. General view of "a number of analyses – detected frequency of violations" relationship for estimating efficiency of laboratory analyses given the preset target level

This assumption indicates that accomplished laboratory tests regarding food safety may have different efficiency.

Actually the model (6) divides the dispersion diagram into some areas where the given curve divides all the analyses into two groups (Figure 1).

Points describing a situation when scopes of accomplished tests do not provide achievement of a target level at the next step in management are located above the curve; that is, control activities do not result in withdrawing all the unsafe food from the market in the current situation in a given region and their preventive effect is not sufficient. A lot of violations are likely to be detected again during the next control cycle.

Points describing a situation when scopes of laboratory analyses provide achieving a target level are located below the curve. And if a target level is well-grounded, in some cases scopes of laboratory analyses can be estimated as redundant and it is possible to reduce them in order to save resources and redistribute expenses to provide control over other indicators.

Management in a specific region is described with an actual ratio between frequency of violations of standardized indicators (p_i) and intensity of laboratory analyses (v_i); its aim is to change a scope of analyses ($v_i + \Delta v_i$) in such a way so that a target frequency of detected violations ($p_i \to p_i^*$) is achieved. A change in a specific scope of analyses is determined as per the ratio (9):

$$\frac{v_i}{\hat{v}_i} = \frac{v_i + \Delta v_i}{v_i^*}. \quad (9)$$

An absolute change in a scope of analyses is determined in accordance with the scale factor (10):

$$\Delta n_i = \Delta v_i M. \quad (10)$$

If we use the equations (9), (10), we can calculate scopes of analyses necessary for a specific region regarding specific indicators and food products and their changes against the last reporting year. These calculations allow planning relevant laboratory support for control and surveillance over food safety.

Basic results. Priority food product groups that were subject to the most frequent surveillance activities were determined at the first stage in developing plans for control over food. Overall, we created the federal register and 85 regional ones containing data on various food products. Table 1 provides a part of a regional register with determined risk categories.

We determined that from 8 to 15 large product groups (various food products) could be assigned into categories of extremely high, high, and considerable risk depending on frequency of detected violations and regional consumption peculiarities. Meat and meat products, milk products, poultry, eggs and products made of them, fish, other seafood, etc. were assigned into these three categories practically in every region.

Since food that is assigned into these three categories (extremely high, high, and considerable risk) is subject to systemic control, necessary volumes of schedules control and surveillance activities seem to be rather considerable.

Table 1

A part of a regional food products register (with risk categories determined for larger product groups)

Food (product group)	*P**	*U***	Risk rate and category***		*N*****	Contribution to total risk, %	A share of a total number of samples, %
Meat and meat products	0.039	5.477	2.16E-01	1	9,121	6.31	12.75
Poultry, eggs, and products made of them	0.107	4.172	4.45E-01	1	3,223	13.01	4.51
Milk and milk products	0.036	28.168	1.01E+00	1	10,241	29.52	14.31
Butter and fat-based products	0.025	6.154	1.52E-01	1	1,995	4.44	2.79
Fish, shellfish, and products made of them	0.16	1.178	3.67E-01	1	2,932	10.73	4.10
Culinary	0.032	1.772	6.59E-02	2	16,675	1.93	23.31
Flour and cereals	0.011	0.420	2.67E-03	3	3,225	0.08	4.51
Bakery	0.01	0.259	1.89E-03	3	2,962	0.06	4.14
Sugar	0.09	0.970	4.46E-02	2	92	1.30	0.13
Confectionary	0.02	2.293	2.66E-02	2	7,754	0.78	10.84
Fruits and vegetables	0.015	15.321	1.71E-01	1	5,320	5.00	7.44
Mushrooms	0.029	0.687	1.38E-02	2	100	0.40	0.14
Non-alcoholic drinks	0.023	2.396	4.23E-02	2	1,008	1.24	1.41
Juices and nectars	0.022	0.725	1.43E-02	2	830	0.42	1.16
Alcoholic drinks	0.018	1.348	1.84E-02	2	2,075	0.54	2.90
Honey and beekeeping products	0.144	0.038	9.50E-03	3	22	0.28	0.03
Food products for children	0.02	6.166	4.59E-01	1	589	13.42	0.82
Canned food	0.062	1.261	4.86E-02	2	1,040	1.42	1.45
Grain (seeds)	0.019	0.075	2.48E-03	3	344	0.07	0.48
Mineral water	0.024	2.909	5.20E-02	2	498	1.52	0.70
Bottled water	0.03	0.562	2.97E-02	2	425	0.87	0.59
Salt	0.028	0.091	1.30E-03	3	559	0.04	0.78
Total	–	–	3.19E+00	–	–	100.00	100.00

Note: * *p* is frequency of detected violations, 95-th percentile over 2010–2020 (taking into account control and surveillance activities and industrial control);

** *U* is potential health risk for consumers; covers both severity and scale of consequences;

*** Risk categories: 1 means extremely high risk; 2, high; 3, considerable;

**** *N* is an average number of samples taken in 2010–2020.

Table 2

Changes in frequency of detected violations of hygienic requirements to food taken in dynamics (per 1 inspection)

Food (product group)	2013	2014	2015	2016	2017	2018	2019	2020	Relative change 2020/2013
Total	0.019	0.020	0.020	0.020	0.018	0.017	0.017	0.016	–15.8
Meat and meat products	0.017	0.017	0.018	0.017	0.018	0.017	0.017	0.017	0.0
Milk and milk products	0.022	0.024	0.025	0.028	0.024	0.024	0.022	0.019	–13.6
Poultry, eggs, and products made of them	0.028	0.030	0.029	0.029	0.026	0.027	0.024	0.023	–17.9
Fish, shellfish and products made of them	0.026	0.044	0.035	0.034	0.028	0.022	0.020	0.021	–19.2
Culinary	0.028	0.025	0.025	0.023	0.022	0.022	0.022	0.021	–25.0
Alcoholic drinks, beer	0.003	0.009	0.009	0.007	0.005	0.004	0.004	0.004	+33.3
Non-alcoholic drinks	0.014	0.018	0.018	0.020	0.018	0.014	0.013	0.013	+7.1
Potato	0.008	0.006	0.005	0.004	0.003	0.002	0.003	0.004	–50.0
Melons and water melons	0.023	0.011	0.013	0.017	0.012	0.014	0.021	0.018	–21.7
Fruits and berries	–	0.004	0.006	0.005	0.005	0.004	0.003	0.003	–
Canned food	0.008	0.019	0.018	0.019	0.020	0.018	0.020	0.016	+100.0
Biologically active additives to food	0.007	0.008	0.009	0.008	0.008	0.007	0.007	0.007	0.0
Mushrooms	0.057	0.045	0.041	0.035	0.040	0.027	0.026	0.021	–63.2
Grain and grain products	0.002	0.002	0.002	0.002	0.001	0.003	0.002	0.002	0.0
Honey and beekeeping products	–	0.017	0.015	0.012	0.008	0.012	0.014	0.017	+1600.0
Mineral water	0.011	0.014	0.016	0.014	0.017	0.015	0.014	0.013	+18.2
Flour and cereals	0.005	0.010	0.010	0.007	0.006	0.005	0.004	0.007	+40.0
Food products for children	0.004	0.006	0.004	0.005	0.006	0.004	0.005	0.006	+50.0
Food provided by catering facilities	0.024	0.022	0.022	0.023	0.021	0.022	0.022	0.019	–20.8
Butter and fat products	0.009	0.010	0.011	0.011	0.010	0.009	0.006	0.008	–11.1
Juices	0.005	0.006	0.007	0.007	0.005	0.007	0.006	0.007	+40.0

And we should remember that laboratory support provided for control activities should be proportionate to health risks and its aim should be constant improvement of a situation (a decreasing share of samples deviating from safety standards as stated in the present research). We comparatively analyzed risk rates and categories determined for various food products to reveal that overall distribution of laboratory analyses wasn't completely relevant to a contribution made by a specific group into potential health risks (Table 1).

In some cases inconsistence between frequency of laboratory analyses and product risks results in absence of any significant positive improvements of food safety on the consumer market.

Thus, a contribution made by the product group "poultry, eggs and products made of them" to the total health risk amounted to 13 % in the analyzed region but a share of product samples amounted to only 4.5 % in the total number of taken samples. But the frequency of detected violations as per microbiological indicators amounted to 9 % for this product group in 2013–2019 in that region and no stable decrease was detected in that period. A share of samples deviating from safety standards as per microbiological indicators amounted to 9.2 % in 2013; 8.13 % in 2015; 9.0 % in 2017; 6.8 % in 2019; and 7.8 % in 2020. Therefore, a target steady growth in safety of this product group and, consequently, food as a whole, is not achieved.

On the contrary, high frequency of analyses performed on culinary products in the region resulted in declining frequency of violations, from 2.5 % in 2013 to 1.03 % in 2019.

We analyzed detected frequencies of violations as per the most common food products in the Russian Federation in dynamics. The analysis revealed that in spite of the overall positive ascending trend in food safety there was no positive dynamics detected for certain product groups or there was even a negative trend (Table 2).

It should be noted that a decrease in a number of samples deviating from hygienic standards was achieved for such food products as "fish, shellfish and products made of them", "butter and fat products", "food provided by catering facilities", "potato", "melons and watermelons" etc. A share of deviating samples tended to grow for such product groups as "juices", "non-alcoholic and alcoholic drinks", "food products for children", "canned food", and some others.

In some cases a growth in a number of deviating samples is due to improved laboratory support provided for control activities and it allows identifying qualitative and quantitative violations that have never been detected before. However, the task to increase safety remains vital even when more developed control systems are now available.

We should note that detected overall frequencies of violations provided in the Table 2 are given taking into account a considerable share of tests that haven't detected any violations or have been detecting them with very low frequency. On one hand, it means that in general food distributed on the consumer market in the country is safe. On the other hand, long-term history of accomplished analyses initially assumes that "detection" is extremely low as per certain indicators and analyses are predicted to yield poor results.

For example, according to data taken from the Statistical Report Form "Data on the results of the federal state surveillance accomplished by Rospotrebnadzor regional offices in 2020" 25 thousand food samples were examined in the country to detect strontium-90 in them. There wasn't any detected sample that deviated from hygienic standard as per this indicator. 120.9 thousand food samples were analyzed to detect arsenic in them and the contaminant was detected only in 17 of them (0.014 %) belonging to 9 product groups (90 product groups were analyzed overall).

But at the same time, a share of samples deviating from hygienic standards as per microbiological indicators amounted to 4.45 % for "poultry, eggs, and products made of them" on average in the country and the total number of analyzed samples amounted to 49.5 thousand for this products group; 5.6 % of 25.18 thousand analyzed samples for "fish and shellfish" product group; 9.7 % of 2.28 thousand analyzed samples for "canned food" products group, etc.

Shares of detected violations are also very different in across regions. Thus, frequency of detected violations as per microbiological indicators amounted to 0.18 % of 556 tests for "poultry, eggs, and products made of them" in Kursk region in 2020 (it was by almost 25 times lower than on average in the country, 4.5 %); but it was 8.69 % of almost the same number of analyzed samples (564) in Vologda region (2 times higher than on average in the country).

This situation requires creating "risk profiles"[9] or such a characteristic of a product that comprises all necessary data on related risks. Table 3 provides an example of a risk profile created for the "milk and milk products" product group in a specific region.

Risk profiles give grounds for determining priority indicators that are provided with the optimal number of laboratory analyses at the next stage in the control cycle. Risk profiles for the same food can be different in different regions; but still, there are common regularities that can be used as a reference in case there are no data available for a specific region.

Table 4 provides priority indicators for some food products. These are indicators that are the most frequently violated in most regions in the Russian Federation and make the greatest contributions to total health risks.

We can see that frequencies of violations making the most considerable contributions to health risks are extremely uneven. Thus, control over safety of milk and milk products most frequently detects violations as per microbiological indicators and benz(a)pyrene and less frequently as per antibiotics and radiation factor, Lead, arsenic, pesticides, pathogenic

[9] Tamozhennyi kodeks Evraziiskogo ekonomicheskogo soyuza. Stat'ya 376 [The Customs Code of the Eurasian Economic Union. Clause 376]. *KonsultantPlus: the reference system for legal documentation*. Available at: http://www.consultant.ru/document/cons_doc_LAW_215315/95bff3c3e7d43c52b5a973884657f2796374a3fe/ (September 14, 2021) (in Russian).

Table 3

Creating a risk profile for a chain "product hazard" – "probable adverse effect on health" – "severity of consequences"

Standardized indicator	Probable health response	Severity of health disorder*	Frequency of violations	Risk created by a factor*	Rank in risk profile
Listeria monocytogenes	Enteric infections	0.27	0.02	0.0054	6
Pseudomonas aeruginosa	Enteric infections Acute enteric infections with pseudomonas etiology	0.27	0.06	0.016	3
Aflatoxin M1	Damage to the liver Immunity suppression Cancer	0.75	0.00	0.00	–
Yeast and mold, total	Pancreatitis	0.498	0.15	0.075	1
Chloramphenicol	Allergic eczema Anaphylactic reactions* Dysbacteriosis	0.235	0.02	0.005	7
Radionuclides	Cancer	0.65	0.00	0.000	–
Melamine	Damage to the kidneys	0.36	0.00	0.000	–
Benz(a)pyrene	Cancer	0.75	0.02	0.015	4
Lead	Immunity disorders Cancer	0.65	0.02	0.013	5
Arsenic	Damage to the nervous system Cancer	0.75	0.01	0.065	2
Cadmium	Damage to the kidneys Damage to the endocrine system Cancer	0.65	0.00	0.00	–

Note: * means that the precautionary principles taken into account, risk calculation involved focusing on the most severe health disorders.

Table 4

Frequency of detected violations of mandatory requirements in the Russian Federation

Indicator	Registered frequency of violations, 2013–2020, %	
	95 % percentile*	Average
Milk and milk products (R = 8.01E-01. Extremely high risk)		
Microbiological indicators	5.97	4.82
Benz(a)pyrene	3.37	1.84
Sanitary-chemical indicators	3.33	0.87
Antibiotics	0.99	0.53
Cesium-137	0.58	0.28
Pathogenic microorganisms	0.12	0.05
Lead	0.06	0.02
Arsenic	0.06	0.02
Pesticides	0.02	0.01
Mycotoxins	0.01	0.00
Mercury	0.01	0.00
Cadmium	0.01	0.00
Imported milk and milk products (R = 1.21E-01. Extremely high risk)		
Microbiological indicators	5.81	4.49
Sanitary-chemical indicators	3.76	0.87
Antibiotics	1.44	0.49
Pathogenic microorganisms	0.08	0.02
Cadmium	0.07	0.01

End table 4

Confectionary (R = 2.8E-02. High risk)		
Parasitological indicators	25.00	25.00
Microbiological indicators	4.99	4.42
Cadmium	0.10	0.05
Pathogenic microorganisms	0.09	0.04
Sanitary-chemical indicators	0.09	0.03
Mycotoxins	0.06	0.01
Pesticides	0.04	0.01
Mercury	0.01	0.00
Lead	0.01	0.00
Fruits and vegetables (R = 1.19E-01. Extremely high risk)		
Microbiological indicators	4.70	3.14
Nitrates	2.25	1.50
Sanitary-chemical indicators	2.00	1.26
Cesium-137	0.76	0.44
Pathogenic microorganisms	0.61	0.31

Note: * means the table provides data on indicators with their value being 0.01 %.

microorganisms etc. are registered in concentrations and quantities exceeding permissible levels less frequently than in 5 samples of analyzed 1,000; mycotoxins, mercury and cadmium are detected in approximately 1 case of 1,000 analyses; copper, nickel, chromium and melamine are detected even less frequently.

Obviously, it is necessary to determine an optimal structure of laboratory support that would provide not only the most reliable detection of unsafe food but also an opportunity to reduce a number of violations during the next cycle of control and surveillance activities.

Accumulated and formalized data on results obtained due to control over food in all regions in the Russian Federation collected over 10 years gave grounds for establishing and analyzing 2,835 relationships between frequencies of violations of standardized safety indicators and a number of detected violations, Figure 2 provides examples of some models and Table 5 provides a wider list of indicators.

When modeling the relationships, we applied moving average to clear the initial data from random spread.

The Figure 2 shows that if analyses are performed with low intensity, it almost always leads to a high percentage of violations ("overestimated" product hazard); however, growing intensity of analyzing doesn't always result in greater shares of detected violations (redundant instrumental research). And getting a complete picture of a product doesn't require analyzing different product indicators with the same frequency.

The built relationships were used to find a solution to the management task (5)–(7) and it allowed determining target volumes of analysis and adjusting analysis programs for different food products during control and surveillance activities.

Table 5 provides an example of calculations accomplished for a specific region in regard to some food products.

It is obvious that indicators contributing to health risks with mandatory requirements to them being violated the most frequently require a much greater number of analyses than are actually accomplished. Thus, if we want to achieve a target frequency of detected violations as per microbiological indicators for meat which is equal to 0.1 % (and an actual detected per cent of deviating samples is 6.5 %), we can clearly see that accomplished analyses are not enough. Analysis intensity should grow practically by three times and it should result in withdrawing products from the market that are unsafe as per this indicator and in preventing them from being distributed again in the next control cycle. Control over physical and chemical indicators and pathogens should also become more intense.

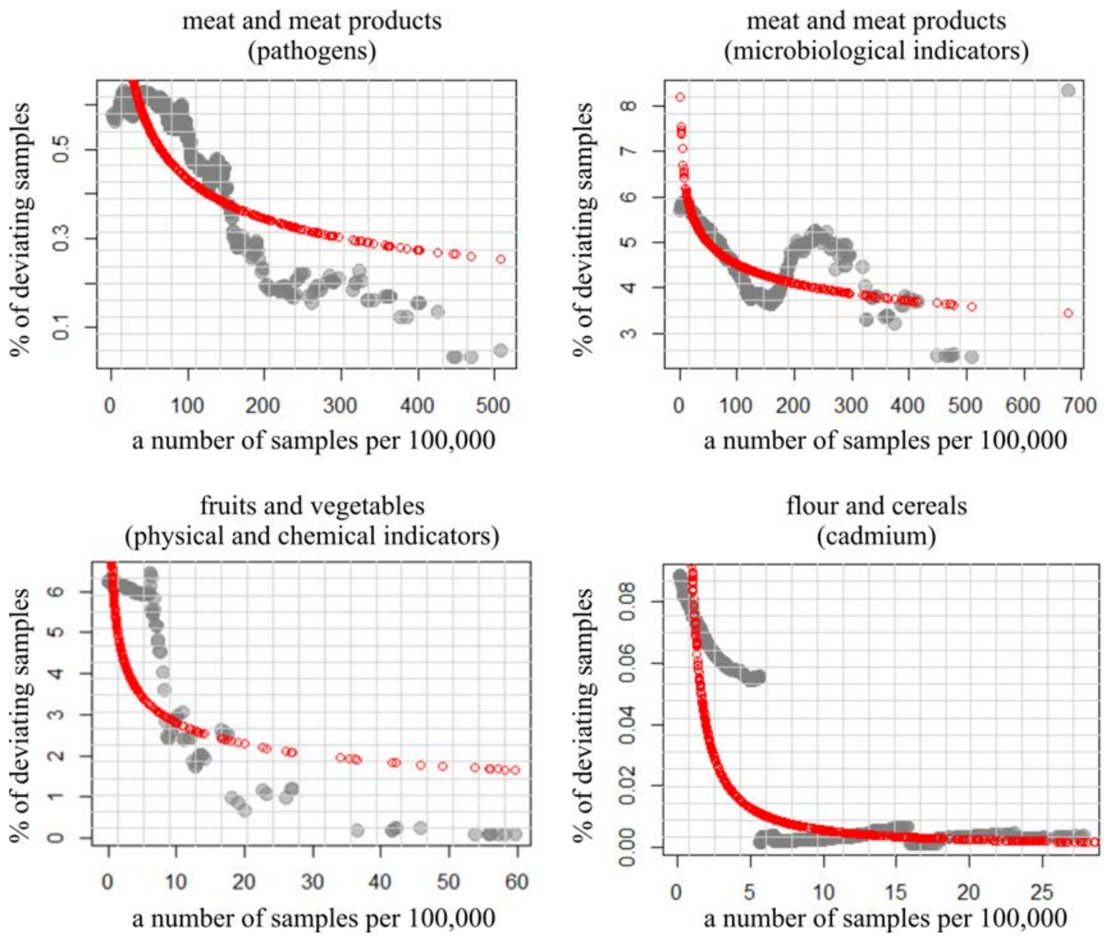

Figure 2. Examples of models that describe relationships between frequencies of violations of standardized product indicators and a number of analyses (analyses/100 thousand people)

More intense and frequent control aims to provide maximum possible detection of unsafe food and to eliminate it from distribution. Another aim is to give a clear signal to economic entities that control over such food will remain frequent and intense.

We should note that if frequency of detected violations as per "risky indicators" goes down to 1 % for meat and meat products, this will lead to reduction in overall risk rates in the country, from 2.16E-01 (extremely high risk) to 3.51E-02 (high risk); that is, this food will be assigned into another risk category as per potential health risk. If, for example, we set a target frequency at 0.1 % as per priority indicators in the next control cycle, then we can expect this food to move into "considerable risk" category, etc. Ultimately, it is exactly these strategic tasks that should be tackled by control and surveillance authorities when they perform their activities regarding food distributed on the market.

In some cases absence of any detected deviating samples might be due to insufficient volumes of analysis in a given region (in our example it concerns parasitological indicators and antibiotics in meat) as it is indicated by relationships obtained for the country as a whole.

But at the same time analyzing aimed at determining antibiotics, arsenic, and lead in milk seems redundant since actual number of analyses doesn't result in declining numbers of detected samples that do not conform to hygienic standards.

Therefore, optimization of laboratory control doesn't necessarily mean an increase in a number of analyses; instead, it involves creating such a structure of laboratory analysis that is relevant to the current sanitary-epidemiologic situations in regard to food distributed on the market.

Table 5

Parameters of models that describe relationships between frequencies of violated safety indicators and a number of analyses for some food products

Safety indicators	*a1*	*a2*	*N*	R^2	*F*	*p*
Meat and meat products						
Microbiological indicators	119.613	-0.108	837	0.372	494.8	1.86E-86
Pathogenic microorganisms	87.239	-0.120	556	0.588	789.8	1.1E-108
Physical and chemical indicators	25.492	-0.153	366	0.443	289.7	3.27E-48
Parasitological indicators	3.367	-0.126	46	0.181	9.71	0.003218
Antibiotics	6.533	-0.135	90	0.362	49.9	3.62E-10
Milk and milk products						
Arsenic	8.431	-0.200	16	0.741	40.08	1.86E-05
Pathogenic microorganisms	125.609	-0.057	135	0.066	9.43	2.60E-03
Lead	9.281	-0.108	20	0.201	4.54	4.73E-02
Physical and chemical indicators	97.323	-0.287	479	0.755	1467.9	1.1E-147
Antibiotics	9.996	-0.064	167	0.123	23.05	3.51E-06
Confectionary						
Microbiological indicators	56.257	-0.077	567	0.204	144.4	8.92E-30
Pathogenic microorganisms	37.080	-0.134	77	0.344	39.40	2.03E-08
Fruits and vegetables						
Cadmium	9.510	-0.238	42	0.519	43.2	7.49E-08
Microbiological indicators	17.666	-0.222	381	0.310	170.3	2.07E-32
Pesticides	19.495	-0.077	23	0.375	12.70	0.001897
Physical and chemical indicators	8.4550	-0.381	153	0.621	247.8	1.18E-33
Parasitological indicators	59.901	-0.054	286	0.152	50.8	8.49E-12
Sanitary-chemical indicators	77.635	-0.015	474	0.016	7.89	0.005176
Canned food						
Microbiological indicators	14.347	-0.119	406	0.341	209.0	1.78E-38
Nitrates	0.849	-0.169	26	0.207	6.26	1.95E-02
Physical and chemical indicators	7.841	-0.179	346	0.504	349.5	2.58E-54

Table 6

An example of calculating volumes of analysis necessary to estimate safety indicators for certain food products in a model region (population is 2,589 thousand people), the target share of deviating samples should not exceed 1 %

Food product / Safety indicator	Actual, 2020			Target values			Δn, analyses
	p	v_{actual}, analyses / 100,000	n_{actual}	*p**	*v**, analyses / 100,000	*n**	
Meat and meat products							
Microbiological indicators	6.15	37.69	976	1.0**	119.61	3,097	+2,118
				5.26* **	**102.3**	**2,649**	**+1,978**
Physical and chemical indicators	4.64	7.49	194	1	25.49	660	+466
				3.1	**9.54**	**441**	**+247**
Pathogenic microorganisms	3.09	37.52	971	1	87.24	2,259	+1,288
Parasitological indicators	0	0.66	17	1	3.37	87	+60
Antibiotics	0	2.82	73	1	6.53	169	+96
Milk and milk products							
Physical and chemical indicators	9.2	81.45	2,109	1	97.32	2,519	+410
				8.9	**94.12**	**2,437**	**+328**
Antibiotics	0.87	17.73	459	1	9.99	259	-200
Arsenic	0	20.89	541	1	8.43	218	-310
Pathogenic microorganisms	0	95.36	2,469	1	105.61	3,252	+30
Lead	0	25.30	655	1	9.28	240	-415

Note: ** recommended (model) frequency of violations of sanitary-epidemiologic requirements;
*** average Russian frequency of violations of sanitary-epidemiologic requirements in 2020.

Target criteria may be set step-by-step in the process and this means that we don't plan a single intense increase in volumes of analysis but consider a step-by-step change in the structure of it. For example, average country value of an indicator might be selected as the first target management criterion.

Thus, if we set 5.26 % as a target management criterion for frequency of detected deviating samples as per microbiological indicators for meat, it will require a lower number of analyses accomplished during a year than for achieving a lower target level of 1.0 % (Table 2, shaded lines). The same goes for a number of analyses accomplished to determine levels of physical and chemical indicators in meat and milk.

Achieving an intermediate target level provides an opportunity to set stricter targets and tasks in the next control cycle.

An indicator that requires the greatest number of analyses (taking into account peculiarities related to sampling for different types of analyses) is a limiting one in determining volumes of product samples necessary to accomplish laboratory research.

Discussion. The suggested approaches that provide implementing the risk-based model for control over food distributed on the market are universal and dynamic in their essence.

Assigning food products into different risk categories as per potential health risks takes into account both how frequently mandatory requirements are violated and severity of consequences these violations might have. Thus, a differentiated approach to selecting types (groups) of food products under control is provided. And food products may be assigned into another risk category only if their safety indicators have changed as it becomes apparent due to a share of detected samples that don't conform to the existing sanitary-epidemiologic standards (severity of consequences is a constant in most cases). And the change can be both for the worse (assigning a product into higher risk category since frequency of detected violations has grown) and for the better (when a product has become safer).

It is important that this approach to assigning food products into different risk categories has a potential for development. Given that the results obtained by control and surveillance activities are integrated taking into account a product type, manufacturer, and supplier, risk assessment may become much more targeted and concrete. Potentially more "problem" products can be spotted in a group of homogenous food and they are subject to first priority and stricter control. The most vital task in this case is to create a unified information space for control and surveillance activities with a possibility to analyze all the collected data on various foods distributed on the market.

Also it seems advisable to create specific "risk profiles" that take into account not only frequency of violations detected by laboratory tests but also severity of negative consequences these violations may have. Scientific substantiation provided for these risk profiles gives an opportunity to estimate the necessity and intensity of control over such most hazardous indicators as radioactivity, occurring carcinogens or mutagenic admixtures, etc. [29].

The suggested approach entails that average country levels of detected deviating samples will decline in each next control cycle (this means annually given the current planning system), that is, food distributed on the consumer market will become safer as per health risks criteria. Programs for instrumental research will be adjusted and optimized according to new available data.

It is also assumed that if due to some reasons a share of deviating samples is growing together with decreasing frequency of analyses thus unavoidably resulting in growing health risks for consumers, then there will be higher frequency of control procedures accomplished in regard to the indicator for which this growth is detected. That is, the higher is a share of detected violations as per a specific indicator and health risks for the consumer, the more targeted a program for laboratory research becomes concentrating on this very indicator.

But at the same time, bearing in mind that food manufacture is developing and there are changes in types and structure of raw materials, applied production technologies, food storage and transportation, it is suggested to analyze approximately 20 % of all food samples as per all standardized indicators. Frequency of sampling for a specific food product is determined based on a risk category this product is assigned into. Any random detections within this stochastic approach can change an overall risk profile and result in more systemic study on indicators that have not been listed among priority ones before.

We should also note that these approaches are feasible provided that the Unified Information and Analytical System of Rospotrebnadzor is available and functioning since all the results obtained by laboratory research and analyses are to be accumulated in its databases.

Results obtained by control and surveillance activities performed within a year control cycle are to be analyzed properly since it provides necessary grounds for efficient planning of contents and volumes of control and surveillance activities for the next cycle.

Conclusions. Risk-based surveillance over products distributed on the market is stipulated in the federal legislation and requires scientific substantiation and methodical support.

The suggested model gives an opportunity to assign food products into different risk categories as per potential health risks for the consumer. Health risk is determined as a combination of a probability that mandatory requirements to product safety would be violated and severity of consequences such a violation may have. Food that is assigned into categories of extremely high, high, or considerable risk is subject to systemic control annually, every 2 or every 3 years accordingly. The model provides a possibility to change a risk category as per potential health risk for a specific food product and to make control procedures less intense in case a product has become safer. On the contrary, in case violations have started to be detected more frequently, a risk category may change for the worse and control will become stricter.

Programs for laboratory control over food are to be developed according to the principle that entails a number of analyses performed to check a specific indicator being relevant to potential health risk for the consumer. It is advisable to apply mathematical models that describe a relationship between a number of analyses and an expected result being a decrease in a number of deviating samples in the next control cycle.

The model also provides a possibility to determine a number of samples that are to be analyzed to achieve a target level or expected number of violations in the next cycle (in the next year) given the preset number of analyses. Target criteria are fixed taking into account risk indicators and can be determined and achieved step by step taking into account actual resources available to laboratory centers in regions.

The suggested approaches can be tested and implemented based on the Unified Information and Analytical System of Rospotrebnadzor where all results obtained by control and surveillance activities are accumulated including all data obtained by laboratory analyses.

The model has prospects for development and improvement. Priority trends in its development include more targeted selection of products to be controlled; creations and systemic revision of risk profiles, regional peculiarities of goods distributed on the market taken into account; optimization of laboratory support provided for control (surveillance) given a lot of dynamic changes occurring on the food market in the country.

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Research article

ESTABLISHING INDICATORS FOR ASSESSING NON-CARCINOGENIC RISKS UNDER CHRONIC INHALATION EXPOSURE TO BENZENE AND AVERAGE ANNUAL MPC FOR BENZENE AS PER HEALTH RISK CRITERIA

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Recently multiple new toxicological and epidemiologic data on negative effects produced by chemicals have become available; given that, it is necessary to improve quantitative criteria applied in health risk assessment. It is advisable to revise previously established reference concentrations and to make more precise lists of organs and systems affected by a chemical in concentrations which are either equal to reference one or exceed it. Our research aim was to establish a reference concentration for benzene and additional quantitative indicators of its effects (additional reference concentrations) on specific organs and systems under chronic inhalation exposure; another aim was to determine average annual MPC verified as per permissible lifetime carcinogenic risk using evolution models. The research allowed recommending 0.005 mg/m^3 to be used as a reference concentration under chronic inhalation exposure to benzene; a decrease in quantity of B-lymphocytes was recommended as a critical effect since this decrease might produce negative effects on the blood and immune system. Additional reference concentrations for benzene were fixed at 0.007 mg/m^3 for the liver as a critical organ and 0.012 mg/mg^3 for violated process of organism development as a critical effect. They can be used as additional indicators for assessing non-carcinogenic health risks under chronic inhalation exposure to benzene in its elevated concentrations. Our research results were used to substantiate average annual MPC for benzene in ambient air; its recommended value was 0.005 mg/m^3 since it provided safety (absence of impermissible (unacceptable) lifetime health risk), probable carcinogenic effects taken into account.

Key words: *reference concentration, additional reference concentrations, average annual MPC, benzene, health risk, indicators for health risk assessment.*

The methodology for assessing health risks caused by exposure to chemicals that pollute the environment is an effective up-to-date tool that allows assessing a probability of harm to health depending on a scope of adverse impacts produced by a chemical [1–3]. The Guide R 2.1.10.1920-04 "Human Health Risk Assessment from Environmental Chemicals" is the policy document in risk assessment[1]. In accordance with the Guide, assessment of risks caused by chronic exposure to adverse chemicals in ambient air involves comparing all the established concentrations with reference ones (RfC). A reference concentration is a daily

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[1] R 2.1.10.1920-04. Rukovodstvo po otsenke riska dlya zdorov'ya naseleniya pri vozdeistvii khimicheskikh veshchestv, zagryaznyayushchikh okruzhayushchuyu sredu [The Guide R 2.1.10.1920-04. Human Health Risk Assessment form Environmental Chemicals]. Moscow, The Federal Center for the State Sanitary and Epidemiologic Surveillance of the RF Public Healthcare Ministry, 2004, 143 p. (in Russian).

lifetime exposure to a chemical that can probably fail to cause unacceptable health risks for sensitive population groups[1, 2]; it should be established taking into account all the available latest scientific data

According to the Guide R 2.1.10.1920-04 RfC are fixed for a wide range of chemicals. Also, the Guide determines critical organs and systems for each chemical, that is, organs or systems that are primarily influenced by a given chemical. Some chemicals have quite a wide list of critical organs and systems under chronic inhalation exposure, for example, 1,3-butadiene (critical organs and systems: the reproductive system, respiratory organs, cardiovascular system, blood, and carcinogenic effects), acetone (the liver, kidneys, blood and the CNS), benzene (development, blood, red bone marrow, the CNS, immune, cardiovascular and reproductive systems), dioxins (overall systemic effects, development, liver, the reproductive and hormonal systems, respiratory organs, and blood) and some others. However, our preliminary analysis of literature data on action mechanisms typical for various chemicals has revealed that in most cases adverse effects initially occur in an organ or a system under a certain exposure and this exposure level is then used as grounds for establishing a reference concentration. When exposure grows beyond this reference concentration, other organs and systems also become involved into pathological processes. Given that, it is necessary to determine such exact exposure levels that produce adverse effects on the specified critical organs and systems; when risks of exposure to combined effects are estimated within the previously applied approach with using hazard quotients and indexes, it results in overestimation of created risk levels. It is also advisable to determine critical effects more precisely according to action mechanisms typical for chemicals bearing in mind critical organs and systems specified for them.

On the other hand, according to results described in several latest research works, statistically authentic effects produced by certain chemicals can be observed under exposure to concentrations lower than RfC, including effects on organs and systems that are not specified as critical and this can results in risks being underestimated as per the existing methodology. This might be due to new data becoming available thanks to the latest toxicological and epidemiological studies on effects produced by chemicals. Given that, it seems advisable to review previously established RfC following a principle of renewal fixed in the Guide R 2.1.10.1920-04 and in some foreign documents on establishing reference values [4–5]. According to this principle all established values are to be revised after occurrence of new data that can be used in developing and substantiating them.

Therefore, it is necessary to establish more precise quantitative criteria (reference concentrations) used in assessing non-carcinogenic health risks caused by chemical contamination of the environment. The obtained results may be applied to substantiate average annual MPC ($MPC_{av.an.}$) of chemicals in ambient air, carcinogenic effects also taken into account.

This approach seems appropriate to be tested on the example of benzene since the list of critical organs and systems specified for this chemical under chronic inhalation exposure in the Guide R 2.1.10.1920-04 is among the widest; this chemical is a carcinogen; and also there are several relevant toxicological and epidemiologic studies focusing on benzene that contain renewed data on its effects [6–10]. Besides, benzene is among chemicals mentioned in priority lists of ambient air pollutants such as the Air Quality Standards of European Commission and ATSDR’s Substance Priority List; it is also included into a list of priority pollutants in accordance with the Letter “On

[2] Onishchenko G.G., Zaitseva N.V., May I.V. [et al.]. Analiz riska zdorov'yu v strategii gosudarstvennogo sotsial'no-ekonomicheskogo razvitiya: monografiya [Health risk analysis in the strategy of the state social and economic development: monograph]. In: G.G. Onishchenko, N.V. Zaitseva eds. Moscow, Perm, Perm National Research Polytechnic University Publ., 2014, 738 p. (in Russian).

the list of priority pollutants in the environment and their influence on population health" No. 11/109-111 dated August 07, 1997[3] [11–13]. Benzene is listed among priority environmental factors that cause medical and demographic losses in the State Report "On sanitary-epidemiologic welfare of the population in the Russian Federation in 2020"[4].

Our research aim was to establish a reference concentration for benzene and additional quantitative indicators of its effects on specific organs and systems under chronic inhalation exposure (additional reference concentrations); another aim was to determine average annual MPC for the chemical.

To achieve this aim, the following tasks were set:

1. To establish exposure levels that could be used as initial ones to substantiate RfC and additional RfC of benzene.
2. To substantiate RfC of benzene under chronic inhalation exposure and relevant critical organs and systems.
3. To substantiate additional quantitative indicators (additional reference concentrations) under exposure to which benzene would produce effects on other organs and systems apart from those specified as critical ones in establishing RfC.
4. To substantiate $MPC_{av.an}$ for benzene and verify it as per carcinogenic risk criteria and using evolution models.

Materials and methods. NOAEL (non-effective dose), LOAEL (threshold value), BMC (benchmark concentration) and BMCL (lower confidence limit of BMC) for effects produced by benzene on various organs and systems were taken as exposure levels that could be used as initial ones in substantiating RfC and additional RfC [14–15]. To do that, we performed an analytical review of domestic and foreign research works that focused on examining effects produced by benzene on various organs and systems, were cited in internationally acknowledged databases including Scopus, Research Gate, Web of Science, CyberLeninka, NCBI PubMed, eLibrary, Google Scholar, Elsevier, and were relevant to the present research. All the results obtained in this analysis were combined to build tables that provide data on effects produced by benzene on specific organs and systems. The tables provide data on a type of a study (toxicological / epidemiologic), research object, properties of a sampling, exposure (duration and intensity), research designs / experimental conditions, data on effects / responses, procedures applied to collect and analyze data, models of "exposure – effect" relationships, NOAEL / LOAEL, limitations in a study, and data sources. The next step was profound analysis aimed at estimating whether we had enough data for establishing statistically authentic minimal exposure levels that produced certain adverse effects on specified organs and systems; these minimal exposure levels gave grounds for further development of quantitative indicators for exposure to benzene. Overall, we carefully revised more than 150 published works and report.

RfC and additional RfC of benzene were established in conformity with approaches applied by the US Environmental Protection Agency (US EPA) [4–5, 16]. They were calculated as per the formula 1:

$$RfC = POD \Big/ \prod MF, \qquad (1)$$

where RfC is a reference concentration of benzene in ambient air, mg/m^3; POD is point of departure (concentration), mg/m^3; MF is a value of the total uncertainty factor.

Uncertainty factors in substantiating reference concentrations were established and $MPC_{av.an}$ for benzene was substantiated and

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[3] O spiske prioritetnykh veshchestv, soderzhashchikhsya v okruzhayushchei srede i ikh vliyanii na zdorov'e naseleniya [On the list of priority pollutants in the environment and their influence on population health]. The Federal Service for Surveillance over Consumer Rights Protection and Human Well-being. Available at: https://www.rospotrebnadzor.ru/documents/details.php?ELEMENT_ID=838 (November 15, 2021) (in Russian).

[4] O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2020 godu: Gosudarstvennyi doklad [On sanitary-epidemiologic welfare of the population in the Russian Federation in 2020: the State Report]. Moscow, The Federal Service for Surveillance over Consumer Rights Protection and Human Well-being, 2021, 256 p. (in Russian).

verified in accordance with the principles stated within the scientific research entitled "Developing methodical approaches to substantiating MPC of chemicals in ambient air as per health risk criteria", the State Register No. NIOKTR AAAA-A19-119060390099-5[5].

The formula (2) was applied to verify $MPC_{av.an}$ for benzene in ambient air as per carcinogenic risk since it allowed calculating such a concentration of a chemical in ambient air that provided an acceptable carcinogenic risk level:

$$MPC^{carc}_{av.an.} = \frac{(CR)}{(UR)}, \qquad (2)$$

where *CR* is acceptable carcinogenic risk level ($1 \cdot 10^{-4}$); UR is unit risk, m/mg^3 (calculated in accordance with the Guide R 2.1.10.1920-04[1]).

$MPC_{av.an}$ for benzene that corresponded to acceptable lifetime risk was verified based on principles stipulated in the Methodical Guidelines MR 2.1.10.0062-12 "Quantitative assessment of non-carcinogenic risks under exposure to chemicals based on building up evolution models"[6]; the verification was performed by experts from the Department for Mathematical Modeling of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies.

Results and discussion. Data obtained by analyzing the relevant research works allowed revealing that exposure to benzene in various concentrations produced adverse effects on several organs and systems in the body including the blood system, immune system, nervous system, cardiovascular system, respiratory organs, liver, reproductive system, skin and eyes; benzene also exerted negative influence on a developing organism, produced genotoxic and apparent carcinogenic effects [6–10, 16, 17].

Profound analysis provided us with sufficient relevant data for determining exposure levels regarding the blood system, the liver, and influence on a developing body; these exposure levels could be used as initial ones in substantiating RfC and additional RfC for benzene. Few research works that concentrated on estimating potential effects produced by chronic inhalation exposure to benzene on other organs and systems could not be used in our research due to multiple limitations, such as absence of qualitative and/or quantitative descriptions of exposure levels and effects, research being not designed properly, simultaneous exposure to benzene and other chemicals examined in a study etc. [7–10, 16, 17].

We selected several studies that established statistically authentic effects produced by benzene on the blood system under chronic inhalation exposure to lower doses of the chemical than those examined in all other works available at the moment. These studies included works by Scnhatter et al. [18], Rothman et al. [19], and Lan et al. [20]. Additional searching allowed revealing BMCL levels were calculated by USEPA and OEHHA based on the results described in these studies [16, 17]. These levels were used as points of departure in calculating various reference levels and establishing relevant uncertainty factors (Table 1).

We calculated three variants of RfC characterizing the exposure that might result in adverse effects produced on the blood system under chronic inhalation exposure to benzene; these concentrations amounted to 0.005, 0.07 and 0.09 mg/m^3. The minimal calculated concentration 0.005 mg/m^3 was taken as a reference one and the critical effect was a decrease in a number of B-lymphocytes. Since this effect characterizes both disorders in the blood and the immune system, these two systems were specified as critical ones for this RfC.

[5] Zaitseva N.V., Shur P.Z. Razrabotka metodicheskikh podkhodov k obosnovaniyu PDK khimicheskikh veshchestv v atmosfernom vozdukhe po kriteriyam riska zdorov'yu naseleniya: otchet o nauch.-issled. rabote [Developing methodical approaches to substantiating MPC of chemicals in ambient air as per health risk criteria: the report on the accomplished scientific research]. Perm, The Federal Scientific Center for Medical and Preventive Health Risk Management Technologies, 2019, 145 p. (in Russian).

[6] MR 2.1.10.0062-12. Kolichestvennaya otsenka nekantserogennogo riska pri vozdeistvii khimicheskikh veshchestv na osnove postroeniya evolyutsionnykh modelei: metodicheskie rekomendatsii [The Methodical Guidelines MR 2.1.10.0062-12. Quantitative assessment of non-carcinogenic risks under exposure to chemicals based on building up evolution models]. Moscow, The Federal Center for Hygiene and Epidemiology of Rospotrebnadzor, 2012, 36 p. (in Russian).

Table 1

Calculations of benzene RfC under chronic inhalation exposure based on key studies focusing on effects produced by this chemical on the blood system

	Study (year)		
	Rothman et al. (1996)	Lan et al. (2004)	Scnhatter et al. (2010)
Research object	44 people	250 people	928 people
Exposure	Occupational exposure, on average 6.3 years	Occupational exposure, on average 6.1 years	Occupational exposure, on average 6.5 years
Critical effect	A decrease in absolute number of lymphocytes	A decrease in number of B-lymphocytes	A decrease in number of neutrophils and declining volume of thrombocytes
Threshold concentration	LOAEL = 7.6 ppm (24.8 mg/m^3)	LOAEL = 0.57 ppm (1.86 mg/m^3)	LOAEL = 7.8 ppm (25 mg/m^3)
Recalculation into BMCL (Source)	BMCL = 8.2 mg/m^3 (US EPA, 2003) [16]	BMCL = 0.204 ppm (0.665 mg/m^3) (OEHHA, 2014) [18]	BMCL = 3.3 ppm (10.8 mg/m^3) (OEHHA, 2014) [18]
Point of departure (POD)	BMCL = 8.2 mg/m^3	BMCL = 0.665 mg/m^3	BMCL = 10.8 mg/m^3
Total uncertainty factor (MF)	MF = 120 10 is intraspecific extrapolation factor; 2 is a factor taking into account extrapolation form controlled mode onto real life; 6 is a factor taking into account a scope of initial database	MF = 120 10 is intraspecific extrapolation factor; 2 is a factor taking into account extrapolation form controlled mode onto real life; 6 is a factor taking into account a scope of initial database	MF = 120 10 is intraspecific extrapolation factor; 2 is a factor taking into account extrapolation form controlled mode onto real life; 6 is a factor taking into account a scope of initial database
Calculated RfC	RfC = 0.07 mg/m^3	RfC = 0.005 mg/m^3	RfC = 0.09 mg/m^3
Selected RfC	RfC = 0.005 mg/m^3		

We also selected several studies that focused on effects produced by benzene on the liver; these studies established statistically authentic effects produced by the chemical in lower doses than those examined in all other available research works. These studies were performed by Perez et al. [21, 22] and Uzma et al. [23]. They gave grounds for establishing threshold benzene concentrations that produced various adverse effects and relevant uncertainty factors; these concentrations were used as points of departure in calculating various reference levels (Table 2).

We calculated two additional RfC characterizing an exposure level that might result in adverse effects on the liver under chronic inhalation introduction of benzene; they amounted to 0.007 and 0.016 mg/m^3. The minimal value out of two, 0.007 mg/m^3, was selected as an additional reference concentration. This value can be applied as an additional quantitative indicator of effects produced by benzene on the liver when health risks are assessed under elevated exposure.

Having analyzed all available studies focusing on impacts exerted by chronic inhalation exposure to benzene on a developing organism, we selected two key works, namely Chen et al. [24] and Lupo et al. [25]. Minimal exposure levels that caused adverse effects were determined based on the results described in these two works and applied as point of departure for substantiating reference concentrations (Table 3).

We calculated two additional RfC that might produce negative effects on a developing organism under chronic inhalation exposure to benzene; they amounted to 0.012 and 0.015 mg/m^3. The minimal value out of two, 0.012 mg/m^3, was selected as an additional reference concentration characterizing an exposure level that might exert negative influence on a developing organism. This value can be applied as an additional quantitative indicator of effects produced by benzene on a developing organism when health risks are assessed under elevated exposure.

Table 2

Calculations of additional benzene RfC under chronic inhalation exposure based on key studies focusing on effects produced by this chemical on the liver

	Study (year)	
	Perez et al. (2006)	Uzma et al. (2008)
Research object	Human	Liver cells
Exposure	Occupational, 9 months	Experimental (liver cells were cultivated during 8 hours with different concentrations of benzene)
Critical effect	Hypertransaminasemia	Hepatocytes viability going down by 30 %
Threshold concentration	Benzene concentration in ambient air is 4.7 mg/m^3	1 ppm (3.26 mg/m^3)
Point of departure (POD)	4.7 mg/m^3	3.26 mg/m^3
Total uncertainty factor (MF)	MF = 300 10 is intraspecific extrapolation factor; 5 is a factor taking into account point of departure; 6 is a factor taking into account a scope of initial database	MF = 480 10 is intraspecific extrapolation factor; 6 is a factor taking into account a scope of initial database; 8 is a factor taking into account extrapolation of research results obtained under short-term exposure onto chronic (long-term) exposure
Calculated additional RfC levels	0.016 mg/m^3	0,007 mg/m^3
Selected additional RfC	Additional RfC_{liver} = 0.007 mg/m^3	

Table 3

Calculations of additional benzene RfC under chronic inhalation exposure based on key studies focusing on effects produced by the chemical on a developing organism

	Study (year)	
	Chen et al. (2000)	Lupo et al. (2011)
Research object	Pregnant women	Pregnant women
Exposure	Chronic, 9 months	Chronic, 9 months
Critical effect	Lower body weight at birth	Spina bifida (the spinal column not fully formed)
Threshold concentration	Average effective concentration is 0.36 mg/m^3	Effective concentration starting from 0.45 mg/m^3
Point of departure (POD)	0.36 mg/m^3	0.45 mg/m^3
Total uncertainty factor (MF)	MF = 30 10 is a factor taking into account point of departure; 3 is a factor taking into account a scope of initial database	MF = 30 10 is a factor taking into account point of departure; 3 is a factor taking into account a scope of initial database
Calculated additional RfC levels	0.012 mg/m^3	0.015 mg/m^3
Selected additional RfC	Additional $RfC_{development}$ = 0.012 mg/m^3	

All the obtained results on substantiating benzene RfC under chronic inhalation exposure allowed suggesting that $MPC_{av.an}$ should amount to 0.005 mg/m^3 for this chemical.

Since benzene is a proven carcinogen [6], this calculated value has been also verified as per a carcinogenic risk criterion:

$$MPC^{carc}_{av.an.} = (1 \cdot 10^{-4})/(0.027 \cdot 1/70 \cdot 20) = 0.1 \text{ mg/m}^3$$

This result indicates that the suggested value provides health safety as per carcinogenic risk.

We applied evolution models to establish that exposure to benzene in a concentration equal to 0.005 mg/m^3 would result in additional risk that didn't exceed $2 \cdot 10^{-5}$ by an age of 70 and it means that lifetime inhalation exposure to benzene in this concentration is quite safe.

Therefore, since this suggested concentration provides life and health safety (absence of impermissible (unacceptable) risk) for a whole life span, carcinogenic effects taken into account, it can be applied as average annual MPC for benzene in ambient air.

Conclusion. We have established that a reference concentration of benzene should amount to 0.005 mg/m^3 under chronic inhalation exposure and a decrease in a number of B-lymphocytes should be considered a critical effect; this decrease can determine negative effects occurring in the blood and immune systems. We have also determined additional quantitative indicators (additional reference concentrations) for benzene, 0.007 mg/m^3, the liver as a critical organ, and 0.012 mg/m^3, violated process of organism development being a critical effect.

These additional RfC can be used as additional indicators when non-carcinogenic health risks are assessed under chronic inhalation exposure to elevated concentrations of benzene.

We suggest average annual MPC for benzene to be equal to 0.005 mg/m^3 since the value is verified to provide life and health safety (absence of impermissible (unacceptable) risk) for a whole life span, probable carcinogenic effects taken into account.

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Research article

HYGIENIC ASSESSMENT OF POPULATION HEALTH RISK UNDER EXPOSURE TO CHEMICALS THAT PENETRATE DRINKING WATER FROM HOUSEHOLD WATER MIXERS

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At present a truly vital task is to evaluate possible changes in the structure and properties of drinking water occurring in the process of delivering it to end customers.

Our research aim was to perform hygienic assessment of health risks caused by consumption of drinking water with changed chemical structure influenced by domestic faucets made from zinc alloys.

Hygienic assessment of drinking water was performed to test its conformity with the requirements fixed in the Sanitary Rules and Standards SanPiN 1.2.3685-21 "Hygienic standards and requirements to providing safety and (or) harmlessness of environmental factors for people". Water samples were aged in new household water mixers with their cases made from ZAM zinc alloy (a zinc alloy doped with aluminum, magnesium, and copper) at pH6 and pH9 in accordance with the State Standard GOST 34771-2021 "Sanitary-technical water mixing and distributing accessories. Testing procedures". Health risks for children and adults and population risks were assessed for situations involving oral and cutaneous introduction according to the Guide R 2.1.10.1920-04 Human Health Risk Assessment from Environmental Chemicals.

We established that water samples aged in household water mixers contained authentically elevated concentrations of metals included into ZAM alloy, namely copper, nickel, lead, and zinc, both at pH = 6 and pH = 9. We also detected enhanced organoleptic properties: color grew by 2–2.3 times and turbidity by 2.3–5 times. Carcinogenic risks caused by consuming water with changed properties turned out to be unacceptable both for children and adults. We also established that calculated hazard index for the blood system didn't conform to hygienic requirements; calculated hazard indices for the central nervous system, liver, hormonal and reproductive systems were statistically significantly higher when people consumed drinking water with changed properties. We also calculated population carcinogenic risks for the whole population in the Russian Federation based on the maximum possible exposure to drinking water with changes in its chemical properties due to household water mixers. The total population risks amounted to approximately 131 thousand cases. Our research indicates it is necessary to develop prevention activities with a carefully planned monitoring system and control over quality and use of domestic faucets.

Key words: *drinking water, domestic faucets, heavy metals, health risks.*

Providing population with qualitative drinking water is among primary tasks the state has to tackle. Priority activities in the sphere, health risk assessment included, are determined within "Ecology" National Project which is aimed at optimizing waste disposal, decreasing ambient air pollution, and raising quality of drinking water [1–4]. Drinking water quality should conform to hygienic standards at each point in water supply

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networks [4, 5]. There are multiple factors that can influence chemical structure of drinking water on its way to consumers [6, 7]. Ageing underground water supply networks are a major factor here and they create both chemical and biological health risks [8–11]. Besides, chemical structure of drinking water is influenced by equipment located directly in consumers' homes including water hoses, low quality filters and domestic faucets [6, 12]. Impacts exerted by domestic faucets on drinking water quality are primarily determined by chemical composure of an alloy a faucet is made from as well as its inactivity under exposure to natural components occurring in drinking water under different temperatures and operating conditions [9]. Aerobic and anaerobic corrosion can occur both in water supply networks and in faucets due to effects produced by iron bacteria, oxygen, and other reactive compounds in drinking water thus making for not only destruction of a faucet but also for drinking water contamination [5, 13, 14]. Simultaneously there are changes in both organoleptic and chemical properties of drinking water. When drinking water with changed chemical properties is consumed for a long time, it leads to metabolic disorders in the body, activated peroxidation, and developing environmental diseases [15–19]. At present there are multiple works available in scientific literature with their focus on mechanisms and outcomes of drinking water getting contaminated during its transportation through water supply networks but there are very few studies concentrating on changes in drinking water quality that occur due to domestic faucets. The issue becomes even more vital given the new interstate standard that has been introduced recently, namely GOST 34771-2021 "Sanitary-technical water mixing and distributing accessories. Testing procedures"[1]; the standard stipulates testing procedures for water mixing accessories that have not been applied previously to grant permissions to distribute such products on the market. Bearing this in mind, it is truly important to analyze actual exposure to compounds that come into drinking water from domestic faucets made from zinc alloys and to perform further assessment of carcinogenic and non-carcinogenic health risks [20, 21].

Our research aim was to perform hygienic assessment of health risks caused by consumption of drinking water with changed chemical structure influenced by domestic faucets made from zinc alloys.

Data and methods. Drinking water was hygienically assessed to check its conformity with the requirements fixed in the Sanitary Rules SanPiN 1.2.3685-21 "Hygienic standards and requirements to providing safety and (or) harmlessness of environmental objects for people" (issued on January 28, 2021)[2]. Water samples were tested according to the procedure stipulated in the State Standard GOST 34771-2021 "Sanitary-technical water mixing and distributing accessories. Testing procedures". This procedure is directly developed to test this type of products taking into account their construction peculiarities and operating conditions. Water samples were taken in a consumer's apartment located in Admiralteiskiy district in Saint Petersburg in accordance with the State

[1] GOST 34771-2021. Armatura sanitarno-tekhnicheskaya vodorazbornaya. Metody ispytanii: prinyat Federal'nym agentstvom po tekhnicheskomu regulirovaniyu i metrologii 16 sentyabrya 2021 g. (vstupaet v silu s 1 iyunya 2022 g.) [GOST 34771-2021. Sanitary-technical water mixing and distributing accessories. Testing procedures: approved by the Federal Agency on Technical Regulation and Metrology on September 16, 2021 (comes into force on June 1, 2022)]. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/572732675 (July 07, 2021) (in Russian).

[2] 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 N 2 [SanPiN 1.2.3685-21. Hygienic standards and requirements to providing safety and (or) harmlessness of environmental factors for people: approved by the Order by the RF Chief Sanitary Inspector on January 28, 2021 No. 2]. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573500115 (July 07, 2021) (in Russian).

Standard GOST 31861-2012 "General requirements to taking water samples"[3]. Drinking water taken from centralized cold water supply network was used as a research object. Water samples (the test and the reference ones) were preliminarily prepared only to adjust pH up to 6 and 9 (the maximum and minimum permissible levels according to SanPiN 1.2.3685-21). The samples were prepared as follows. First, the test medium No. 1 or drinking water with pH = 6 was created by adding sulfuric acid solution 0.1N and controlling the result with pH-meter until pH = 6 was reached. Second, the test medium No. 2 or drinking water with pH = 9 was created by adding sodium hydrocarbonate solution 1N and controlling the result with pH-meter until pH = 8.43 was reached; after that, sodium hydroxide solution 1N was added until pH = 9.0 was reached (a detailed testing procedure is described in Item 14.3 of the GOST 34771-2021 (comes into force on June 01, 2022)). Therefore, prior to the test all the test and reference samples 1 and 2 corresponded to hygienic standards as per all the examined indicators (color, turbidity, hydrogen indicator, iron, manganese, copper, nickel, zinc, lead, aluminum, and nitrates). Both test and reference samples were prepared so that the maximum and minimum permissible pH levels were reached. Water samples with extreme pH values were aged in new domestic faucets with their cases made from ZAM zinc alloy (a zinc alloy doped with aluminum, manganese, and copper). Water from the centralized cold water supply system was kept inside the faucets for 16 or 64 hours. 16 hours were taken as a usual period of time during which a faucet was not actively used in households on working days; during this time water usually remains in a faucet case entering contacts with its inside surfaces and various admixtures can migrate from them. 64 hours were taken as a period of time during which a faucet was not used on weekends (GOST 34771-2021, comes into force on June 01, 2022). Water samples were kept under relevant temperatures during the whole test. The test was performed on a volume of water which usually fills a faucet and amounts to 250–300 ml. Overall, 90 drinking water samples were analyzed; 54 out of them were the test ones (27 samples per each extreme pH value) and 36 were the reference ones (18 samples per each extreme pH value).

Health risks were assessed for oral introduction and cutaneous exposure for children and adults in accordance with the Guide "Human Health Risk Assessment from Environmental Chemicals"[4]. Chemicals doses under oral introduction and cutaneous exposure were calculated using recommended reference values of exposure factors (Appendix 1 to the Guide R 2.1.10.1920-04). When calculating doses, we used simple mean values of maximum chemical concentrations obtained after water samples ageing in faucets for 16 hours (50 % samples) and 64 hours (50 % samples). Comparative hygienic assessment of population carcinogenic risks was performed as per maximum exposure to the analyzed chemicals in drinking water for people living in Orenburg, Saint Petersburg, Moscow, and the Russian Federation. We determined the upper limit of possible population carcinogenic risk

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[3] GOST 31861-2012. Mezhgosudarstvennyi standart. Voda. Obshchie trebovaniya k otboru prob vody: prinyat Mezhgosudarstvennym sovetom po standartizatsii, metrologii i sertifikatsii (protokol ot 15 noyabrya 2012 g. N 42), vveden v deistvie s 1 yanvarya 2014 g. [GOST 31861-2012. Interstate standard. Water. General requirements to taking water samples: approved by the Interstate Council on standardization, metrology and certification (the meeting report dated November 15, 2012 No. 42), came into force on January 1, 2014]. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200097520 (July 07, 2021) (in Russian).

[4] P 2.1.10.1920-04. Rukovodstvo po otsenke riska dlya zdorov'ya naseleniya pri vozdeistvii khimicheskikh veshchestv, zagryaznyayushchikh sredu obitaniya: utv. i vvedeno v deistvie Pervym zamestitelem Ministra zdravookhraneniya Rossiiskoi Federatsii, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii G.G. Onishchenko 5 marta 2004 g. [R 2.1.10.1920-04. Human Health Risk Assessment from Environmental Chemicals: approved and enacted by G.G. Onishchenko, the First Deputy to the RF Public Healthcare Minister and the RF Chief Sanitary Inspector on March 5, 2004]. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200037399 (July 10, 2021) (in Russian).

that was calculated as a sum of population risks caused by all carcinogens in water.

All data were statistically analyzed using Statistica 10.0. Analyzed quantitative attributes corresponded to normal distribution ("chi-square" test), therefore, all obtained quantitative attributes were described with mean value (*M*) and standard error of the mean (*m*). Statistical significance of differences between independent groups was evaluated with Student's parametric t-test.

Differences were considered statistically significant at $p \le 0.05$ and were calculated with Fisher's exact test.

Results and discussion. Hygienic assessment of drinking water quality revealed an authentic 2–2.3 times increase in color and 2.3–5.0 times increase in turbidity in the test samples. Changes in organoleptic properties, notably turbidity, were due to elevated concentrations of metals in the samples (Table 1).

We established that analyzed water samples aged in domestic faucets contained authentically higher concentrations of metals included in ZAM alloy, namely copper, nickel, lead, and zinc, both at pH = 6 and pH = 9. Copper concentration was by 30 times authentically higher in both test samples (pH = 6 and pH = 9). The test samples also contained lead in concentrations exceeding MPC and they were by 6.7 times higher than in the reference samples. We also established that nickel contents grew by almost 6 times at pH = 9 thus violating the hygienic standards; but they grew only by 2 times at pH = 6 and remained within permissible levels. Zinc was established to contaminate drinking water more intensely at lower pH values (pH = 6) against higher ones (pH = 9); its concentration exceeded MPC in the former case.

Overall drinking water contamination grew by 3.0–3.5 times at both pH values. We should note that hydrogen indicator grew in the test samples and this was due to oxidation and lower oxygen concentration.

Heavy metals penetrate drinking water in high quantities due to effects produced by domestic faucets; these metals belong to the first hazard category (lead and nickel) and their occurrence results in changes in chemical structure of drinking water. According to data obtained in multiple studies, elevated lead concentrations in drinking water induce metabolic disorders which, in their turn, cause various diseases of the endocrine, immune, and nervous systems. Besides, lead is able to accumulate in organs and tissues as well as penetrate through the placental and blood-brain barriers [17, 19]. Lead produces negative effects on the reproductive system violating spermatogenesis in men and facilitating hormonal disorders in women that are usually accompanied with more frequent miscarriages and congenital malformations. We should note that lead and nickel influence hemopoiesis by activating peroxidation that results in damage to cellular membranes; they can also act as a strumogenic factor.

Table 1

Chemicals concentrations in drinking water ($M \pm m$, compared to MPC)

Parametr	Test	Reference 1	Test	Reference 2
	pH = 6		pH = 9	
Color	**1.91 ± 0.06***	0.88 ± 0.06	**1.53 ± 0.04***	0.98 ± 0.02
Turbidity	**2.42 ± 0.09***	0.47 ± 0.07	**1.33 ± 0.07***	0.58 ± 0.03
Hydrogen indicator	0.79 ± 0.02	0.70 ± 0.07	0.96 ± 0.07	0.87 ± 0.09
Iron	0.77 ± 0.04	0.75 ± 0.06	0.75 ± 0.01	0.60 ± 0.04
Manganese	0.24 ± 0.01	0.19 ± 0.001	0.15 ± 0.01	0.15 ± 0.01
Copper	**0.15 ± 0.02***	0.005 ± 0.001	**0.16 ± 0.01***	0.002 ± 0.0001
Nickel	**0.94 ± 0.07***	0.40 ± 0.001	**3.54 ± 0.12***	0.64 ± 0.01
Zinc	**1.78 ± 0.09***	0.01 ± 0.001	**0.51 ± 0.06***	0.004 ± 0.0001
Lead	**1.93 ± 0.03***	0.29 ± 0.01	**1.65 ± 0.11***	0.27 ± 0.03
Aluminum	0.28 ± 0.04	0.21 ± 0.01	0.38 ± 0.07	0.19 ± 0.07
Nitrates	0.01 ± 0.001	0.02 ± 0.001	0.02 ± 0.001	0.02 ± 0.004

Note: * means validity of differences $p \le 0.05$.

Hygienic assessment of carcinogenic risk for adult population revealed unacceptable carcinogenic risks caused by consuming drinking water with its chemical properties changed due to domestic faucets. Total carcinogenic risk under oral introduction was by 4 times higher at pH = 6 and by 6 times higher at pH = 9 than for reference samples. Besides, unacceptable total carcinogenic risk (CR_{wo} = 1.13E^{-04} at pH = 6 and CR_{wo} = 1.59E^{-04} at pH = 9) for adult population under oral introduction was also associated with consuming drinking water from centralized cold water supply systems (reference samples) (Table 2).

Acceptable carcinogenic risks were established for children for consuming drinking water from centralized water supply systems whereas drinking water aged in faucets created unacceptable carcinogenic risks for them (Table 2). Therefore, there is statistic authentic evidence that carcinogenic risks caused by chemicals occurring in drinking water due to its exposure to faucets are not only unacceptable but are also significantly (by many times) higher than risks caused by consuming common drinking water form centralized water supply systems.

It is important to mention that carcinogenic risks caused by consuming drinking water with changed chemical properties are within the 3rd range both for adults and children and require urgent health-improving and preventive activities.

Our hygienic assessment of non-carcinogenic risks revealed that maximum hazard indices, both for adults and children, were determined by contents of zinc, copper, nickel and lead in water samples. An important fact is that hazard indices calculated for all samples at different pH values are significantly higher for children than for adults; it is primarily due to greater exposure to chemicals relative to an average body mass (Table 3).

Table 2

Individual (*CR*) and total carcinogenic risks (CR_{wo}) caused by drinking water consumption

Population	pH	Sample	Nickel	Lead	CR_{wo}
Adults	pH6	test	**1.94E^{-04}***	**1.98E^{-04}***	**3.93E^{-04}***
		reference 1	8.28E^{-05}	3.00E^{-05}	1.13E^{-04}
	pH9	test	**7.28E^{-04}***	**1.69E^{-04}***	**8.97E^{-04}***
		reference 2	1.31E^{-04}	2.78E^{-05}	1.59E^{-04}
Children	pH6	test	**9.06E^{-05}***	**9.26E^{-05}***	**1.83E^{-04}***
		reference 1	3.86E^{-05}	1.40E^{-05}	5.26E^{-05}
	pH9	test	**3.40E^{-04}***	7.90E^{-05}	**4.19E^{-04}***
		reference 2	6.13E^{-05}	1.30E^{-05}	7.42E^{-05}

Note: * means differences are valid at $p \leq 0.05$.

Table 3

Hazard indices (*HI*) for chemicals in drinking water

Chemical	Adults				Children			
	pH = 6		pH = 9		pH = 6		pH = 9	
	test	reference 1	test	reference 2	test	reference 1	test	reference 2
Iron	0.022	0.021	0.021	0.017	0.05	0.05	0.05	0.04
Manganese	0.005	0.004	0.002	0.003	0.01	0.01	0.01	0.01
Copper	0.228*	0.007	0.240*	0.003	0.53*	0.02	0.56*	0.01
Nickel	0.027	0.012	0.101*	0.018	0.06	0.03	0.24*	0.04
Zinc	0.847*	0.004	0.243*	0.002	1.98*	0.01	0.57*	0.00
Lead	0.157*	0.024	0.134*	0.022	0.37*	0.06	0.31*	0.05
Aluminum	0.002	0.001	0.002	0.001	0.00	0.00	0.01	0.00

Note: * means differences are valid at $p \leq 0.05$.

Table 4

Hazard indices (*HI*) for critical organs and systems affected by the analyzed chemicals

Organs / systems	Adults				Children			
	pH = 6		pH = 9		pH = 6		pH = 9	
	test	reference 1	test	reference 2	test	reference 1	test	reference 2
GI tract	0.25	0.02	**0.34***	0.02	**0.59***	0.04	**0.80***	0.05
CNS	**0.16***	0.03	0.14	0.03	**0.38***	0.07	**0.32***	0.06
Blood	**1.07***	0.08	**0.52***	0.08	**2.50***	0.18	**1.21***	0.19
CVS	0.04	0.03	0.12	0.04	0.09	0.06	0.27	0.09
Immune system	0.02	0.02	0.02	0.02	0.05	0.05	0.05	0.04
Liver	**0.25***	0.02	**0.34***	0.02	**0.59***	0.04	**0.80***	0.05
Mucosa	0.02	0.02	0.02	0.02	0.05	0.05	0.05	0.04
Hormonal system	**0.16***	0.02	**0.13***	0.02	**0.37***	0.06	**0.31***	0.05
Reproductive system	**0.16***	0.02	**0.13***	0.02	**0.37***	0.06	**0.31***	0.05

Note: * means differences are valid at $p \leq 0.05$.

Table 5

Health risks under cutaneous exposure to chemicals in drinking water with changed chemical properties

Sample	pH	Children		Adults	
		HI	CR_{wd}	*HI*	CR_{wd}
Test	pH6	$5.45E^{-09}$	$2.32E^{-12}$	$3.32E^{-09}$	$7.07E^{-12}$
Reference 1		$1.04E^{-09}$	$6.66E^{-13}$	$6.35E^{-10}$	$2.03E^{-12}$
Test	pH9	$6.95E^{-09}$	$5.3E^{-12}$	$4.24E^{-09}$	$1.61E^{-11}$
Reference 2		$1.19E^{-09}$	$9.39E^{-13}$	$7.25E^{-10}$	$2.86E^{-12}$

Table 6

Probable population carcinogenic risk caused by consuming drinking water with its chemical quantities changed due to domestic faucets (CR pop), a number of cases

Chemical	pH	Orenburg	Saint Petersburg	Moscow	Russian Federation
Nickel	pH = 6	111	1,046	2,455	28,357
	pH = 9	417	3,920	9,213	106,413
Lead	pH = 6	113	1,066	2,506	28,942
	pH = 9	97	910	2,139	24,703
An upper limit of probable population carcinogenic risk	pH = 6	225	2,116	4,973	57,445
	pH = 9	5,148	4,830	11,352	131,115

Having assessed risks of adverse effects for critical organs and systems, we established that risks for blood didn't conform to hygienic requirements when drinking water aged in faucets was consumed and this was so both for adults and children. Besides, we detected statistically significant differences in non-carcinogenic risk rates for the central nervous system, liver, hormonal and reproductive systems (Table 4).

We also performed hygienic assessment of hazard indices for chemicals in drinking water under cutaneous exposure and established that risks of adverse effects on critical organs and systems were acceptable both for adults and children. At the same time probability of carcinogenic effects due to cutaneous exposure to drinking water with changed chemical properties was within a range from $6.66E^{-13}$ to $5.3E^{-12}$ for children and from $2.03E^{-12}$ to $1.61E^{-11}$ for adults at various pH values; this meant that risks were acceptable (Table 5).

Assessment of population health risk caused by consuming drinking water with its chemical properties changed due to using domestic faucets is a most vital stage in assessing risks of possible carcinogenic effects.

This work involved comparative assessment of population carcinogenic risks caused by drinking water aged in domestic faucets made from zinc alloys for people living in Orenburg, Saint Petersburg, Moscow, and the RF as a whole.

Probable population carcinogenic risk calculated for maximum exposure amounted to 225 (at pH = 6) and 513 (at pH = 9) additional oncologic disease cases for population in Orenburg that was equal to 572.82 thousand people; 2,116 at pH = 6 and 4,829 at pH = 9 additional cases for population in Saint Petersburg that was equal to 5,384.34 thousand people. In a megacity (Moscow as an example, overall population amounts to 12,655.1 thousand people) population carcinogenic risk may vary from 4.97 thousand additional cases (at pH = 6) to 11.35 thousand (at pH = 9). Given that domestic faucets of this label are used everywhere in the Russian Federation, a number of additional oncologic disease cases may exceed 131 thousand (Table 6).

Health risk assessment always involves assessing uncertainty. In our research this uncertainty is associated with assessing exposure under just a conditional scenario of effects produced by chemicals. Besides, only 7 metals penetrating drinking water from domestic faucets were taken into account since the analyzed alloy was made from them; exposure scenarios and routes can't be considered complete either. We should also bear in mind that the tests were accomplished according to the State Standard GOST 34771-2021 "Sanitary-technical water mixing and distributing accessories. Testing procedures" that comes into force on June 01, 2022, that is, all the existing laboratories have not been certified to performed tests according to it yet. Nevertheless, comparative assessment of risks caused by drinking water with its chemical properties changed due to domestic faucets provides a quite truthful picture of occurring adverse effects for organs and systems in the body, including some probable remote consequences (malignant neoplasms).

Conclusions. The research revealed that drinking water changed due to destruction of metals used for manufacturing domestic faucets from zinc alloys. The process results in heavy metals penetrating drinking water and these metals are tropic for organs and systems in the body.

Hygienic assessment revealed that water with changed chemical properties contained nickel and lead in quantities deviating from hygienic standards; this water also didn't conform to these standards as per its organoleptic properties (color and turbidity).

Total carcinogenic risk caused by oral introduction of chemicals with drinking water was unacceptable both for children ($4.19E^{-04}$) and adults ($8.97E^{-04}$) and was by 10 times higher than risk calculated for reference samples.

Bearing in mind that rather small amount of drinking water is exposed to faucets for a long time, non-carcinogenic risks for critical organs and systems conformed to hygienic requirements both under oral introduction and cutaneous exposure, excluding the blood system (*HI* for blood = 2.5 for children, *HI* for blood = 1.07 for adults at pH = 9); the major contribution into *HI* was made by exposure to lead.

We should note that risks were calculated taking into account only 7 metals and it created the greatest uncertainty in our risk assessment.

Our research indicates it is necessary to develop preventive activities with a well-planned system for monitoring and control over quality and operation conditions for domestic faucets used in the Russian Federation.

Future prospects in further investigations in the sphere might involve examining effects produced on health of pregnant women, newborns and other vulnerable population groups by drinking water with its chemical properties changed due to used of domestic faucets made form zinc alloys. Future studies should take into account complete exposure routes and scenarios and involve assessing all chemicals that may occur in drinking water.

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Research article

ENVIRONMENTAL CONTAMINATION WITH METALS AS A RISK FACTOR CAUSING DEVELOPING AUTOIMMUNE THYROIDITIS IN CHILDREN IN ZONES INFLUENCED BY EMISSIONS FROM METALLURGIC ENTERPRISES

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Chemical environmental factors trophic for the endocrine system and its organs produce negative influence on it that becomes apparent through growing incidence and pathomorphism of endocrine diseases.

Our test group was made up of 102 children with diagnosed autoimmune thyroiditis (AIT) who were chronically exposed to metals (lead, manganese, nickel, chromium, and zinc) being components in emissions from metallurgic enterprises in Perm region. Our reference group included 46 children with AIT who lived beyond zones influenced by the aforementioned enterprises in areas with the sanitary-hygienic situation being relatively favorable. We comparatively analyzed the results of clinical and ultrasound examinations that focused on evaluating children's thyroidal and immune state.

A growth in incidence with thyroiditis amounted to 63.6 % on the test territory over 10 years and it was 1.6 times higher than on average in the region (40.8 %); there was no growth in the indicator detected on the reference territory. Concentrations of chromium, nickel, lead, zinc, and manganese higher than regional background level were 1.7–5.5 times more frequently detected in blood of children from the test group against the reference one. A number of AIT cases was higher among exposed boys (by 2.0 times, p = 0.070); exposed children also had higher Ig A, M, and G contents in blood serum (by up to 2.9 times, p = 0.015–0.056), higher TSH levels (by 2.0 times, p = 0.096), and lower free T4 contents (by 5.4 times, p = 0.057). Diffuse damage to the thyroid gland was by 1.3 times more frequent under exposure to adverse factors created by metallurgic production; AIT combined with other diseases was also more frequent (p = 0.041).

Rates and growth in incidence of thyroid gland diseases and thyroiditis are by 1.3–2.3 times higher among children and teenagers living on territories where metallurgic enterprises are located against the same indicators on territories where sanitary-hygienic situation is relatively favorable. We detected less apparent gender-related differences in AIT frequency, a greater number of improper thyroidal state, elevated risks of diffuse changes in the thyroid gland and activation of humoral immune response that was by 2.2–3.4 times more frequent together with concomitant damage to other systems under elevated contents of metals in blood.

Key words: *incidence, autoimmune thyroiditis, children and teenagers, metals, less apparent gender-related differentiation, cause–effect relations, diffuse structural changes, hypothyroidism.*

According to federal statistical data provided by the Public Healthcare Ministry of the Russian Federation, diseases of the thyroid gland hold the second rank place among endocrine pathologies following obesity and their prevalence amounts to 10.6 cases per 1,000 children. Analysis of statistical data in dynamics has revealed that there hasn't been any drop in this prevalence since 2015 [1, 2].

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Reversible risk factors taken into account, early detection and treatments of diseases of the thyroid gland in children and teenagers are vital for preventing compensatory hyperplasia of the thyroid gland tissue, hormonal imbalance and associated delays in sexual, physical, and mental development. Efficient diagnostics of the pathology is provided by detecting risk factors, early clinical signs and symptoms [3–6].

Autoimmune thyroiditis (AIT) is a multifactorial disease with complicated etiopathogenesis when genetically determined peculiarities of immune responses are realized under exposure to environmental factors including technogenic chemicals and iodine deficiency [1, 7–9].

Metals are widely spread in environmental objects and are able to seriously damage the body when penetrating it from the environment. Research results described by L.N. Palagina indicate that thyroid gland pathologies become much more frequent when blood is contaminated with chromium and lead [10].

Autoimmune processes play a significant role among various immune pathologic impacts exerted by metals. B.A, Rozhko reviewed the current situation with autoimmune thyroiditis and highlighted that environmental factors induced an autoimmune process in people who were genetically predisposed to AIT; these factors accounted for 31.8 % among cause-effect relations regarding development of autoimmune diseases of the thyroid gland [11].

A child's body is the most vulnerable to technogenic environmental factors with their contribution to health disorders reaching 30 % [12][1]. Excessive introduction of metals into children's bodies in cities where metallurgic enterprises are located produces direct thyreocytotoxic effect; they can make for developing chronic inflammatory diseases of the thyroid gland that have autoimmune genesis or aggravate their clinical course in case they are already present. These diseases are often combined with other autoimmune pathologies [13, 14].

Our research aim was to establish clinical, laboratory and ultrasound peculiarities of autoimmune thyroiditis in children who were chronically exposed to metals in the environment.

Materials and methods. Our test group was made up of 102 children with previously diagnosed autoimmune damage to the thyroid gland; they lived on territories where metallurgic plants were located. Our reference group included 46 children with diagnosed AIT who lived on a territory where sanitary-hygienic situation was relatively favorable.

To reveal AIT peculiarities in exposed children, we comparatively analyzed average group results of clinical, laboratory and ultrasound examinations and frequency of their deviations from physiological standards. Both groups were comparable as per age (13.79 ± 12.63 in the test group and 13.10 ± 7.95 in the reference one, $p = 0.688$) and social status ($p > 0.05$).

Incidence of thyroid gland diseases and thyroiditis among children depending on a territory where they lived was comparatively analyzed based on statistical data collected in 2010–2019 and provided by the Perm Regional Medical Information and Analytical Center.

We examined contents of several metals in blood (lead, manganese, nickel, chromium, and zinc) according to the Methodical guidelines[2] on *Agilent 7500cx* mass spectrometer

[1] O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2019 godu: Gosudarstvennyi doklad [On sanitary-epidemiologic welfare of the population in the Russian Federation in 2019: The State report]. Moscow, The Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2020, 299 p. (in Russian).

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("Agilent Technologies Inc."). All the results were compared with background regional levels that amounted to 0.0144 ± 0.0067 mg/dm^3 for lead; 0.013 ± 0.00397 mg/dm^3, manganese; 0.00225 ± 0.00202 mg/dm^3, nickel; 0.0027 ± ± 0.00199 mg/dm^3, chromium^{6+}; 4.77705 ± ± 0.7517 mg/dm^3, zinc.

Thyroidal state was evaluated based on determining levels of thyroid-stimulating hormone (TSH), free thyroxine (T4), and antibodies to thyroperoxidase (AB-TPO) in blood. Levels of immunoglobulins Ig G, M and A were analyzed in blood serum with radial immunodiffusion (Manchini method) to determine the current state of humoral immune response.

Ultrasound examination of the thyroid gland (morphometry and volumetry) was accomplished as per conventional procedures on *"VividE9"* (Vingmed Ultrasound AS) and *"AplioXG"* (Toshiba AplioXGSSA-790A) expert devices and the results were interpreted in comparison with conventional reference values [15].

All the examinations were accomplished in accordance with ethical principles stipulated by the Helsinki Declaration (2013) and the RF National standard GOST-R "Good clinical practice" (ICHE6 GCP).

Statistical and mathematical analysis was performed with conventional parametric statistic procedures. Intergroup differences were analyzed based on comparing mean values of the indicators (M) and standard deviation (SD) ($M \pm SD$). Pearson's chi-square (χ^2) was used to compare qualitative features. Odds ratio (OR) was used to quantitatively measure an effect when relative indicators were compared; a significance of a correlation between an outcome and a factor was considered to be proven in case the confidence interval was beyond the boundary of an area where no effects were detected and this boundary was considered to be equal to 1. Pearson's correlation coefficient (r) was calculated to quantitatively assess correlations between the indicators and correlation intensity was evaluated as per the Chaddock scale. "Metal concentration in blood – incidence with AIT, morphological and functional disorders in the thyroid gland" dependence was analyzed by building up one-factor regression models with included values of regression coefficient ($b1$) and calculated determination coefficient (R^2). The results were considered statistically significant at $p \leq 0.05$.

Results. The environment in Perm region where all the examined children live has moderate and mild natural iodine deficiency. Incidence of thyroid gland diseases in the region grew by 1.5 times over 10 years and reached 6.91 ‰. Official statistical data were analyzed in detail to establish that overall incidence of thyroid gland diseases grew by 1.65 time among children who lived in a zone exposed to metallurgic production (from 6.16 to 10.17 ‰) whereas it grew only by 1.3 times on territories where the sanitary-hygienic situation was relatively favorable (from 2.1 to 2.62 ‰). Average regional growth in incidence of thyroiditis amounted to 40.8 % (from 0.49 to 0.69 ‰); it was 63.6 % on the test territory but the incidence rates were stable on the reference territory (Table 1).

Table 1

Incidence of thyroid gland diseases and thyroiditis among children in 2010 and 2019, ‰

Year of research	Perm region	Test territory	Reference territory
Incidence of thyroid gland diseases			
2010	4.69	6.16	2.1
2019	6.91	10.17	2.62
Incidence of thyroiditis			
2010	0.49	0.55	0.40
2019	0.69	0.90	0.35

Metal contents in blood were analyzed using chemical-analytical procedures; the examination revealed that a share of children with lead contents in blood being higher than background levels was by 2.3 times higher in the test group against the reference one ($p < 0.001$); elevated lead contents, by 5.5 times ($p < 0.001$); elevated nickel contents, by 2.0 times ($p = 0.027$); elevated chromium contents, by 1.7 times ($p < 0.001$); elevated zinc contents, by 2.7 times ($p < 0.001$) (Table 2).

Table 2

A share of samples with elevated metal contents in children's blood, %

Metals	Test group, $n = 102$		Reference group, $n = 46$		χ^2	p
	n	%	n	%		
Chrome^{6+}	96	94.1	26	56.5	23.85	< 0.001
Zinc	95	93.1	16	34.8	57.58	< 0.001
Lead	61	59.8	12	26.0	14.42	< 0.001
Manganese	61	59.8	5	10.8	30.73	< 0.001
Nickel	36	35.3	8	17.4	9.44	0.003

Table 3

Results obtained through examining hormone and immunological status in children, $M \pm SD$

Indicator	Test group, $n = 102$	Reference group, $n = 46$	p
TSH, µIU/cm^3	2.41 ± 3.87	1.87 ± 2.56	0.317
Free T4, pmol/dm^3	13.8 ± 6.62	14.6 ± 4.07	0.369
Antibodies to TPO, IU/cm^3	189.91 ± 658.59	79.56 ± 164.94	0.115
IgG, g/dm^3	12.42 ± 3.77	11.32 ± 2.73	0.047
IgM, g/dm^3	1.49 ± 0.66	1.36 ± 0.40	0.144
IgA, g/dm^3	1.81 ± 0.92	1.66 ± 0.64	0.254

We established a statistically significant correlation between growing incidence of AIT and elevated contents of lead ($R^2 = 0.68$; $b1 = 125.6$; $p \leq 0.0001$), manganese ($R^2 = 0.17$; $b1 = 83.9$; $p \leq 0.05$), nickel ($R^2 = 0.32$; $b1 = 98.9$; $p = 0.02$) and zinc ($R^2 = 0.70$; $b1 = 18.1$; $p = 0.04$) in blood.

We didn't reveal any authentic differences between the groups regarding age structure of patients with AIT since pre-adolescent children (aged 7–13) accounted for 26–27.4 % in both groups and adolescent children (older than 13) accounted for 72.6–74 % ($p > 0.1$).

Having examined sex structure in two groups, we revealed that males tended to have AIT 2 times more frequently than females in the test group in comparison with the reference one (26.4 against 13 %, $p = 0.070$).

Average group levels of hormones in blood (TSH and free T4) didn't have any statistically significant differences in both groups ($p = 0.31$–0.23) (Table 3). However, there was an ascending trend in a number of children with signs of sub-clinical and manifest hypothyroidism detected in the test group as it was indicated by 2.2–5.4 times greater share of samples with elevated TSH contents (20 (19.6 %) against 4 (8.7 %); $\chi^2 = 2.78$; $p = 0.096$) and lower free T4 contents (12 (11.8 %) against 1 (2.2 %); $\chi^2 = 3.64$; $p = 0.057$) in blood. We established a statistically significant correlation between growing TSH contents and elevated nickel and zinc contents in blood ($b1 = 2.99$–3.2; $R^2 = 0.49$–0.51; $p < 0.001$).

Average group contents of antibodies to thyroidal peroxidase were by 2.4 times higher among children from the test group against those from the reference one but this difference was not statistically significant ($p = 0.11$) (Table 3).

Having evaluated humoral immunity, we established that children with metal contents in their blood exceeding background levels had elevated contents of immunoglobulins in their blood serum by 1.8–2.9 times more frequently; it was true for IgG (30 (29.4 %) against 5 (10.9 %); $\chi^2 = 6.04$; $p = 0.015$; $OR = 3.42$, $CI = 1.23$–9.49); IgM (19 (18.6 %) against 3 (6.5 %); $\chi^2 = 3.67$; $p = 0.056$; $OR = 3.28$, $CI = 0.92$–11.71); IgA (37 (36.3 %) against 9 (19.6 %); $\chi^2 = 4.13$; $p = 0.043$; $OR = 2.34$, $CI = 1.02$–5.38).

Ultrasound examination of the thyroid gland and surrounding tissues revealed certain changes; their frequency is given in Table 4. Children who were chronically exposed to adverse chemical factors had diffuse changes in thyroidal tissues revealed by ultrasound examination of the thyroid gland; these changes were typical for AIT and were registered in such children by 1.3 times more frequently than in children from the reference group (74 (72.5 %) against 25 (54.3 %); $\chi^2 = 4.74$, $p = 0.030$) who mostly tended to have only minimal changes in the organ and tissues (28 (27.5 %) against 21 (45.7 %); $\chi^2 = 4.74$, $p = 0.03$). A probability of diffuse changes in the thyroid gland was by 2.2 times higher for children with AIT who were exposed to metals against children with the same pathology who lived on a territory where the sanitary-hygienic situation was relatively favorable ($OR = 2.22$, $CI = 1.08$–4.58).

Table 4

A share of children with changed indicators revealed through ultrasound scanning of the thyroid gland, %

Ultrasound scanning results	Test group, $n = 102$		Reference group, $n = 46$		χ^2	p
	n	%	n	%		
Increased volume of the thyroid gland	65	63.7	24	52.2	1.76	0.185
Diffuse structural changes	74	72.5	25	54.3	4.74	0.030
Minimal structural changes	28	27.5	21	45.7	4.74	0.030
Enhanced vascularization of the gland	77	75.4	33	71.7	0.23	0.629
Increased linear blood flow velocity	35	34.3	16	34.8	0.003	0.956
Decrease in peripheral resistance indices	38	37.2	19	41.3	0.22	0.640
Reactive hyperplasia of regional lymph nodes	58	56.8	26	56.5	0.002	0.970

Growing volume of the thyroid gland, enhanced vascularization, and reactive changes in regional lymph nodes as per hyperplasia type were detected with similar frequency regardless of a territory where examined children lived ($p = 0.185$–0.97) (Table 4).

Correlation analysis confirmed a moderate inverse correlation between lead contents in blood and values of peripheral resistance indices ($r = -0.35$, $p = 0.045$); a significant direct correlation between nickel contents in blood and volume of the thyroid gland ($r = 0.58$, $p = 0.027$).

Having analyzed concomitant pathologies, we revealed that children who were exposed to adverse chemical factors due to metallurgic production tended to have alopecia areata (L63) more frequently than children from the reference group (15 (14.7 %) against 2 (4.3 %); $\chi^2 = 3.34$; $p = 0.068$). Although diseases that occur due to immunologic reactivity disorders, such as dermatitis (L20–30) (15 and 16 %), bronchial asthma (J45) (12 and 18 %), and other disorders involving the immune mechanism (D89.8; D89.9) (25 and 25 %) as well as such endocrine pathologies as obesity and other hyperalimentation (E65–E68) (24.5 and 17.4 %) were detected with similar frequency, overall burden of concomitant diseases was by 1.3 times higher for children who lived in a zone influence by emissions form metallurgic production than for children from the reference group (4.2 ± 4.07 against 3.1 ± ± 2.36 diseases, $p = 0.041$).

Results and discussion. Our study on incidence of thyroiditis in Perm region revealed that average regional incidence rates were similar to those in the country in general (0.69 ‰ in 2019 in Perm region and 0.81 ‰ in the RF in 2018) [1, 8]. Our data on higher incidence of thyroid gland diseases and thyroiditis among children living on territories where certain industries are located against their counterparts living on territories where the sanitary-hygienic situation is relatively favorable are well in line with data obtained by other authors in previous studies [16, 17].

We established that children who lived on a territory where metallurgic production was located tended to have hormonal disorders by 2.0–4.5 times more frequently. Although most examined children (80.0–88.0 %) didn't have any functional disorders in the thyroid gland in spite of the disease, we should bear in mind that untimely detection of hypofunction has negative consequences for children's development. This substantiates the necessity to perform control over thyroidal status in children with AIT [17–19].

A greater burden of AIT and concomitant diseases in children who are chronically exposed to adverse chemical factors determines deteriorating forecasts for the disease development and creates additional difficulties in diagnosing and treating it. This increased burden is probably due to common risk factors and common involvement of different sections in pathogenetic mechanisms of the disease development [13, 14, 20, 21].

Results obtained by ultrasound scanning of the thyroid gland indicate that more significant changes in the thyroid gland structure are a cardinal sign of developing AIT associated with chemical environmental factors. This confirmed that ultrasound scanning remains a valuable diagnostic instrument. Absence of any apparent differences between results of hormonal and ultrasound scanning might be due to Perm region being somewhere in between territories with mild and moderate iodine deficiency [22–24].

Created mathematical models and revealed correlations prove negative effects produced by lead, manganese, nickel, and zinc and leading to adverse changes in the structure and functioning of the thyroid gland.

Conclusions:

1. In Perm region rates and growth in incidence of thyroid gland diseases is by 1.7 times higher among children living on territories with developed metallurgic production than on average in the region and by 2.6 times higher than on a territory where the sanitary-hygienic situation is relatively favorable.

2. Gender-related differences in frequency of detecting AIT tend to decrease among children with nickel, lead, zinc, and manganese contents in blood being higher than background regional levels; such children also tend to have sub-clinical and manifest hypothyroidism by 2.2–4.5 times higher than their counterparts from the reference group.

3. A probability of diffuse changes in the thyroid gland structure and activation of humoral immune response is by 2.2–3.4 times higher under exposure to chemical environmental factors that are tropic for the endocrine system and its organs.

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Research article

FUEL AND ENERGY ENTERPRISES AS OBJECTS OF RISK-ORIENTED SANITARY-EPIDEMIOLOGIC SURVEILLANCE

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The present research aims to provide analytical support for the risk-oriented model of sanitary-epidemiologic control over fuel and energy enterprises. The research task were to reveal the most common violations of sanitary-epidemiologic requirements by fuel and energy enterprises; to determine priority environmental indicators that should be included into a program of laboratory support for control and surveillance activities; to estimate actual impacts exerted by fuel and energy enterprises.

We established that in 2020 there were totally more than 6 thousand economic entities that performed their activity in the sphere of "Electric energy, gas and steam supply; air conditioning". Since fuel and energy enterprises tend to be located close to residential areas, violations in the sphere of ambient air protection (Clause 20) involve negative influence on a considerable number of people. In 2020 the greatest number of revealed violation regarding requirements to ambient air quality was registered for heat and power engineering enterprises in the Far East Federal District (FEFD), Siberian FD (SFD), Central FD (CFD), and Ural FD (UFD) and varied from 10.6 to 42.9 %. Average potential health risk (R^l_{av}) per one economic entity amounted to $5.44 \cdot 10^{-4}$ for heat and power engineering. A share of economic entities dealing with this economic activity and assigned into extremely high and high (the 1st and 2nd accordingly) risk categories as per potential health risk amounts to 21.7 %. A scale of exposure (M^l_i) for economic entities operating in heat and power engineering can reach 930 thousand people. The greatest share of economic entities belonging to the 1st and 2nd risk categories as per potential health risk is registered in the SFD, Volga FD, CFD, UFD, and FEFD and amounts to 78.5 %.

The greatest average potential health risk per one economic entity (R^l_{av}) in the sphere of "Electric energy, gas and steam supply; air conditioning" was registered in the Siberian Federal District and amounted to $9.88 \cdot 10^{-4}$. The greatest numbers of economic entities operating in the sphere of "Electric energy, gas and steam supply; air conditioning" that belonged to the 1st and 2nd risk categories as per potential health risk are located in the Krasnoyarsk region (37.9 %), Kemerovo region (32.6 %), Tomsk and Omsk regions (29.7 % each).

Key words: *heat and power engineering enterprises, emissions, ambient air quality, potential health risk, a scale of exposure, violation of legislation.*

Energy security of the country and its regions, providing necessary support to socio-economic development, preservation of existing workplaces in the brunch and creation of new ones together with providing sufficient personnel and industrial competences are top priorities outlined in the State Energy Strategy of the Russian Federation [1]. The most significant trends in the development of the Russian Energy System are being implemented in each of its seven components or so called combined energy systems (CES): The Central, Middle Volga, Urals, Northwestern, South, Siberia, and Eastern CES [2]. Energy consumption in Russia is predicted to grow by 35–45 % by 2030 (against 2005) and its growth rates are likely to be approximately by two times higher than on average in the world [3].

The Russian fuel and energy complex is a necessary basis and integral part of the country economy, its industrial and communal sectors; at the same time the complex is a source of envi-

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ronmental hazards and pollution [4, 5]. Energy-producing enterprises exert negative influence on ambient air, water objects and soils and, consequently, on population health [6–9]. The gravest and most apparent environmental issues are associated with coal-powered thermal power stations and stations powered by other fossil fuels (peat or shale oil) and/or heavy oil [10].

At present coal accounts for approximately 15 % in the energy balance of the Russian Federation. Bearing in mind that next generations are very likely to face oil and gas deficiency, coal, together with developing non-organic energy production, will remain a basic organic fuel used for different purposes, including production of electricity [11–14][1].

Without doubt, coal processing and utilization technologies are going to be developed further; a predicted technology in the sphere is coal being converted into synthetic liquid or gaseous fuel [3, 12]. However, at present coal-powered heat and power engineering enterprises still exert significant adverse impacts on the environment and ambient air on urbanized territories [13, 14]. These issues are aggravated on some territories due to orographic, climatic, and layout-related peculiarities of their location. Thus, potential of emission dispersion is rather low in the Eastern Siberia and it creates elevated concentrations of pollutants in ground air [9, 15]. And we should remember that coal is a prevailing energy carrier in this part of the country. In the Siberian Federal District (SFD) a share of thermal power stations that are primarily powered by coal, heavy oil and peat amounts to 90.7 %; it exceeds 53 % in the far Eastern Federal District (FEFD) (Figure 1).

Thermal power stations located on lowlands or in close proximity to residential areas create significant health risks. Besides, we should remember that, apart from thermal power stations, there are large numbers of private boiler stations and autonomous heat sources that operate on "problem" territories in Russia; in 2018 more than 74.8 thousand such objects were registered in the country. Private boiler stations tend to have low chimneys and, consequently, they create greater ambient air pollution in the bottom layers in the atmosphere from which people breathe air [14]. The greatest number of autonomous heat sources powered by fossil fuels is also located in the Siberian and Far Eastern Federal Districts (Krasnoyarsk region, Transbaikalia, Kemerovo region, Irkutsk region, and Novosibirsk region). Such objects are usually located within residential areas or in the closest proximity to them and it may result in negative effects on ambient air quality and, consequently, on exposed population's health [16].

Such pollutants as carbon oxide, carbon dioxide, nitrogen oxides, sulfur dioxide, hydrocarbons, benz(a)pyrene, particular matter and ammonia are basic components in emissions from heat and power engineering enterprises [8, 9, 16–19][2]. Apart from them, heat and power engineering objects emit greenhouses gases (methane and ozone), fluorides, volatile organic compounds (VOC), carbon (soot), non-organic, abrasive and wood dust, heavy oil ashes, mineral petroleum oil and some other admixtures into the atmosphere. Some Russian and foreign authors provide data in their works on metal oxides occurring in emissions from fuel and energy enterprises including oxides of vanadium, aluminum, iron, calcium, magnesium, etc. [16, 20]. We should note that instrumental measurements in zones influenced by fuel and energy objects often allow detecting such dust admixtures in environmental objects and ambient air that are not usually included into inventory environmental lists. As it has been shown by Revich [4] and Petrov [5], solid particles in emissions from fuel and energy enterprises can contain compounds of manganese, chromium, copper, nickel, arsenic, lead, cadmium, and other toxic metals.

[1] Energeticheskaya strategiya Rossiiskoi Federatsii na period do 2035 goda (utv. rasporyazheniem Pravitel'stva Rossiiskoi Federatsii ot 9 iyunya 2020 g. № 1523-r) [The Energy Strategy of the Russian Federation for the period up to 2035 (approved by the RF Government Order dated June 9, 2020 No. 1523-r)]. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/565068231 (August 20, 2021) (in Russian).

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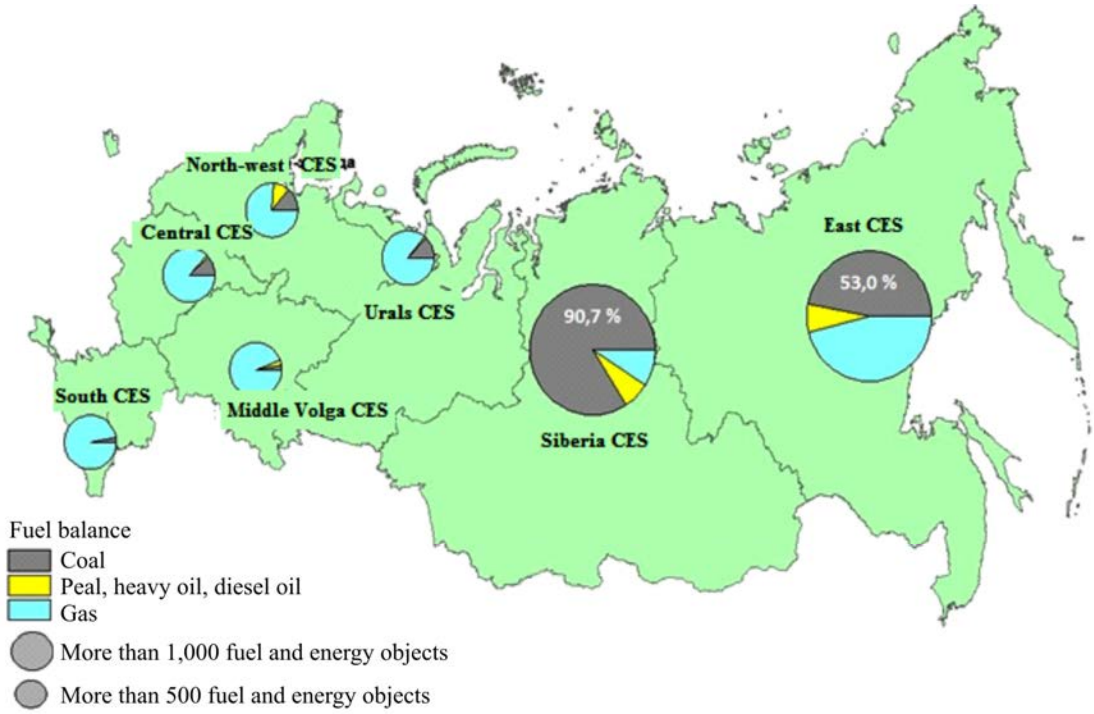

Figure 1. Fuel balance of the RF Combined Energy System, %
(A size of a pie chart corresponds to a number of fuel and energy objects powered by different fuels)

Over the last 10 years ambient air pollution has been characterized as "very high" and "high" in large industrial centers in the Siberian and Far Eastern Federal Districts with air pollution index varying from 9.3 to 22[2]; a significant contribution to these pollution levels and poor quality of the environment is made by fuel and energy enterprises.

According to data taken from the state reports on the ecological situation in the country[2] ambient air quality in SFD and FEFD doesn't correspond to hygienic standards. A lot of pollutants are registered in concentrations exceeding maximum permissible ones; first of all, we should mention carbon oxide (its concentration is by 9.1 times higher than MPC), nitrogen oxide (3.4 times), nitrogen dioxide (2.9 times), sulfur dioxide (4.0 times), benz(a)pyrene (2.15 times), particulate matter (7.6 times), ammonia (9.7 times), xylene (36.5 times), toluene (14.8 times), phenol (24.3 times), formaldehyde (39.0 times) etc.

Results of environmental and social-hygienic monitoring indicate that in 2020 the greatest number of ambient air samples that contained pollutants in quantities deviating from hygienic standards was registered in the Siberian, Ural, and Far Eastern Federal Districts (1.4–2.0 %)[2]. The greatest number of deviating ambient air samples in 2020 were registered as per carbon oxide (0.12–1.9 %), benz(a)pyrene (3.8–21.1 %), hydrocarbons (3.9–4.9 %), particulate matter (1.12–2.5 %), toluene (2.3–9.8 %), xylene (4.3–19.2 %), formaldehyde (0.7–3.1 %), and ammonia (0.4–1.4 %) and we can conclude that these pollutants prevailed in emissions into ambient air from stationary sources, heat and power engineering enterprises included.

Elevated concentrations of chemicals in ambient air that typically occur in emissions from heat and power engineering enterprises can induce negative effects in the respiratory organs, immune, nervous, genitourinary, musculoskeletal and reproductive system, circulatory system etc; they can also make for development of various malignant neoplasms [4, 18, 21–23]. Up to 50 % cases of exacerbated chronic non-specific respiratory diseases that occur in industrial cities in Siberia are likely due to ambient air being polluted with emissions from industrial objects, heat and power engineering enterprises included [22, 24].

All the aforementioned calls for targeted risk-oriented control performed by sanitary-epidemiologic surveillance authorities; their primary task is to ensure than economic entities comply with the obligatory hygienic requirements to environmental protection and providing sanitary-epidemiologic welfare of the country population.

Our research aim was to provide analytical support for the risk-oriented model of sanitary-epidemiologic control over activities performed by fuel and energy enterprises complying with the obligatory requirements fixed in the sanitary legislation. The research tasks were to detect the most common violations of sanitary-epidemiologic requirements by fuel and energy enterprises; to determine priority environmental indicators that should be included into a program of laboratory support for control and surveillance activities; to estimate actual impact exerted by fuel and energy enterprises.

Materials and methods. According to the All-Russian classifier of types of economic activities, heat and power engineering enterprises operate in the sphere "Electric energy, gas and steam supply; air conditioning" (Code 35).

We took data from the Federal Register of juridical persons and private entrepreneurs that were subject to epidemiologic surveillance (hereinafter called the Register) as of December 2020 to estimate a number of economic entities who operated in the sphere "Electric energy, gas and steam supply; air conditioning".

Potential health risk (R^l) associated with economic activities performed by fuel and energy enterprises was determined as a probability that the sanitary-epidemiologic legislation would be violated (p^l) multiplied by gravity of outcomes for health (relative health harm) caused by violation of the legislation (u^l) and a scale of exposure caused by an economic entity (M^l_i); average risk rate (R^l_{av}) was calculated as a sum of all risks divided by a number of economic entities according to the Provisions on the federal state sanitary-epidemiologic control (surveillance) approved by the RF Government Order issued on June 30, 2021 No. 1100[3] and the Methodical Guidelines MR 5.1.0116–17[4].

Frequency of detected violations committed by economic entities that operated in the sphere "Electric energy, gas and steam supply; air conditioning" was estimated as per data taken from Rospotrebnadzor's departmental statistical report, The Federal statistical observation form No. 1-control "Data on accomplishing state control (surveillance) and municipal control" issued in 2014–2020.

Results and discussion. According to data taken from the Register of economic entities (juridical persons / private entrepreneurs or JP / PE for short) that were subject to sanitary-epidemiologic control / surveillance (as of December 2020), the overall number of economic entities operating in the sphere "Electric energy, gas and steam supply; air conditioning" amounted to more than 6 thousand. As for their distribution in the Federal Districts, in 2019 the greatest number of enterprises that provided population and industries with electricity, gas, and steam, were located in the Central FD (1,292 economic entities), Siberian FD (1,114 economic entities), Volga FD (1,100 economic entities) and Far Eastern FD (883 economic entities).

[3] O federal'nom gosudarstvennom sanitarno-epidemiologicheskom kontrole (nadzore): Postanovlenie pravitel'stva RF № 1100 ot 30 iyunya 2021 goda [On the federal state sanitary-epidemiologic control (surveillance): The RF Government Order No. 1100 dated June 30, 2021]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_389344/ (August 22, 2021) (in Russian).

[4] MR 5.1.0116-17. 5.1. Organizatsiya Gossanepidsluzhby Rossii. Risk-orientirovannaya model' kontrol'no-nadzornoi deyatel'nosti v sfere obespecheniya sanitarno-epidemiologicheskogo blagopoluchiya. Klassifikatsiya khozyaistvuyushchikh sub"ektov, vidov deyatel'nosti i ob"ektov nadzora po potentsial'nomu risku prichineniya vreda zdorov'yu cheloveka dlya organizatsii planovykh kontrol'no-nadzornykh meropriyatii: metodicheskie rekomendatsii (utv. Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii A.Yu. Popovoi 11.08.2017) [The Methodical guidelines MR 5.1.0116-17. 5.1. Organization of the State sanitary-epidemiologic service in Russia. The risk-oriented model of control and surveillance activities in the sphere of providing sanitary-epidemiologic welfare. Classification of economic entities, types of activity and objects under surveillance as per potential human health risks for organization of scheduled control and surveillance activities: methodical guidelines (approved by the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, the RF Chief Sanitary Inspector A.Yu. Popova on August 11, 2017)]. Moscow, the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2017, 30 p.

Table 1

Frequency of violations of obligatory requirements fixed in the sanitary legislation by fuel and energy enterprises (a number of detected priority violations per 1 inspection)*

Clauses in the 52-FZ		2018	2019	2020	Growth rate, %
No.	Essence of a clause (requirements)				
Cl. 13	Requirements to products	0.095	0.031	0.015	–84.21
Cl. 17	To organization of catering	0.012	0.019	0.002	–83.33
Cl. 18	To water objects	0.105	0.054	0.032	–69.52
Cl. 19	To drinking water	0.586	0.539	0.727	**+24.06**
Cl. 20	To ambient air	0.387	0.395	0.415	**+7.24**
Cl. 21	To soils, industrial grounds	0.044	0.031	0.051	**+15.91**
Cl. 22	To waste disposal	0.348	0.351	0.134	–61.49
Cl. 23	To living premises	0.047	0.054	0.044	–6.38
Cl. 24	To maintenance of building and constructions	1.254	1.307	0.729	–41.87
Cl. 25	To working conditions	1.154	0.921	0.798	–30.85
Cl. 27	To sources of physical factors	0.381	0.271	0.129	–66.14

Note: * The table provides data on Clauses in the Federal Law 52-FZ that are violated the most frequently (> 0.05).

Table 2

A share of violations of requirements to ambient air fixed in the sanitary legislation (Clause 20 in the 52-FZ) by economic entities operating in the sphere “Electric energy, gas and steam supply; air conditioning” as per Federal Districts in the RF, 2014–2020, %

Federal District	2014	2015	2016	2017	2018	2019	2020	Growth rate, %
Central	8.9	15.1	13.8	4.4	8.5	4.8	20.0	+123.5
Northwestern	16.3	6.6	14.7	3.7	5.0	2.2	2.9	–85.6
Southern	0.5	3.9	9.2	8.1	2.5	3.2	1.8	+235.3
North-Caucasian	1.1	1.3	1.2	0.4	0.4	0.0	1.8	+67.6
Volga	7.9	11.5	4.0	2.2	3.6	15.0	5.9	–25.5
Ural	20.5	28.2	23.6	71.7	62.3	49.0	14.7	–28.4
Siberian	38.4	25.2	29.8	6.5	9.6	15.6	10.6	–72.4
Far Eastern	6.3	8.2	3.7	3.1	8.2	10.2	42.9	+579.9

Our analysis of data taken from the departmental statistical report Form No. 1-control “Data on accomplishing state control (surveillance) and municipal control” issued in 2014–2020 revealed that enterprises most frequently violated obligatory sanitary-epidemiologic requirements to working conditions, to maintenance of buildings, constructions, and premises, to quality of drinking water and water sources, and to ambient air (Table 1).

And if violations regarding safe working conditions or quality of drinking water at an object under surveillance mostly influence only workers employed at this object, then violations regarding ambient air protection (Clause 20) exert their influence on a significant number of people living in urban and rural settlements where fuel and energy enterprises are located. It was revealed that, according to the Register, in the Russian Federation a scale of exposure created by economic entities operating in fuel and energy sphere could reach up to 930 thousand people. In large cities where electricity and heat are usually supplied to population and industries by several generating enterprises, negative exposure due to emissions can cover the whole population.

In 2020 the greatest share of detected violations of obligatory requirements to ambient air protection (Clause 20) was established for fuel and energy enterprises located in Far Eastern FD, Central FD, Ural FD, and Siberian FD and varied from 10.6 to 42.9 % (Table 2).

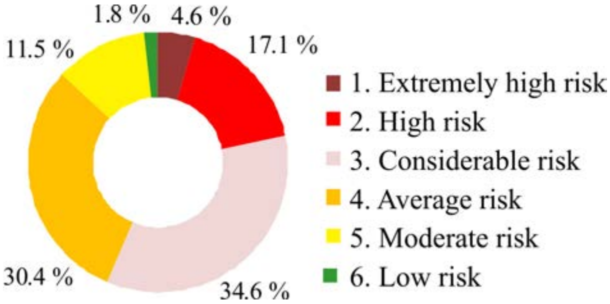

Figure 2. The structure of economic entities (JP / PE) operating in the sphere "Electric energy, gas and steam supply; air conditioning" as per potential health risk categories in the Russian Federation

Average potential health risk per one economic entity (R^l_{av}) operating in the sphere "Electric energy, gas and steam supply; air conditioning" amounted to $5.44 \cdot 10^{-4}$ in the RF but the indicator was higher in the primary group, "Activities performed by industrial enterprises", and mounted to $4.62 \cdot 10^{-4}$.

A share of economic entities that operated in the sphere and belonged to the extremely high risk and high hazard categories (hazard categories 1 and 2 accoridngly) as per potential health risk amounted to 21.7 %; 34.6 % economic entities belonged to the hazard category 3 (considerable potential health risk); 30.4 %, average risk (hazard category 4); 11.5 %, moderate risk (hazard category 5); and only 1.8 %, low risk (hazard category 6) (Figure 2).

The greatest share of economic entities operating in the sphere and belonging to the extremely high potential health risk and high potential health risk categories (hazard categories 1 and 2 accordingly) is registered in the Siberian, Volga, Central, Ural and Far Eastern FDs and amounts to 78.5 % (Table 3).

Comparative analysis performed as per the Federal Districts in the RF revealed the greatest average potential health risk per one economic entity (R^l_{av}) operating in the sphere "Electric energy, gas and steam supply; air conditioning" in the Siberian Federal District where this indicator amounted to $9.88 \cdot 10^{-4}$ (Figure 3).

Table 3

Distribution of economic entities (JP / PE) operating in the sphere "Electric energy, gas and steam supply; air conditioning" belonging to extremely high and high risk categories as per the Federal Districts in the RF, %

Risk category / Federal District	FEas	Vol	NWes	NCau	Sib	Ur	Cen	Sou	RF
A number of economic entities dealing with fuel and energy production in the hazard category 1 and 2	169	227	142	64	258	190	210	82	1,342
A share of economic entities belonging to the hazard categories 1 and 2, %	12.6	16.9	10.6	4.8	19.2	14.2	15.6	6.1	100

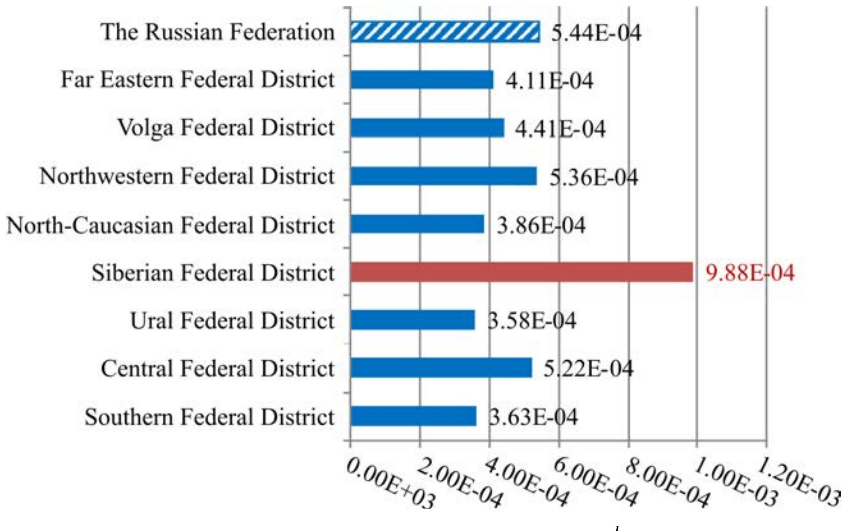

Figure 3. Average potential health risk per one economic entity (R^l_{av}) in the sphere "Electric energy, gas and steam supply; air conditioning" taken as per the Federal Districts in the RF

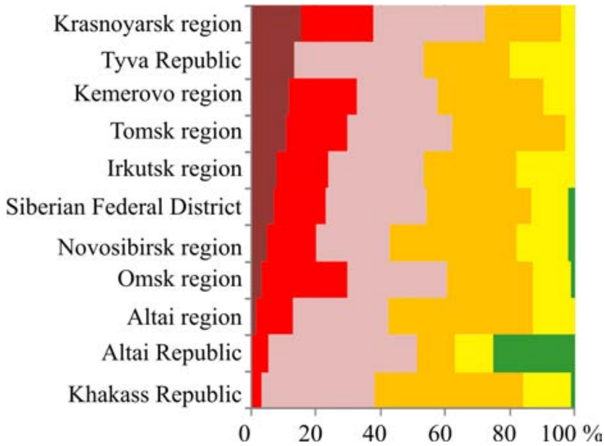

Figure 4. Distribution of economic entities (JP / PE) operating in the sphere "Electric energy, gas and steam supply; air conditioning" as per potential health risk categories as per regions located within the Siberian Federal District

The highest numbers of economic entities operating in the sphere "Electric energy, gas and steam supply; air conditioning" and belonging to the extremely high and high health risk categories were detected in Krasnoyarsk region (37.9 %), Kemerovo region (32.6 %), Tomsk and Omsk regions (29.7 % each) within the boundaries of the Siberian Federal District (Figure 4).

We performed more profound analysis of the situation in developed industrial centers in the Siberian and Far Eastern Federal Districts that were included into "Clean air" Federal project (Krasnoyarsk, Norilsk, Bratsk and Chita). The analysis revealed that in Krasnoyarsk and Norilsk (Krasnoyarsk region) potential health risk (R^l) caused by heat and power engineering enterprises amounted to $1.12 \cdot 10^{-4}$–$3.57 \cdot 10^{-3}$ for extremely high and high risk categories and exposure scale (M^l_i) amounted to 0.00103–0.0329 million people; in Bratsk (Irkutsk region) potential health risk (R^l) amounted to $1.09 \cdot 10^{-4}$–$7.92 \cdot 10^{-3}$ for economic entities operating in the sphere and exposure scale (M^l_i) was 0.001–0.073 million people; potential health risk (R^l) and exposure scale (M^l_i) amounted to $1.28 \cdot 10^{-4}$–$1.66 \cdot 10^{-3}$ and 0.00118–0.0153 million people accordingly in Chita (Transbaikalia).

Violations of hygienic standards are registered in these cities at posts for monitoring over ambient air quality located in zones influenced by fuel and energy enterprises; chemicals that are detected in concentrations exceeding MPC include particulate matter (up to 34.8 single maximum MPC, 1.4 average daily MPC), sulfur dioxide (up to 34.8 MPC_{sm}, 1.9 $MPC_{av.d}$), carbon oxide (up to 5.8 MPC_{sm}), nitrogen oxide (up to 2.9 MPC_{sm}, 1.3 $MPC_{av.d}$), and nitrogen dioxide (up to 1.5 MPC_{sm}, up to 2.1 $MPC_{av.d}$). A contribution made by fuel and energy enterprises to the total emissions from all sources varies from 75 to 90 %.

When requirements to ambient air quality and its protection are violated by fuel and energy enterprises, it can cause secondary pollution of soils, snow cover and surface water thus leading to health disorders and making the environment less comfortable for people. Bearing this in mind, we should stress that laboratory control and monitoring over ambient air quality in zones influenced by such objects are of primary importance.

In such cases results obtained through social-hygienic monitoring and/or targeted examinations can give grounds for interdepartmental inspections, reviewing inventory lists of emissions for such objects, establishing new standards for permissible emissions and / or projects of sanitary protection zones around such objects.

Therefore, the risk-oriented model for surveillance over compliance with obligatory requirements fixed in the sanitary legislation at fuel and energy enterprises should involve the following:

– priority control over compliance with the legislative requirements to protection of ambient air as well as other environmental objects including surface waters and soils on adjoining territories and natural water basins (Clauses 19, 20 and 21 In the Federal Law No. 52-FZ);

– a number of exposed population stated by an economic entity itself when a hazard category is determined should be controlled and verified by surveillance activities. This verification will allow avoiding underestimation of exposure scales for a specific object under surveillance. Fuel and energy enterprises located in the far eastern, Siberian and Ural

Federal Districts should be paid special attention when numbers of exposed population are determined for them;

– control and surveillance activities are to be provided with obligatory laboratory support regarding quantitative determination of components in emissions that pollute ambient air at boundaries between sanitary protection zones and the closest residential areas.

It seems advisable to provide scientific substantiation for risk indicators that are applied to determine whether obligatory requirements to ambient air protection are violated by heat and power enterprises. And a type of a fossil fuel a specific object is powered by is a key component in the procedure. Another vital task is to determine exact component and disperse structure of dusts emitted by a specific energy producing object since it allows the most precise determination of actual environmental pollution on adjoining territories and potential health risks for exposed population.

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Research article

AGE-RELATED ASPECTS IN RISK OF DEVELOPING NERVOUS SYSTEM PATHOLOGY IN GYMNASIUM STUDENTS

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Growing neuropsychic disorders caused by intensified educational process are a peculiar feature of schoolchildren's health at present.

Our research aim was to examine age-related peculiarities in risks of developing nervous system pathology in schoolchildren attending a gymnasium.

We performed clinical examination of 94 children in primary school (Group A) and 56 children in middle school (Group B) who attended a gymnasium. The examination included determining contents of neuromediators and neurotrophic factors in blood, neuro-psychological computer testing (reaction test and STROOP-test). Educational activities were evaluated to determine whether the educational process conformed to hygienic standards. Statistical data analysis involved determining relative risk and odds ratio as well as establishing cause–effect relations.

Hygienic assessment of educational activities revealed several adverse factors that made for developing disorders of the nervous system. They included growing weekly educational loads, irrational distribution of school subjects in schedules, and too long use of interactive whiteboards during lessons. We established that nervous system pathology was already developing in 62.8 % children in primary school and 42.9 % children in middle school. We also revealed that asthenoneurotic syndrome and neurosis-like syndrome were by 2.2 times more probable among primary schoolchildren whereas vegetative dysfunction was by 1.6 times more probable among middle school children. Asthenoneurotic syndrome in primary school children was accompanied with lower NOTCH-1 levels in 41.9 % cases; lower acetylcholine content in blood, in 66.7 %; greater serotonin content in blood, in 29.2 %. The disorder became apparent through increased fatigability and weakness, as well as children being too whiny and moody. Middle school children had by 3.1–6.4 times higher risks of lower neuregulin-1β and tumor necrosis factor contents in blood; developing vegetative dysfunctions in them were accompanied with sleeping disorders, headaches, and palpitation. Primary school children were established to have slower perception of a visual and sound stimulus, developing fatigue of kinesthetic reactions as well as rigid cognitive control and poorly automated gnostic functions.

Key words: *schoolchildren, gymnasium, educational activities, nervous system pathology, neuromediators, neurotrophic factors, neuro-psychological testing.*

Latest scientific data available in literature indicate that negative trends in schoolchildren's health persist at the moment since pathologies of visual organs and musculoskeletal system, endocrine diseases, and disorders of neuropsychic development are becoming more and more frequent [1–6]. A number of healthy children drops by 4–10 times by the end of school and practically each second student who completes his or her school education has a certain chronic pathology [2, 4, 7–9]. It has been noted due to preventive medical examinations that diseases of the nervous system hold the third rank place in overall morbidity among primary school children and the fourth or fifth one among middle and senior school children [5, 7].

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Accomplished studies indicate that health of contemporary schoolchildren including developing neuro-psychic disorders is influenced by many factors related to the educational environment; these factors are growing and intensifying educational loads, an educational process not being hygienically optimal, irrational use of IT resources, wider range of additional education, low physical activity, etc. [10–14]. According to some authors, excessive informatization of the educational processes, especially in primary school, results in lower mental working capacity, makes for more apparent fatigue, creates elevated anxiety and slows down intellectual development [15–17].

School age is a period in life when a child grows and develops intensively; this is especially true for adaptation systems in the body with the central nervous system playing the leading role among them [14, 17–21]. As per data obtained by psychophysiological studies schoolchildren tend to have plastic nervous processes and this becomes apparent via peculiar sensorimotor reactions to psychoemotional loads [21–23]. It is a known fact that effector mechanisms in the brain develop intensely in children aged 7–10 including both responsible for highly specialized movements and for voluntary management of information processes [23, 25–26]. When puberty starts, integration of afferent and efferent signals in the central brain structures becomes more developed, learning activity grows, and abstract thinking starts to evolve [27–29]. Contemporary educational processes are organized in such a way that they don't correspond to psychophysiological capabilities of a child's body; they make for developing disorders of nervous regulation and cognitive functions and growing strain of adaptation mechanisms. All this leads to growing anxiety and fatigue, lower working capacities, poor progress in studies and developing psychosomatic pathology [21, 22, 30–32].

Therefore, it is vital to get better insight into how disorders develop in the nervous system during school years, especially when it comes down to secondary schools with specialized educational programs.

Our research aim was to examine age-related peculiarities in development of nervous pathologies among schoolchildren attending a gymnasium.

Materials and methods. We performed clinical examination of 150 schoolchildren (43.4 % boys and 56.6 % girls) to examine peculiarities in development of nervous pathologies among them. All the examined children attended Gymnasium No. 6 in Perm; Group A was made up of 94 primary school children (their average age was 8.85 ± 0.34); Group B, 56 middle school children (their average age was 12.82 ± 0.26). Both these groups were created by random sampling and were comparable as per social parameters and sex structure (p = 0.17–0.89). A child was excluded from the study in case he or she had an acute respiratory disease, a chronic somatic pathology in acute condition, or an organic pathology of the nervous system detected during the examination.

The accomplished clinical examination conformed to ethical principles stated in the Helsinki Declaration (with alterations and addenda made in 2008) and the RF National Standard GOST-R 52379-2005 "Good clinical practice" and was approved by the Ethical Committee of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies (the meeting report No. 3, 2020). Children's legal representatives gave their voluntary informed consent prior to the examination.

Educational processes in the gymnasium were evaluated to determine whether they conformed to the existing hygienic standards[1, 2] (the focus was on educational programs and

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[1] SP 2.4.3648-20. Sanitarno-epidemiologicheskie trebovaniya k organizatsiyam vospitaniya i obucheniya, otdykha i ozdorovleniya detei i molodezhi: utv. glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii 28.09.2020 [SR 2.4.3648-20. Sanitary-epidemiologic requirements to organizing education, rest and health improvement for children and youth: approved by the RF Chief Sanitary Inspector on September 28, 2020]. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/566085656 (August 23, 2021) (in Russian).

[2] SanPiN 1.2.3685-21. Gigienicheskie normativy i trebovaniya k obespecheniyu bezopasnosti i (ili) bezvrednosti dlya cheloveka faktorov sredy obitaniya: utv. glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii 28.01.2021 [SanPiN 1.2.3685-21. Hygienic standards and requirements to providing safety and (or) harmlessness of environmental factors for people: approved by the RF Chief Sanitary Inspector on January 28, 2021]. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573500115 (August 23, 2021) (in Russian).

a typical weekly schedule including lessons and breaks that were applied in educational activities).

All children took part in medical-social questioning and were examined by medical experts (pediatrician and neurologist); their medical case histories (Form No. 026/u-2000) were analyzed; also the study involved profound laboratory diagnostics (total blood count and biochemical test, determination of neurotransmitters in blood including adrenalin, noradrenalin, dopamine, serotonin, acetylcholine; determination of a stress hormone hydrocortisone; determination of neurotrophic factors including ciliary neurotrophic factor, neuregulin-1β, tumor necrosis factor, and transmembrane protein). All examinations and diagnostics were performed according to conventional procedures; determined laboratory indicators were compared with physiological standards established for a relevant age.

Peculiarities of children's reflex reactions were examined by using a reaction test (RT) that involved assessing a reaction time and a motor reaction time and was performed with Vienna Test System. During a test a child was presented with visual and / or sound stimuli. A respondent had to push the key and then return his or her finger on the rest key when a specific stimulus was presented. The data were interpreted as per a mean reaction time (a time passed from the moment a stimulus was presented up to the beginning of a reactive mechanic movement, ms), reaction time dispersion (standard deviation in reaction time, ms), a mean motor reaction time (a time from the beginning of a reactive mechanic movement up to pushing the reaction key, ms), motor reaction time dispersion (standard deviation in motor reaction time, ms).

Executive mental functions were examined by using STROOP-test based on Vienna Test System. First, basic reading and naming lines were evaluated by pressing a relevant color key. Then the participants had to accomplish tasks related to "Reading interference" (pressing a color key that corresponded to a given word) and "Naming interference" (pressing a color key for a color of a given word). Test results were interpreted as per the following variables: susceptibility to interference when reading and naming (a difference in reaction time for a basic line and a reaction time under interference, sec), as well as reaction time medians (sec) and a number of incorrect reactions.

All research results were statistically analyzed using conventional descriptive statistic procedures. We calculated relative risk (*RR*) of developing nervous pathology, odds ratios (*OR*) and their 95 % confidence intervals (*CI*) with authenticity of their bottom limit being higher than 1.0. Cause-effect relations were established through mathematical modeling performed with one-factor dispersion analysis involving evaluation of Fischer's test (F), determination coefficient (R^2) and Student's t-test with statistical significance taken at $p \leq 0.05$ [30].

Results and discussion. Hygienic assessment of the educational processes in the gymnasium revealed that all children had their classes in the morning and afternoon (so called first shift). A lesson lasted for 45 minutes even in primary school (the obligatory requirement is not longer than 40 minutes). Small breaks conformed to hygienic standards (10 or 15 minutes) apart from the last break between the 6^{th} and 7^{th} lessons that was shortened to 5 minutes. Long breaks lasted for 20 minutes in accordance with the hygienic standards (item 3.4.16 in the Sanitary Rules 2.4.3648-20[1]).

Having analyzed weekly schedules applied in the gymnasium, we revealed that weekly educational loads amounted to 22–26 lessons in primary school; the educational load for a 5-day learning week was by 1 hour longer in the first grade than it was allowed by the sanitary rules (item 3.4.16 in the Sanitary Rules 2.4.3648-20[1]). Educational loads reached maximum permissible levels for a 6-day learning week in the 7^{th} grade (35 lessons per week) and were even higher than stipulated by the standards in the 8^{th} grades (37 lessons per week). At the same time, a number of school subjects included into one learning day in middle school conformed to hygienic standards and didn't exceed 7 lessons (item 3.4.16 in the Sanitary Rules 2.4.3648-20[1]).

We should note that the gymnasium schedules didn't always follow a principle demanding that a day schedule should include subjects that were different in their complexity; the same principle should be followed when weekly schedules were created. In middle school double lessons in one subject were quite possible and this made for faster fatigue development in schoolchildren. We also evaluated complexity of different school subjects as per score estimates to reveal that the highest educational loads in primary school occurred on Wednesday (29–31 scores) and easy days were either Monday (19 scores) or Tuesday (21 score) instead of Thursday or Friday when children's working capacities were already low by the end of a week. Weekly loads in middle school didn't correspond to optimal levels of mental working capacities either since maximum loads were detected on Thursday and Friday (51–56 scores in the 8th grades) and Saturday was an easy day (18–20 scores). Physical training in the gymnasium corresponded to the maximum permissible weekly loads, however, sometimes physical training lessons were at the beginning of a day and were followed by lessons that required accomplishing writing tasks (item 3.4.16 in the Sanitary Rules 2.4.3648-20[1]).

We examined how technical teaching aids were applied in the gymnasium and revealed that an interactive whiteboard (SMART Board, SBD600 series) was used in every subject excluding physical training. SMART Board, SBD600 series, was used during a period of time that conformed to the hygienic standards and varied from 3 to 20 minutes in primary school (median time was 11.75 minutes) and from 5 to 20 minutes in middle school (median time was 12.5 minutes). However, a whiteboard was used during the whole lesson in arts and this was by 1.5–1.8 times longer than permitted by the standards in different grades (Sanitary Rules[1] and Standards SanPiN 1.2.3685-21[2]).

The questioning revealed that practically all primary school children attended additional education programs (95.9 %) as opposed to middle school children (60.7 %, p = 0.0001). Each second schoolchild in both examined groups went to sport clubs (54 % in Group A and 50 % in Group B, p = 0.72). 19.2 % primary school children attended art school (against 3.6 % in group B, p = 0.046); and only primary school children (from the 1st–4th grade) visited a chess club (16.4 %). We should note that primary school children did additional homework by 1.3 times more frequently than middle school children (41.1 % against 32.1 % in Group B, p = 0.41).

Frequency of complaints was comparatively analyzed in both groups to reveal that primary school children (from the 1st–4th grades) complained about increased fatigability and weakness authentically more frequently (24.7 % against 7.1 % in Group B, p = 0.046); they were also more often whiny and moody (47.9 % and 25 % accordingly, p = 0.037). Middle school children more frequently complained about sleeping disorders (39.3 % against 19.2 % in Group A, p = 0.034), headaches (39.3 % and 13.7 % accordingly, p = 0.004), and palpitation (32.1 % and 9.6 % accordingly, p = 0.005).

Clinical examination allowed establishing that primary school children tended to have nervous system pathology by 1.5 times more frequently (62.8 % against 42.9 % among middle school children, p = 0.018). Asthenoneurotic, neurosis-like syndrome accounted for 55.4 % in overall morbidity with these nosologies among primary school children (against 25 % in middle school, p = 0.012); disorders of the autonomic nervous system were by 1.6 times more frequent among middle school children (66.7 % against 42.9 % in primary school, p = 0.03). We established that asthenoneurotic and neurosis-like syndrome was by 2.2 times more probable among primary school children (RR = 2.21; CI: 1.06–4.60) whereas vegetative dysfunction was by 1.6 times more probable among middle school children (RR = 1.56; CI: 1.03–2.35).

Levels of hydrocortisone (a stress hormone) in blood were not significantly different in two analyzed groups (Table 1).

Average contents of neuromediators in examined children's blood were within physiological standards excluding acetylcholine

Table 1

Laboratory indicators in examined children, $M \pm m$

Indicator	Reference value	Group A	Group B	Validity of differences between groups
Hydrocortisone, nmol/cm^3	140–600	207.41 ± 15.75	199.09 ± 21.86	0.59
Serotonin, ng/ml	70–270	222.83 ± 31.02	179.96 ± 34.39	0.06
Dopamine, pg/cm^3	10–100	53.93 ± 5.49	50.30 ± 6.91	0.32
Noradrenalin, pg/cm^3	70–600	298.08 ± 45.65	334.41 ± 42.12	0.25
Adrenalin, pg/cm^3	10–100	54.43 ± 4.37	54.31 ± 5.92	0.97
Acetylcholine, pg/ml	28.43–57.49	19.67 ± 5.93*	20.00 ± 8.84*	0.94
CNTF, pg/ml	0–27	0.26 ± 0.04	0.21 ± 0.02	**0.046**
NRG-1β, pg/ml	32–432	49.94 ± 10.84	27.43 ± 8.24	**0.017**
TWEAK, pg/ml	425–925	564.64 ± 35.79	431.19 ± 54.77	**0.0001**
NOTCH-1, pg/ml	50–130	69.92 ± 19.55	72.22 ± 18.44	0.68

Note: * means differences from reference values are valid ($p < 0.05$).

levels; there were no significant differences in these indicators between the analyzed groups (p = 0.06–0.97). Average acetylcholine levels were authentically by 1.4 times lower than physiological standards in both analyzed groups ($p < 0.05$). Lower acetylcholine levels were by 1.4 times significantly more frequently detected in children from the Group B (92 % against 66.7 % in Group A, p = 0.05). We should note that 29.2 % of primary school children had elevated contents of serotonin, an inhibitory neurotransmitter, in blood and this was by 1.6 times more frequent than in Group B (18.5 %, p = 0.31). We established an authentic cause-effect relation between developing asthenoneurotic syndrome and elevated serotonin contents in blood (b_0 = –2.47; b_1 = 0.009; R^2 = 0.51; F = 62.37; p = 0.0001).

Our assessment of neurotrophic factors (Table 1) revealed that levels of ciliary neurotrophic factor (CNTF) that facilitated differentiation of developing neurons and glia cells were within reference ranges and were by 1.2 times higher in children from Group A (p = 0.046). Average contents of neuregulin-1β (NRG-1β), a protein that participated in neuronal development and formation of neuromuscular junctions were by 1.2 times lower than physiological standards in middle school children (p = 0.31) and also by 1.8 times lower than in Group A (p = 0.017). Low NRG-1β levels were detected in 58.3 % of schoolchildren from Group B and this was by 1.9 times more frequent than in another group (31.2 %, p = 0.02). We established that middle school children had by 3.1 times higher chances to have lower neuregulin-1β contents in blood (OR = 3.08; CI: 1.17–8.11).

Although average contents of TWEAK that activated cell growth and angiogenesis were within physiological ranges in the analyzed groups, 45.8 % children from Group B still had a bit lower levels of it and this was by 3.7 times more frequent than in primary school children (Group A) (12.5 %, p = 0.001). Odds ratio of low TWEAK levels was by 6.4 times higher for middle school children (OR = 6.42; CI: 2.13–19.35). We established an authentic cause-effect relation between developing diseases of the nervous system and elevated TWEAK contents in blood serum (b_0 = –1.41; b_1 = 0.0026; R^2 = 0.13; F = 8.60; p = 0.005). Levels of transmembrane protein NOTCH-1 that regulated proliferation and differentiation of neuroglia cells and neuron arborization didn’t have any significant differences between the groups. However, low NOTCH-1 levels in blood were detected by 1.7 times more frequently in children from Group A (41.9 %) than in middle school children from Group B (25 %, p = 0.07). We established an authentic cause-effect relation between developing nervous pathologies and asthenoneurotic syndrome and lower NOTCH-1 levels in blood serum (b_0 = –0.56–0.43; b_1 = –0.0061 – –0.0078; R^2 = 0.40–0.48; F = 52.54–68.68; p = 0.0001). Overall, all these data show that the structural and functional organization of the brain is

Table 2

RT-test indicators in examined children, $M \pm m$

Indicator	Group A	Group B	Validity of differences between the groups
Mean reaction time, ms	581.42 ± 38.97	473.4 ± 56.31	**0.0017**
Reaction time dispersion, ms	106.79 ± 19.42	71.1 ± 11.97	**0.0023**
Mean motor time, ms	251.87 ± 25.27	217.4 ± 60.11	0.25
Motor time dispersion, ms	42.33 ± 8.18	35.3 ± 11.71	0.29

Table 3

STROOP-test indicators in examined children, $M \pm m$

Indicator	Group A	Group B	Validity of differences between the groups
A time spent on working with all parts of a text, sec	10.29 ± 0.99	7.59 ± 0.39	**0.0007**
Susceptibility to interference when naming, sec	0.23 ± 0.08	0.09 ± 0.06	**0.022**
Susceptibility to interference when reading, sec	0.34 ± 0.09	0.19 ± 0.13	0.06
Median of reaction times when naming 1, sec	0.88 ± 0.06	0.70 ± 0.06	**0.0004**
Median of reaction times when naming 2, sec	1.11 ± 0.13	0.79 ± 0.07	**0.0017**
Median of reaction times when reading 1, sec	0.94 ± 0.07	0.79 ± 0.08	**0.014**
Median of reaction times when reading 2, sec	1.29 ± 0.13	0.98 ± 0.08	**0.0048**

developing unevenly and we should remember that this organization provides neurophysiologic grounds for learning activities at different ages.

Our evaluation of sensorimotor activities revealed that a mean reaction time and its dispersion were authentically by 1.2–1.5 times higher in primary school children (p = 0.0017–0.0023) indicating that perception of a visual-sound stimulus was slow and afferent reactions were fatigued (Table 2).

We didn't reveal any significant differences between the groups as per a time and fatigability of a response motor reaction to a stimulus (p = 0.25–0.29).

We analyzed the results of examining executive cognitive functions to reveal that reading speed and a speed of recognizing a color were by 1.4 times higher in middle school children (p = 0.0007).

Having compared basic lines values for naming and reading, we revealed that indicators were by 1.2 times lower in middle school children; this might be due to relevant information processing being faster and better automated in them.

We also established that susceptibility to interference when reading was by 1.8 times higher in primary school children (p = 0.06) due to lower speed of information processing in case there was a cognitive conflict. High susceptibility to interference when naming was detected in children from Group A as opposed to those from Group B (0.23 ± 0.08 sec and 0.09 ± 0.06 sec accordingly, p = 0.022); this indicated that primary school children had difficulties in switching from verbal functions to sensory-perceptual ones due to low automation of the latter. These data indicate that cognitive control is rigid and cognitive functions are poorly automated in primary school children. This might be associated with physiological peculiarities of nervous processes at this age.

Conclusions:

1. Growing weekly educational loads, irrational distribution of subjects over a day and a week schedule and whiteboards being used for too long time during a lesson are adverse factors that make for developing pathologies of the nervous system in schoolchildren attending the gymnasium.

2. Pathologies of the nervous system have been detected in most primary school children and in 42.9 % of middle school children; risks of asthenoneurotic and neurosis-like syndrome were by 2.2 times higher for primary school children and risks of vegetative dysfunction were by 1.6 times higher for middle school children.

3. Each second schoolchild in primary school suffers from asthenoneurotic syndrome that becomes apparent through increased fatigability and weakness as well as children being whiny and moody; the syndrome is determined by lower levels of transmembrane protein NOTCH-1 and acetylcholine and elevated contents of serotonin in blood.

4. Vegetative regulation disorders in middle school children involve sleeping disorders, headaches, and palpitation and are accompanied with lower levels of neuregulin-1β and tumor necrosis factor in blood.

5. Neuropsychological testing allowed revealing that primary school children tended to have lower speed of perceiving a visual and sound stimulus and fatigued afferent reactions; their cognitive control was rigid and cognitive functions were poorly automated.

6. Age-related peculiarities regarding risks of developing nervous pathologies in primary school children should include plasticity of nervous processes involving slowed development of nervous cells and enhance inhibitory mechanisms in the brain; these peculiarities in middle school children are mostly underdeveloped synaptic transmission in brain neurons.

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Research article

TYPOLOGIZATION OF RUSSIAN REGIONS AS PER ENVIRONMENTAL FACTORS, FACTORS RELATED TO EDUCATIONAL PROCESS AND SCHOOLCHILDREN'S HEALTH

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The structure of children population determined as per health groups is an integral characteristic of population health in this age group; it can be used as a criterion in creating medical and preventive programs aimed at managing demographic processes and assessing their efficiency. Health disorders among children occur due to many reasons including influence by socioeconomic and sanitary-epidemiological factors, peculiarities of the educational process, eating habits, lifestyle, etc. Our research aim was to determine types of regions in Russia as per environmental factors, the educational process and schoolchildren's health. Determining different types of regions was considered to be an information basis for developing common strategies and mechanisms for improving schoolchildren's health. Typologization of regions as per health groups revealed that the most favorable situation was in 31 regions; the last favorable, only in 2. The most favorable situation as per the educational process was in 55 regions where schools operated in one shift; the least favorable situation was observed in two RF regions where schools had to operate in two or even three shifts. Relative sanitary-epidemiological welfare was found in 20 regions and the situation in 21 regions was the least favorable as per several markers that characterized quality of drinking water, ambient air, and soils. Socioeconomic situations in the regions were analyzed to reveal that only 3 regions could be considered the most favorable and 28 regions were the least favorable; the latter were combined into one cluster with the lower values of the relevant markers including gross regional products per capita, living standard, provision with qualified medical personnel and in-patient hospital beds.

A situation in each particular region is a reflection of regularities related to influence exerted by a set of aforementioned factors on children's health; this proves the necessity to create a road map for each region in the RF with feasible mechanisms aimed at improving the existing situation as per specific aspects.

Keywords: *children's population, health groups, factors related to the educational process, sanitary and epidemiological state, socio-economic state, nutrition, cluster analysis.*

To provide sanitary-epidemiological well-being of the population in the Russian Federation and to preserve citizens' health is among priority activities performed by the RF Government. This was fixed in the Order by the RF President[1] and the Program of priority activities to be performed by the RF Government for a period up to 2024[2].

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[2] Osnovnye napravleniya deyatel'nosti Pravitel'stva Rossiiskoi Federatsii na period do 2024 goda (utv. Predsedatelem Pravitel'stva Rossiiskoi Federatsii D. Medvedevym 29 sentyabrya 2018 g.) [Priority activities to be performed by the Government of the Russian Federation for a period up to 2024 (approved by Dmitry Medvedev, the Head of the RF Government on September 29, 2018)]. *The RF Government.* Available at: http://static.government.ru/media/files/ne0vGNJUk9SQjlGNNsXlX2d2CpCho9qS.pdf (September 13, 2021) (in Russian).

All the activities concerning children are given special attention. Thus, in order to improve the state policy in the sphere of childhood protection, the RF President issued an order declaring the decade 2018–2027 to be The Childhood Decade.

In this respect it seems vital and well-timed to reveal a set of factors that influence children's health and to develop relevant activities aimed at minimizing their adverse impacts. A pilot project by the RF Public Healthcare Ministry which is called "Contemporary model of children's health protection in secondary educational establishments ("School medicine")" is a vital component in the Childhood Decade; the project involves transforming a typical intra-school environment into a powerful resource for improving health of each schoolchild [1–3].

Given overall deterioration of population health over the last years, the situation with children's health is also becoming worse; it is especially true for schoolchildren [4]. Some authors mention substantial increase in exertion of students' functional capacities and high physiological costs of studying due to considerable growth in educational loads created by the more intensified educational process in the contemporary school [5, 6]. The Federal Law "On sanitary-epidemiological well-being of the population" (Clause 40) (last edited by the Federal Law issued on January 10, 2003 No. 15-FZ) ranks education among activities that are potentially hazardous for people[3]. Many authors state in their works that conditions existing inside an educational establishment are comparable as per their influence on children's health to such powerful factors as environmental ones [7][4]. International community considers physical environment in educational establishments to be critically important for optimal education [8]. According to data provided by the WHO experts and Russian scientists, a contribution made by social-hygienic factors into children's health varies from 25 to 40 % [9, 10]. Multiple research works indicate that there is a correlation between a sanitary-epidemiological situation in an educational establishment, a territory where a given educational establishment is located, and health disorders among schoolchildren [11, 12]. Impacts exerted by combined factors, for example, a set of chemical factors and factors related to the educational process, are especially tangible in occurrence of various pathologies [13–15].

Nutrition is another most significant factor that influences children's health; influence is exerted by both meals provided by school and taken at home, the latter being determined by a socioeconomic status of a child's family and eating habits in general. Long-term deviations from so-called balanced nutrition result in violated anthropometric parameters, improper body composition, and overall functional disorders in the body [16, 17]. Some authors insist that health disorders caused by improper nutrition can develop not only in childhood but also at later stages in ontogenesis [18–20].

Therefore, children's health is influenced by a complex set of various factors; at present it is vital to reveal these factors and manage them successfully.

Our research aim was to determine types of regions in Russia as per a set of environmental factors, factors related to the educational process, and those related to children's health. Determining types of RF regions was considered as an information basis for developing common strategies and mechanisms aimed at improving schoolchildren's health.

Materials and methods. We applied methodical approaches based on cluster analysis to determine types of RF regions; the typolo-

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gization was accomplished in the present research to examine trends in influence exerted by environmental factors on distribution of children into different health groups.

The basic idea of this methodology was to develop several systems for classification of regions; these systems reflected differences between the regions in the RF as per several sets of indicators that characterized various socioeconomic and sanitary-epidemiological aspects and factors related to lifestyle influencing children's health. The next stage involved analyzing regularities in determining what type a given region belonged to.

Our initial data were taken from statistical departmental reports issued by the Federal Service for Surveillance over Consumer Rights Protection and Human Well-being (Form No. 18 "Data on the sanitary situation in a RF region"; Form No. 9 "Data on the sanitary-epidemiological situation in facilities for children and adolescents"); we also took data provided by the Federal State Statistics Service and data from collections issued by the RF Public Healthcare Ministry "Resources and activities of medical organizations".

The following sets of indicators were selected to be examined within the present research:

– indicators that described distribution of children as per different health groups (5 indicators overall: a share of children in the health group I; a share of children in the health group II; a share of children in the health group III; a share of children in the health group IV; a share of children in the health group V);

– indicators that described educational loads on children (4 indicators overall: a number of schools operating in one shift (in %); a number of schools operating in two shifts (in %); a number of schools operating in three shifts (in %); a share of children attending sport clubs or other establishments for children and adolescents);

– indicators that described socioeconomic conditions in a region (7 indicators overall: gross regional product per capita (rubles); living standard per capita and as per basic socio-demographic groups (children); a number of experts in children and adolescent hygiene (per 10,000 people); a number of in-bed hospital beds for children (per 10,000 children); a number of beds in pediatric hospitals (per 10,000 children of respective age); etc.);

– indicators that described sanitary-epidemiological situations in regions and living and educational environment (29 indicators overall: a share of drinking water samples taken in educational organizations that deviated from hygienic standards as per sanitary-chemical indicators; a share of urban population provided with conditionally qualitative water; a share of urban population provided with low quality water; a share of drinking water samples taken in educational organizations that deviated from hygienic standards as per microbiological indicators, etc.);

– indicators that described children's nutrition (11 indicators overall: a share of cooked meals that deviated from hygienic standards as per caloric content and chemical structure; a share of cooked meals deviating from hygienic standards as per microbiological indicators; a share of cooked meals that deviated from hygienic standards as per vitamin C contents; a share of sample cooked meals deviating from hygienic standards as per sanitary-chemical indicators; a share of schools with a canteen or a buffet (% of the overall number of schools) etc.).

The present research required creating an electronic database with values of 56 indicators as per 5 sets of factors over a period from 2010 to 2019. Preliminary analysis and data preparation involved calculating relative values and determining average long-term values for each indicator.

All the RF regions were distributed into different clusters as per each set of indicators using k-means clustering; it was done with STATISTICA 10 software package for statistical data analysis. Standardized indicators attributed to the examined sets were used as variables in clustering procedures. Standardization of indicators allowed excluding any influence on clusterization results by measuring scale and was performed as per the following ratio (1):

$$\tilde{x}_i = \frac{x_i - \bar{x}_i}{\sigma_i}, \quad (1)$$

where x_i is a value of the *i*-th indicator; $\bar{x}_i$, σ_i are mean value and standard deviation of the *i*-th indicator accordingly.

Having repeated the procedure for each set of indicators, we managed to distribute RF regions into four clusters (4 types).

We created a system of weight coefficients to comparatively assess different types of territories for specific sets of indicators; these coefficients described adverse influence exerted by given indicators on children's health. Weight coefficients were set by an expert opinion and their values varied from 0 to 1. Values close to 0 indicated that adverse influence on children's health was insignificant; values close to 1 indicated that influence was high. Thus, weight coefficients for indicators that described how children were distributed as per health groups varied from 0 to 0.8; indicators that described educational loads on children, from 0.1 to 0.3; indicators describing socioeconomic conditions, within 0.3–0.6; indicators describing the sanitary-epidemiological situation on a given territory and conditions at home and at school, within 0.3–0.6; indicators that described meals provided for children, within 0.2–0.7.

A weight of a cluster for each set of indicators was determined as weighted average of all values of the weight coefficients relative to the cluster averages (2):

$$W_k = \frac{\sum_i \bar{x}_{ki} w_i}{\sum_i \bar{x}_{ki}}, \quad (2)$$

where W_k is a weight coefficient for the *k*-th cluster; $\bar{x}_{ki}$ is a mean value of the *i*-th indicator for the *k*-th cluster; w_i is a weight coefficient for the *i*-th indicator.

Calculated cluster weights were used as an integral characteristic of the situation in regions in different clusters in regard to children's health which was assigned into different health groups and they were also used as a criterion in determining rank estimates.

Calculations allowed creating a system of rank properties as per five sets of indicators that gave an opportunity to assess probable adverse influence exerted by them on children's health.

Results and discussion. Typologization of RF regions ***as per children's health groups*** gave an opportunity to distribute RF regions into four clusters. The 1st cluster included 19 regions; the 2nd one, 33; the 3rd one, 31; the 4th cluster included only 2 regions (Figure 1).

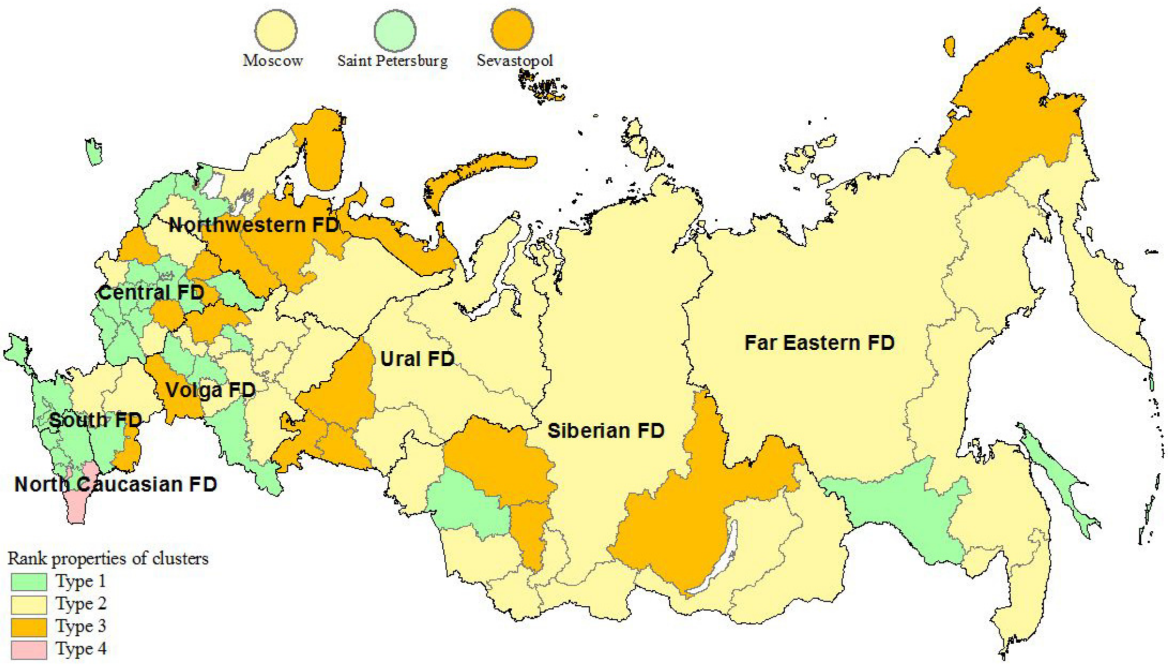

Figure 1. RF regions distributed into clusters as per children's health groups

The most favorable situation is in the 3rd cluster (1 type) where the average cluster share of children in the health group I is the highest and amounts to 29 %. It is by 1.2 times higher than on average in the country. The 3rd cluster includes such regions as Belgorod, Vladimir, Moscow, Novosibirsk, and Leningrad regions; city of Moscow; Adygei, Crimea, Chechnya, Krasnodar region, Stavropol region, Sevastopol, and some other RF regions. Average cluster shares of children in the health groups III, IV and V correspond to those detected for the country as a whole: 16 %, 1 %, 1 % accordingly (Table 1).

The most unfavorable situation is in the 4th cluster (Type 4) where average cluster shares of children in the health groups IV and V are the highest, 4.3 % and 2.8 % accordingly. This is by 4.4 and by 2.9 times higher than on average in the country accordingly. This cluster includes Dagestan and Ingushetia.

Typologization of the RF regions ***as per conditions of the educational process*** revealed that 28 RF regions were included into the 1st cluster; 37, the 2nd one; 18, the 3rd one; and 2 RF regions were included into the 4th cluster (Figure 2).

The situation is the most favorable in the 3rd cluster (Type 1) where 88.79 % schools operate in one shift on average in the cluster and there are no schools that operate in three shifts. The 3rd cluster includes such RF regions as Moscow City, Leningrad, Murmansk, Tyumen, Novosibirsk, and Tomsk regions, Kabardino-Balkaria, Karachay-Cherkessia, and Tatarstan.

Table 1

Average cluster values and regions ranked as per children's health groups

Indicator	Cluster				Long-term average value in the RF
	1	2	3	4	
A share of children in the health group I	0.16	0.20	0.29	0.24	0.23
A share of children in the health group II	0.59	0.65	0.53	0.49	0.59
A share of children in the health group III	0.23	0.13	0.16	0.20	0.16
A share of children in the health group IV	0.009	0.009	0.010	0.043	0.010
A share of children in the health group V	0.010	0.008	0.010	0.028	0.010
Rank value for the cluster	0.22	0.20	0.18	0.23	
A number of RF regions in the cluster	19	33	31	2	
Rank of the cluster	3	2	1	4	

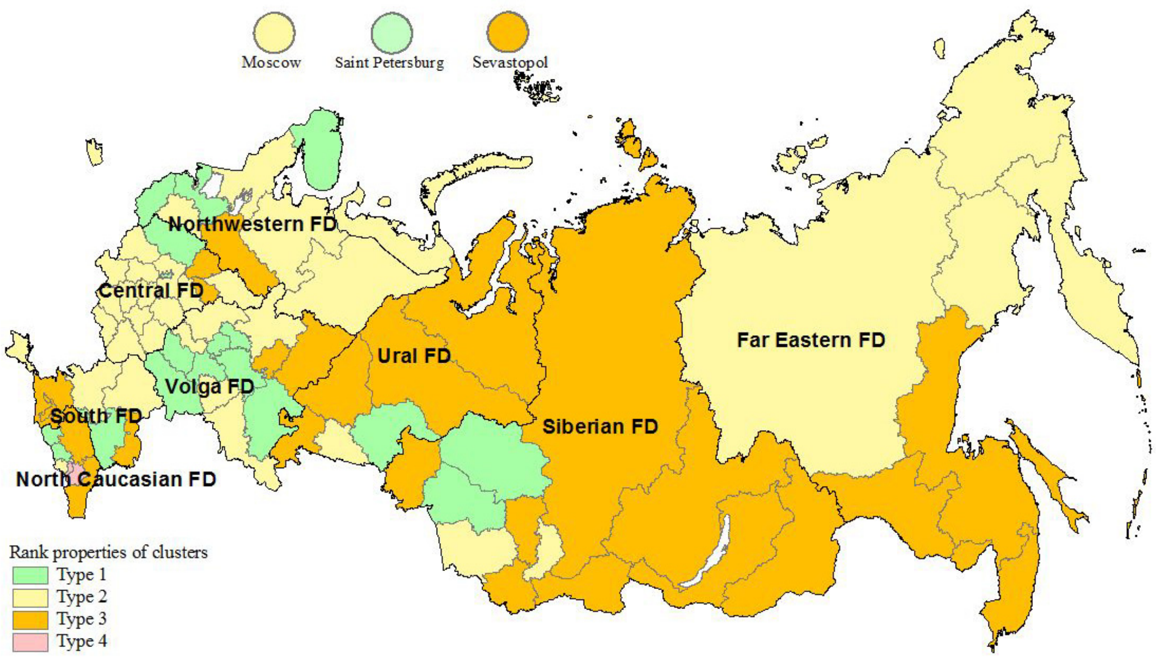

Figure 2. RF regions distributed into clusters as per indicators related to the educational process

Average cluster values in the 2nd cluster (Type 2) are close to those determined for the 3rd cluster. Differences are detected only in the indicator "A share of children attending sport clubs or other establishments for children and adolescents". This indicator has the highest value in the 2nd cluster and amounts to 55 %. The 2nd cluster includes such regions as Belgorod, Vladimir, Voronezh, Moscow, Orel, Ryazan, Arkhangelsk, Kaliningrad, Novgorod, Kurgan, and Magadan regions, Karelia, Crimea, Komi Republic, Yakut Republic, Saint Petersburg, Kamchatka, Chukotka and some others.

The least favorable situation is in the 4th cluster (Type 4) with the highest average cluster shares of schools operating not only in two but also in three shifts, 59.58 % and 6.6 % accordingly. It is by 3.1 and 40.8 times higher than on average in the country. The 4th cluster includes Chechnya and Ingushetia.

Typologization of the RF regions ***as per the sanitary-epidemiologic situation, living and educational environment*** revealed there were 4 clusters as well. The 1st cluster included 38 RF regions; the 2nd one, 6; the 3rd one, 21; and the 4th cluster included 20 regions (Figure 3).

The most favorable situation is in the 4th cluster (Type 1). There are a set of indicators with their average cluster values being the lowest in this cluster including a share of water samples taken from water supply networks that do not conform to hygienic standards as per sanitary-chemical, microbiological, and parasitological indicators; a share of water samples taken from distribution networks that deviate from the standards as per sanitary-chemical, microbiological, and parasitological indicators and total alpha-and-beta activity; a share of water samples taken in educational establishments that don't conform to the standards as per microbiological indicators; a specific weight of population provided with conditionally qualitative water; a share of soil samples taken on territories around children facilities and playgrounds that don't conform to the standards as per sanitary-chemical indicators including contents of heavy metals; a share of ambient air samples with contaminants in concentrations exceeding MPC. This cluster includes such regions as Voronezh, Orel, and Astrakhan regions, Adygei, Crimea, Altai, Krasnodar and Stavropol regions, Kamchatka and some others.

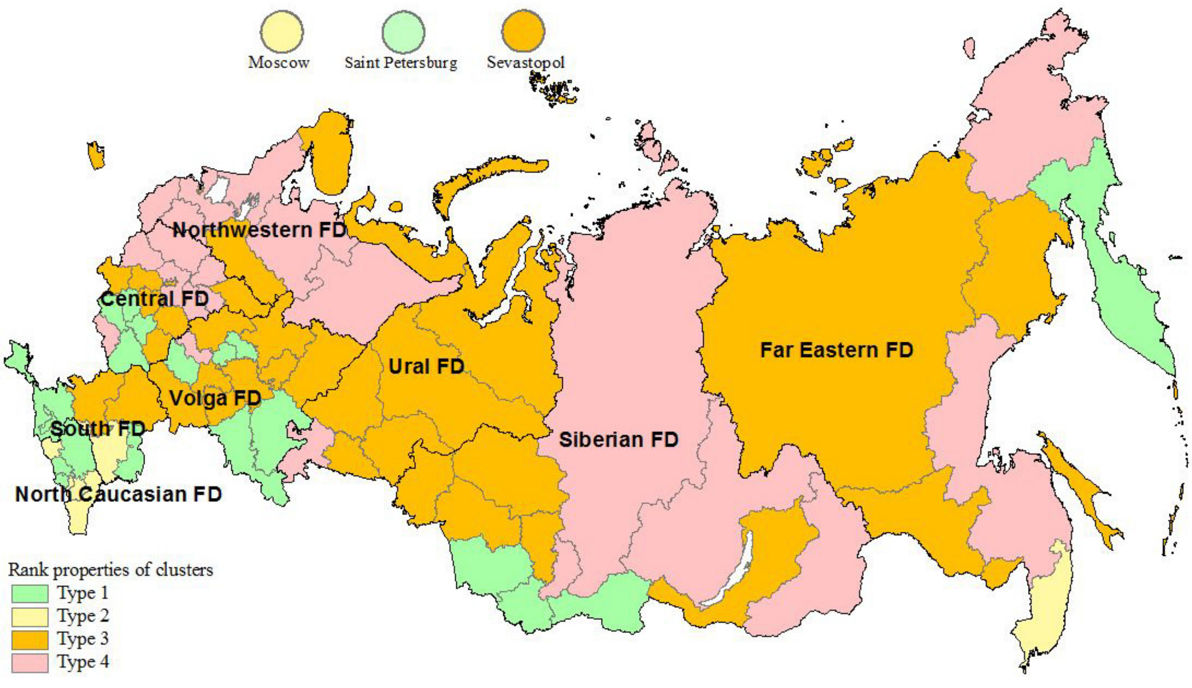

Figure 3. RF regions distributed into clusters as per sanitary-epidemiological well-being, living and educational environment

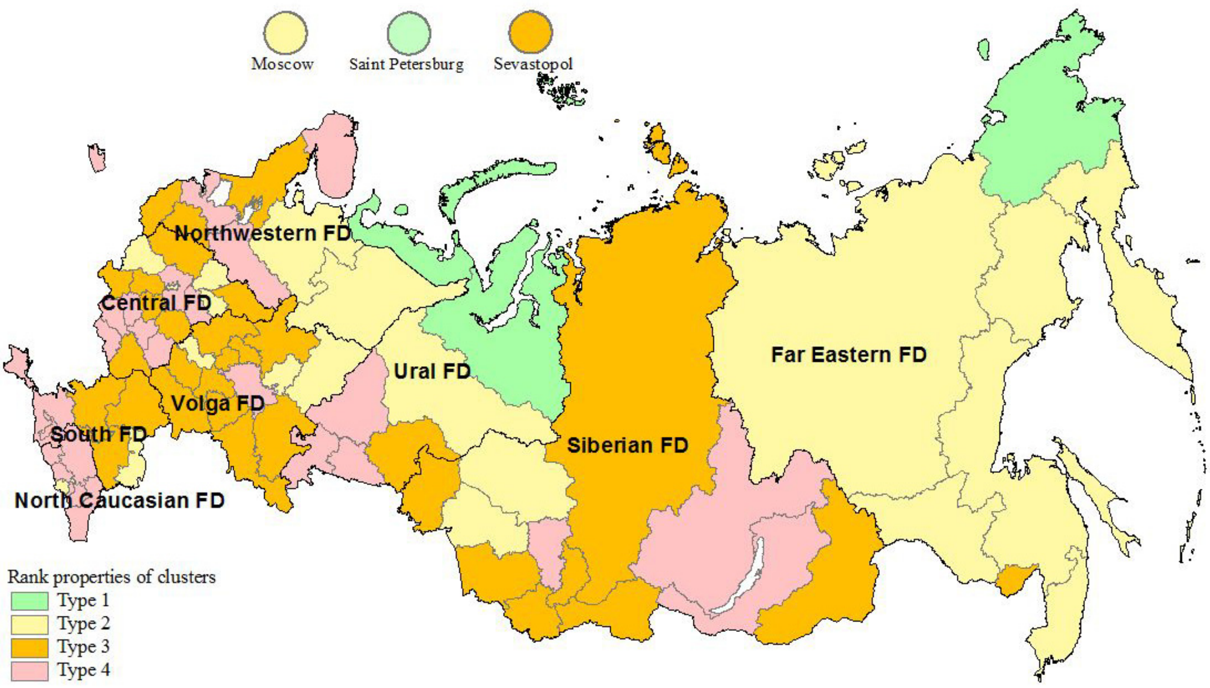

Figure 4. RF regions distributed into clusters as per socioeconomic factors

The complex assessment revealed the least favorable situation in the 3rd cluster (Type 4). There is the highest average cluster specific weight of urban population provided with conditionally qualitative water. There are 21 regions in the cluster including Belgorod, Vladimir, Ivanovo, Moscow, and Smolensk regions, Karelia, Komi Republic, Mordovia, Khakassia, Krasnoyarsk and Khabarovsk regions, Transbaikalia etc..

Typologization of the RF regions ***as per socioeconomic factors*** showed that the 1st cluster included 3 RF regions; the 2nd one, 22; the 3rd one, 32; and the 4th cluster included 28 RF regions (Figure 4).

The most favorable situation is the regions included into the 1st cluster (Type 1). The following indicators were detected in the cluster: living standard amounted to 19,917.4 rubles; gross regional products per capita, 3,823 thousand rubles; a number of experts in children and adolescent hygiene, 0.32 doctors per 10,000 children; a number of in-patient hospital beds, 83.9 beds per 10,000 children; a number of pediatric in-patient beds, 50.5 beds per 10,000 children. The 1st cluster includes only Nenets Autonomous Area, Yamal-Nenets Autonomous Area, and Chukotka.

The least favorable situation is in the 4th cluster (Type 4). The average cluster values tend to be low; thus, gross regional product per capita amounts to only 334.2 thousand rubles; living standard, 10,133.4 rubles, a number of in-patient hospital beds and pediatric beds, 51.74 and 18.03 beds per 10,000 children accordingly; a number of pediatricians and district pediatricians, 14.1 and 8.1 doctors per 10,000 children accordingly. The 4th cluster includes 28 RF regions such as Voronezh, Kursk, Lipetsk, and Orel regions, Adygei, Crimea, North Ossetia, Krasnodar and Altai regions, Kamchatka and some others.

Typologization of RF regions as per indicators ***describing nutrition provided for children*** distributed the regions into 4 clusters, the 1st one including 16 regions; the 2nd one, 36; the 3rd one, 18; and the 4th one, 15 regions (Figure 5).

The most favorable situation as per this set of indicators is in regions included into the 4th cluster (Type 1) as described by the following: the lowest average cluster shares of cooked meals that don't conform to hygienic standards as per caloric content and chemical structure, microbiological and sanitary-chemical indicators, and contents of vitamin C;

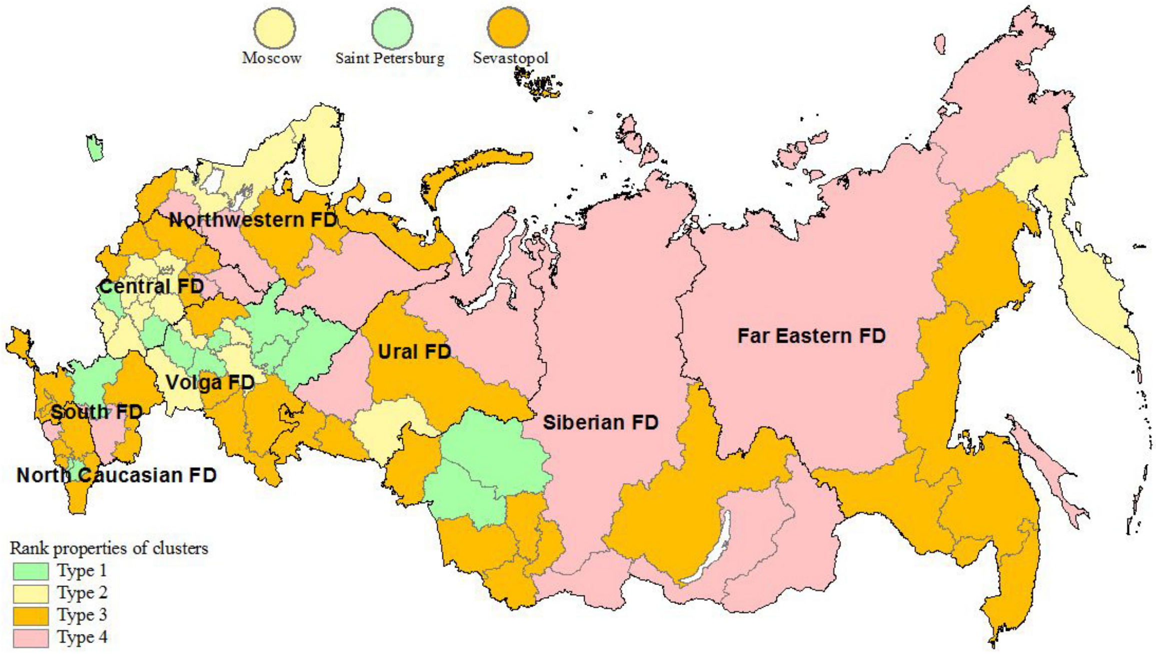

Figure 5. RF regions distributed into clusters as per peculiarities nutrition provided for children

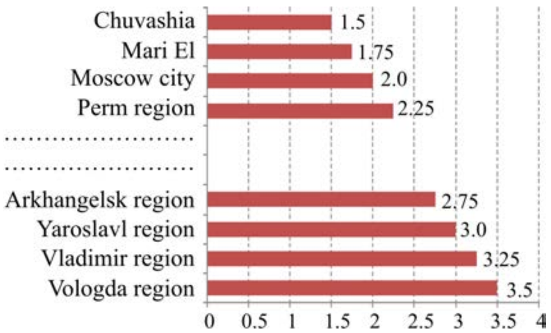

Figure 6. Examples of average rank values for the sets of indicators

the highest average cluster shares of children provided with hot meals, 43.2 %. The cluster includes such regions as Kursk, Tambov, Kaliningrad, and Perm regions, Saint Petersburg, and some others.

The least favorable situation is in the 1st cluster (Type 4). There are the highest values of the following parameters: a share of cooked meals not conforming to the hygienic standards as per caloric contents and chemical structure, 16.2 %; microbiological and sanitary-chemical indicators, 3.8 % and 6.8 % accordingly; contents of vitamin C, 18.2 %; there is also the highest share of educational organizations that don't provide any meals for schoolchildren, 3.3 %.

We calculated all average rank properties for the examined sets of indicators that described their influence on children's health. This calculation revealed that values varied within 1.5–3.5 in various RF regions. The highest values were detected in Vologda, Sverdlovsk, Chelyabinsk, Krasnoyarsk, and Irkutsk regions, Buryatia, and Transbaikalia (Figure 6).

Clusterization accomplished as per the sets of modifying indicators shows that there is an unfavorable situation in 49 RF regions as per a certain set of indicators and this allows us to assign these regions to Type 4.

Weighted values of cluster rank properties vary from Type 1 (the most favorable) to Type 3 (average) in 36 RF regions. This group includes such regions as Bryansk, Voronezh, Kaluga, Ryazan, and Tula regions, Moscow (city), Saint Petersburg, North Ossetia, Bashkortostan, Mari El, Perm region, Altai region, The Jewish Autonomous Region etc. Average ranks values varied from 1.2 to 2.4 in this regions for such modifying set of indicators as educational loads, the sanitary-epidemiological situation in the region, living and educational environment, socioeconomic conditions, and nutrition provided for children.

Profound analysis performed for each region describes the current situation in it and a role played by the analyzed factors in children's health. Thus, Penza region (average rank value is 1.5) that belongs to Type 3 as per socioeconomic conditions, provides the most favorable sanitary-epidemiological situation (Type 1), has the best conditions in regard to educational loads (Type 1) and children are provided with qualitative nutrition at schools in the region (Type 1); consequently, the region is included into the cluster with the highest share of children in the health group I (Type 1, the cluster value is 29 %; the regional value, 24 %).

Chelyabinsk and Irkutsk regions hold the last rank place (Type 4) both as per socioeconomic living conditions and sanitary-epidemiological situation; they belong to Type 3 as per quality of nutrition and educational loads in schools. So it's no wonder that both these regions are in the cluster with the lowest share of children in the health group I (16 %) and high shares of children in health groups III, IV and V (25 %). These regions need a set of activities aimed at improving the socioeconomic and sanitary-epidemiological situation there; educational programs and organization should be adjusted as well. Besides, it is advisable to make changes in school menus to provide children with nutrition that is able to fully satisfy all needs of children's growing and developing bodies. In particular, it is necessary to reach balance between energy requirements of the body, need in basic nutrients and their actual introduction with food rations; menus should include a lot of variable meals so that schoolchildren are able to choose what they like since this ensures an increase in actual food consumption; rations should be added with vegetables, fish and meat. Given the transition to state funding provided for meals in primary schools it is vital to determine necessary volumes of subsidizing sufficient to provide children with meals that can fully satisfy their physiological needs and conform to the standards stipulated by the sanitary legislation. The current standards fixed for nutrition provided in schools need to be revised.

Therefore, the current situation in each region reflects regularities related to influence exerted by a set of factors on children's health. This indicates the necessity to create a road map for each RF region with feasible mechanisms aimed at improving this situation as per specific aspects.

Conclusions:

1. The accomplished assessments and typologization of RF regions allowed revealing certain regularities and trends related to influence exerted by various sets of factors on children's health bearing their regional differentiation in mind.

2. Typologization of the RF regions as per health groups has revealed the most favorable situation in 31 regions where a share of children in the health group I amounts to 29 % being by 1.2 times higher than on average in the country. The least favorable situation is in two regions (Dagestan and Ingushetia), where shares of children in the health groups IV and V amount to 4.3 % and 2.8 % accordingly and this is by 4.4 and 2.9 times higher accordingly than on average in the country.

3. The most favorable situation as per the educational process has been detected in 55 regions (Types 1 and 2) where schools predominantly operate in one shift (87.1 % and 88.8 % accordingly). The least favorable situation is in two regions (Ingushetia and Chechnya) where schools operate in two or three shifts (59.6 % and 6.6 % accordingly).

4. Typologization of the RF regions as per sanitary-epidemiological well-being and living and educational environment also divides the country into 4 clusters where 20 regions are the most favorable (Type 1) as per the indicators describing quality of water, ambient air and soils, and 21 regions are the least favorable (Type 4).

5. Analysis of the socioeconomic situation in the RF regions has revealed that only three regions can be called the most favorable as per the set of the analyzed indicators here (Nenets Autonomous Area, Yamal-Nenets Autonomous Area and Chukotka) where we have detected high average cluster values of gross regional products per capita, 3,823 thousand ru-

bles, and living standard, 19,917 rubles. The least favorable situation is in 28 regions (Type 4), where these two indicators are equal to 334.2 thousand rubles and 10,133 rubles accordingly.

6. All the revealed priority regularities that determine influence exerted by sets of regionally differentiated factors related to living and educational environment on schoolchildren's health call for creating a road map for each RF region with feasible mechanisms aimed at improving the current situation as per specific aspects.

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Research article

ASSESSING AND PREDICTING INDIVIDUAL OCCUPATIONAL RISK AND DETERMINING ITS EXACT CATEGORIES USING PROBABILISTIC METHODS

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Existing approaches to occupational risk assessment more often involve evaluating its group levels and individual risks are assessed less frequently. These approaches provide deterministic risk assessment which doesn't take into account uncertainty in risk categorizing when its values are close to boundaries between adjoining risks categories. It substantiates the necessity to assess occupational risk levels using probabilistic methods.

Our research object was occupational risk and the basic subject was distribution of individual occupational risk levels among workers. Our test group was made up of oil and gas extraction operators exposed to noise equal to 80–85 dBA at their workplaces (173 people). Our control group included oil and gas extraction operators and engineering and technical personnel occupationally exposed to noise equal to 60–77.8 dBA (259 people). We performed a priori assessment of occupational health risks; accomplished epidemiologic analysis of a cause-effect relation between health disorders and work; calculated group occupational health risks; calculated and predicted individual occupational risk using mathematical modeling of dependence between probable negative responses and working conditions, age, and period of employment; determined risk categories more precisely using fuzzy sets by calculating the membership function.

As a result, we established that proven individual risk levels were distributed unevenly ($1.06 \cdot 10^{-4}$–$1.47 \cdot 10^{-2}$) as per categories within a group characterized with a suspected average risk level. A category of proven individual risk levels was determined more precisely using fuzzy sets; after that distribution of probability of their membership was evaluated to detect that at the moment of the research a share of workers with their proven individual occupational risks falling into lower risk categories ($p > 0.5$) amounted to 89.6 %.

We attempted to predict risks for the whole employment period given that working conditions remained the same and no prevention activities were provided. Our prediction revealed that individual occupational risks would remain unacceptable for all workers in the test group and would amount to $2.53 \cdot 10^{-2}$–$3.51 \cdot 10^{-2}$; a risk category was also expected to become higher. Individual occupational risk would be categorized as average for most workers and as high for 23 % of them ($p < 0.5$).

Key words: *occupational risk, noise, probabilistic assessment, risk level categorizing, regression models, risk level prediction, sensorineural hearing loss, fuzzy sets.*

Existing methodical approaches to occupational risk assessment mostly involve assessing it on a group level [1–4] and much less frequently on an individual one [5]. In foreign practice occupational risk is also mostly calculated on a group level and the procedure usually involves epidemiologic evaluation of relationships between morbidity and working conditions as well as relative risk calculation [6–8].

These aforementioned approaches allow assessing occupational risks for big occupa-

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tional groups based on data on working conditions and workers' health predominantly focusing on occupational morbidity. These approaches provide deterministic risk assessment that can lead to occurring uncertainty in risk categorization when occupational risks rates are close to boundaries between adjoining risks categories.

Meanwhile, individual peculiarities related to development of diseases that occur due to exposure to adverse factors at a workplace determine the necessity to quantitatively assess occupational risks not only on a group level but also on an individual one. Categorization of group occupational risks performed for big occupational groups doesn't allow for peculiar distribution of individual risk rates as per different categories within a group.

The most significant deviations in individual risk assessment from group ones can be expected in a situation when group risk rate is close to a boundary between adjoining risk categories. If we analyze a probability to assign individual risks to a certain category, it will allow us to adjust results of group risk assessment and to create more adequate risk groups for subsequent prevention activities.

By now, certain methodical approaches to probabilistic occupational risk assessment have been suggested; they involve using fuzzy sets theory and aim to determine more precisely which risk category an individual risk belongs to [9].

These approaches seem the most vital when we assess occupational risks for workers exposed to noise levels deviating from hygienic standards at their workplaces. Noise, including its levels exceeding MPL, remains among leading factors that cause a developing occupational pathology, first of all, sensorineural hearing loss [10–13][1]. In several authors' opinion, this is due to growing mechanization and automation in various industries (oil extraction and processing, metallurgy, metal processing, civil engineering, construction, etc.) [14]. Therefore, there are a growing number of people who are exposed to noise at workplaces due to old equipment not conforming to sanitary-hygienic requirements [10, 14, 15][1]. Annually more than 3 million workers are occupationally exposed to noise levels that exceed maximum permissible ones [16].

Since employable age is now prolonged in the country due to the pension reform [17], it is truly necessary to predict occupational risks over the whole period of employment [18, 19]. Given that, we can conclude that it seems vital to assess occupational risks for workers exposed to occupational noise levels exceeding hygienic standards with probabilistic methods.

Our research aim was to assess and predict an individual occupational risk for workers exposed to occupational noise levels deviating from hygienic standards over the whole period of employment and to examine changes in risk categories using probabilistic methods.

Materials and methods. We analyzed data on working conditions (obtained by the special assessment of working conditions (SAWC) and industrial laboratory control), working experience and age; categories of working conditions were estimated in accordance with the Guide R 2.2.2006-05 "The Guide on hygienic assessment of factors related to working environment and labor process / Criteria and classification of working conditions"[2]; risks were categorized in accordance with the Guide R 2.2.1766-03 "The Guide on assessment of occupational risks for workers'

[1] O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2020 godu: Gosudarstvennyi doklad [On sanitary-epidemiologic welfare of the population in 2020: The State Report]. Moscow, The Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2021, 256 p. (in Russian).

[2] R 2.2.2006-05. Rukovodstvo po gigienicheskoi otsenke faktorov rabochei sredy i trudovogo protsessa. Kriterii i klassifikatsiya uslovii truda: utv. Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii 29 iyulya 2005 g. [The Guide R 2.2.2006-05. The Guide on hygienic assessment of factors related to working environment and labor process. Criteria and classification of working conditions (approved by the RF Chief Sanitary Inspector on July 29, 2005)]. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200040973 (August 17, 2021) (in Russian).

health. Organizational and methodical grounds, principles, and assessment criteria”[3].

We applied methodical approaches to probabilistic assessment of occupational risks belonging to a certain risk categories for workers employed in oil extraction and occupationally exposed to noise levels exceeding hygienic standards.

Our test group was made up of oil and gas extraction operators who were exposed to a noise level equal to 80–85 dBA at their workplaces (173 people, average age was 39.7 years; average working experience, 12.7 years). The reference group included oil and gas extraction operators and engineering and technical personnel who were exposed to noise levels equal to 60–77.8 dBA at their workplaces (259 people with their average age being 46.8 years; average working experience, 12.6 years).

Occupational health risks were assessed as per the following algorithm:

1. A priori occupational risk assessment based on SAWC results in accordance with the Guide R 2.2.1766-03 “The Guide on assessment of occupational risks for workers’ health. Organizational and methodical grounds, principles, and assessment criteria”[3];

2. Epidemiologic analysis of cause-effect relations between health disorders and work;

3. Occupational group risk assessment;

4. Occupational individual risk assessment using mathematical modeling of a relationship between a probability of negative responses and working conditions, age and working experience;

5. Assessment of individual health risks due to work-related diseases using obtained model parameters;

6. Adjustment of risk categories using fuzzy sets procedure.

The suggested algorithm involved using a set of procedures including:

– assessing a cause-effect relation between health disorders and exposure to noise; the assessment was performed as per risk ratio (*RR*) and etiological fraction (*EF*) of negative responses.

– analyzing exposure –response relationship using logistic regression models that show dependence between a probability of health disorders and working conditions, age and working experience; the models were created using Statistica 6.0 software package [20] (1).

$$p_1 = \frac{1}{1+e^{-(b_0+b_1x_1x_2+b_2x_3)}}, \qquad (1)$$

where p_1 is a probability of a negative response (an occupational or a work-related disease); x_1 is a level of exposure to a factor; x_2 is working experience; x_3 is age; b_0, b_1, b_2 are parameters of a mathematical model.

The suggested model parameters were used to calculate predictive values of developing diseases and occupational risks by the age of 65 years. Health risk was determined as a probability of a disease multiplied by its severity[4]. A risk equal to $1 \cdot 10^{-3}$ and lower (low and negligibly low risks accordingly) was considered acceptable (permissible) occupational health risk.

Calculated occupational risk rates were considered to be deterministic values that were assessed and assigned into specific risk category according to the scale provided in Table 1 [9].

Probabilistic assessment of individual risk belonging to a certain category was performed by determining a membership function using a scale with fuzzy numbers built on the basis of deterministic scale showing occupational risk rates.

We applied trapezoid fuzzy numbers to determine what risk category various risk levels belonged to: negligibly low risk was within

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[3] R 2.2.1766-03. Rukovodstvo po otsenke professional'nogo riska dlya zdorov'ya rabotnikov. Organizatsionno-metodicheskie osnovy, printsipy i kriterii otsenki: utv. Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii 24 iyunya 2003 g. [The Guide R 2.2.1766-03. The Guide on assessment of occupational risks for workers' health. Organizational and methodical grounds, principles, and assessment criteria (approved by the RF Chief Sanitary Inspector on June 24, 2003)]. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/901902053 (August 17, 2021) (in Russian).

[4] Professional'naya patologiya: natsional'noe rukovodstvo [Occupational pathology: the national guide]. In: N.F. Izmerov ed. Moscow, GEOTAR-Media, 2011, 784 p. (in Russian).

Table 1

The scale showing occupational risk rates

Occupational risk rates	Occupational risk categories
Lower than $1{\cdot}10^{-4}$	Negligibly low risk
$1{\cdot}10^{-4}$–$1{\cdot}10^{-3}$	Low risk
$1{\cdot}10^{-3}$–$1{\cdot}10^{-2}$	Moderate risk
$1{\cdot}10^{-2}$–$3{\cdot}10^{-2}$	Average risk
$3{\cdot}10^{-2}$–$1{\cdot}10^{-1}$	High risk
$1{\cdot}10^{-1}$–$3{\cdot}10^{-1}$	Very high risk
$3{\cdot}10^{-1}$–1	Extremely high risk

0, 0, 0.00005, 0.00033; low risk, 0.00005, 0.00033, 0.00078, 0.00325; moderate risk, 0.00078, 0.00325, 0.0775, 0.015; average risk, 0.0775, 0.015, 0.025, 0.0475; high risk, 0.025, 0.0475, 0.0825, 0.15; very high risk, 0.0825, 0.15, 0.25, 0.53; extremely high risk, 0.25, 0.53, 1.1[5].

To present the scale showing trapezoid fuzzy numbers used to assess occupational risk rates, we applied the following coordinate axes: X-axis showed risk rate and Y-axis showed a value of a membership function for this risk rate (Figure 1).

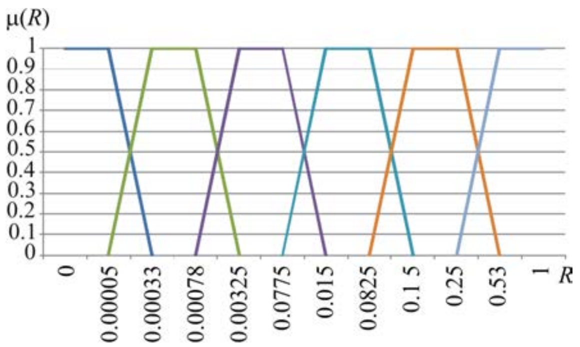

Figure 1. A graph showing the scale with trapezoid fuzzy numbers used to assess occupational risk rates

Use of trapezoid fuzzy numbers allowed determine more precisely what risk category a risk rate belonged to. Taking into account calculated estimates of a membership function for a fuzzy number that showed a probability of a risk belonging to a certain category form 0 to 1, we determined a risk rate more precisely; in case a membership function was equal to 1, a risk category did not need any further adjustment.

Given the calculated estimates of membership functions for a fuzzy number, a weight of a risk category (P_k) was determined as per the following formula (2):

$$P_k = \sum_i q_i \cdot \mu_{ki}(R^{occup}_{OD(WRD)}),$$
$$k = 1, 2, 3, 4, 5, 6, 7, \quad (2)$$

where q_i is a weight contribution made by a risk category i to overall risk rate; k is significance of a risk category.

Weight contribution made by a risk category i to an overall risk rate (q_i) was calculated as per the Fishburne formula (3):

$$q_i = \frac{2(n-i+1)}{(n+1)n}, \ i = 1, 2, 3, 4, 5, 6, 7, \quad (3)$$

where n is a number of risk categories.

The next step was to determine severity in order to determine a risk more precisely; it was done as per the formula (4):

$$SR_k = \sum_{k=1}^{7} \overline{r_k} \cdot P_k, \quad (4)$$

where r is a value of a variable that shows a more precise risk as a disease with certain severity; $\overline{r_k}$ is the middle of each range on the scale showing risk rates; P_k is a weight of a risk category; SR_k is severity applied to determine a risk more precisely for each disease.

We applied trapezoid fuzzy numbers to determine what risk category those more precisely determined risk rates belonged to: negligibly low risk was within 0, 0, 0.042, 0.125; low risk, 0.042, 0.125, 0.208, 0.292; moderate risk,0.208, 0.292, 0.375, 0.458; average risk, 0.375, 0.458, 0.542, 0.625; high risk, 0.542, 0.625, 0.708, 0.792; very high risk, 0.708, 0.792, 0.875, 0.958; extremely high risk, 0.875, 0.958, 1, 1.

[5] Zade L. Ponyatie lingvisticheskoi peremennoi i ego primenenie k prinyatiyu priblizhennykh reshenii [A concept of a linguistic variable and its application in approximate solutions]. Moscow, Mir Publ., 1976, 166 p. (in Russian).

Table 2

Categorization of individual occupational risk rates

Risk category	A number of workers with a risk from this category (people)	A probability of workers belonging to a certain risk category (people)	
		0.51 – 0.99	1
Low:	34	11	23
Workers at a boundary with moderate risk category	11	–	–
Moderate:	121	45	76
Workers at a boundary with low risk category	26	–	–
Workers at a boundary with average risk category	19	–	–
Average:	18	13	5
Workers at a boundary with moderate risk category	13	–	–

Results and discussion. We performed a priori assessment of expected occupational risk as per a category of working conditions (noise level from 80 to 85 dBA corresponds to hazard category 3.1) in accordance with the Guide R 2.2.1766-03[3] and assigned this risk into "low risk" category; occupational risks for workers from the reference group were considered to be "negligibly low" (noise level was lower than 80 dBA, hazard category 2).

Medical examination and analysis of reports issued after previous periodical medical examinations allowed revealing 7 cases of occupational diseases among 173 workers from the test group (sensorineural hearing loss) as well as several other diseases that might be work-related including 40 cases of hypertension, 1 case of migraine, and 52 cases of functional disorders in the autonomic nervous system. 259 workers from the reference group turned out to have 1 case of sensorineural hearing loss, 66 cases of hypertension, 1 case of migraine, and 145 cases of functional disorders in the autonomic nervous system.

We didn't reveal any authentic cause–effect relations between diseases than might be work-related ones (hypertension, migraine, and functional disorders in the autonomic nervous system) and exposure to noise; therefore, all further occupational risk assessments were performed regarding only the detected occupational pathology, sensorineural hearing loss.

A probability of developing sensorineural hearing loss amounted to $3.91\cdot10^{-2}$ in the test group and to $3.86\cdot10^{-3}$ in the reference one. Additional probability of developing sensorineural hearing loss amounted to $3.52\cdot10^{-2}$.

Proven group risk rate, severity (0.3^4) of sensorineural hearing loss taken into account, amounted to $1.13\cdot10^{-2}$ ("average risk" category) and this rate didn't differ greatly from moderate risk. Given that, we calculated individual risk rates and determined categories of calculated risk rates more precisely.

Our assessment of exposure–effect relationship allowed us to obtain parameters of the mathematical model that showed a probability of developing sensorineural hearing loss depending on a noise level, working experience and age: $b_0 = -7.35$, $b_1 = 0.00014$, $b_2 = 0.074$. Proven individual risk rates in the test group that were calculated using these parameters varied from $1.06\cdot10^{-4}$ to $1.47\cdot10^{-2}$. Unacceptable occupational risks (higher than $1\cdot10^{-3}$, "moderate risk" and higher) were detected for 139 workers of 173 (80.35 % of the total number of people exposed to a noise level being higher than 80 dBA).

Table 2 provides the results of categorizing proven individual occupational risk rates that was performed using probabilistic assessment.

Table 3

Probabilistic assessment of individual risk belonging to a specific category at the age of 65 years

Risk category	A number of workers with a risk in this category (people)	A probability of workers belonging to a specific risk category (people)	
		0.51–0.99	1
Average	173	40	133
Workers at the boundary with high risk	40	–	–

More precisely determined risk rates are considered a basis for substantiating activities aimed at managing occupational risks in accordance with their category.

The suggested algorithm allowed assessing what category individual occupational risks belonged to; as a result, we were able to determine the following more precise categories of proven individual risks:

– occupational risk was categorized as "low" for 19.7 % workers from the test group but still 32.4 % of workers exposed to low risks were at the boundary with moderate risk category;

– occupational risk was categorized as "moderate" for 69.9 % workers from the test group; 21.5 % workers with moderate risk were at the boundary with low risk category, and 15.7 % were at the boundary with average risk category;

– occupational risk was categorized as "average" for 10.4 % workers from the test group; 72.2 % workers with average risk were at the boundary with moderate risk category.

We calculated predicted occupational risk rates by the age of 65 to establish that predicted risk rate would grow and reach values from $2.53 \cdot 10^{-2}$ to $3.51 \cdot 10^{-2}$. Probabilistic assessment of individual risk belonging to a certain category allowed categorizing this risk as being average (Table 3).

Probabilistic assessment of individual risk performed to determine its category more precisely indicates that proved individual risk will be categorized as average for the whole test group when they reach the age of 65 years; 23 % of them will be at the boundary with the high risk category.

Conclusion. Our research focused on examining workers' health under occupational exposure to noise levels deviating from hygienic standards. It was established that suspected risk determined by assessing SAWC results belonged to the average risk category. But still, individual proven risk rates occurring due to an occupational disease (sensorineural hearing loss) were distributed unevenly within the group (from $1.06 \cdot 10^{-4}$ to $1.47 \cdot 10^{-2}$). Low (acceptable) individual risk was detected for 19.7 % workers; moderate risk, 69.9 %; average risk, 10.4 % workers.

Having determined risk categories more precisely, we assessed distribution of probability of proven individual health risks belonging to specific risk categories. Our assessment revealed that at the moment of the research a share of workers with their individual risks belonging to lower rick categories with probability exceeding 0.5 amounted to 89.6 %.

Figure 2 shows the results obtained in assessment of proven individual risks belonging to specific risk categories at the moment of the research and at the moment when all workers would reach the age of 65 years.

We made an attempt to predict changes in individual health risk rates for the examined workers during the whole period of employment (up to the age of 65 years) and determined that if they continued working under the same conditions without any prevention activities provided for them, risk categories would be likely to grow. Proven individual risk rates will become unacceptable for all workers in the test group and will vary from $2.53 \cdot 10^{-2}$ to $3.51 \cdot 10^{-2}$. Proven individual risk will be categorized as average for most workers but it will be high for 23 % of them

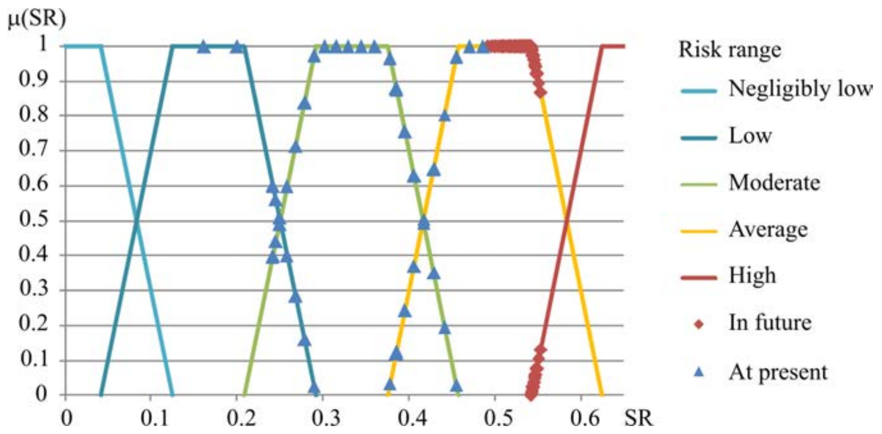

Figure 2. Assessment of proven individual risks belonging to specific risk categories at the moment of the research and at the age of 65 years

(p < 0.5). These workers should be considered a priority risk group and provided with preventive activities aimed at reducing occupational health risks.

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Research article

RISK OF DEVELOPING HYPERTENSION IN UNDERGROUND WORKERS WHEN PSYCHO-VEGETATIVE STATUS IS TRANSFORMING

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The present research work is vital given the importance of studying risk factors that can cause mortality due to diseases of the circulatory system, especially among population of employable age. Our research aim was to establish what factors might induce developing hypertension based on examining psycho-vegetative status, biochemical and functional parameters of the cardiovascular system in underground workers depending on their age.

We examined 109 men who were employed at a chromium mining enterprise and were exposed to occupational and psychosocial factors. The patients were divided into two groups; the test group was made up of 60 men who worked under ground under working conditions ranked as "hazardous" and belonging to hazard category 3.3–3.4; the reference group consisted of 49 men who dealt with surface works under working conditions belonging to hazard category 3.2. The test group was further divided into two sub-groups depending on workers' age: people younger than 45 (n = 20, average age was 38.45 ± 2.95) and people older than (n = 40, average age was 50.90 ± 1.46). The reference group was also divided accordingly. The patients had their psycho-vegetative status examined profoundly with assessing neuropsychic stress, personal and situational anxiety, attention function, and subjective reflection of psycho-vegetative distress. The state of the cardiovascular system (CVS) was examined using results of functional and clinical-laboratory diagnostics.

Decreased attention, greater personal anxiety and a greater number of psycho-vegetative complaints were detected authentically more frequently among patients with hypertension (OR 7.50, 95 % CI 2.39–23.58; OR 11.06, 95 % CI 4.35–28.10; OR 22.50, 95 % CI 7.09–71.41). We detected differences in adaptation psycho-vegetative phenotypes between two sub-groups. A correlation between age and working experience and indicators of psycho-vegetative status was established for patients younger than 45 but there was no correlation with homeostasis indicators. There was a negative correlation between age and working experience and some indicators of psycho-vegetative status revealed for patients older than 45; there was a direct correlation between these parameters and certain homeostasis indicators given hypertension diagnosed in 95 % patients in this sub-group.

As age and working experience grew, adaptation psycho-vegetative phenotype transformed and the process involved inversion of correlations with psycho-vegetative indicators together with aggravating functional disorders of the CVS. When transformation of this phenotype is diagnosed, it allows assessing risks of developing hypertension and makes for primary hypertension prevention through determining risk groups among workers.

Key words: *psycho-vegetative status, hazardous underground work, functional changes, psycho-vegetative phenotype, hypertension, psychosocial factors.*

Occupational and psychosocial factors have great diagnostic significance in occurrence of work-related diseases and it is vital to examine them. Production is becoming more and more intense in many industries, mining included; given that, labor intensity also grows, there are greater loads on workers' psycho-vegetative adaptation mechanisms, elevated risks of cortical-visceral dysfunction and imbalance in the autonomic nervous sys-

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tem. All this leads to distress, basic metabolic disorders, activated free radical lipid oxidation, and endothelial dysfunctions in the vessels [1].

These pathological changes primarily influence the cardiovascular system. As working experience gets longer, adaptive psychological functions are being depleted, and pathologic psychic reactions occur as a response to a situation at a workplace; compensatory role and functions performed by psychological adaptation are also reduced. Psycho-vegetative tension becomes apparent via occurring somatic functional disorders and later leads to growing shares of psychosomatic pathologies, most frequently, developing hypertension [2, 3].

Hypertension is among risk factors that cause diseases of the cardiovascular system (CSDs) among employable population; it makes for growing arterial stiffness (as a pathognomonic syndrome of vascular ageing)[1]. In 2014 mortality due to diseases of the cardiovascular system accounted for 50.1 % of the total deaths in Russia in all age groups and this share remains disproportionately high in old age groups [4].

Psychosocial factors (low self-sufficiency, absence of social support and job dissatisfaction, depression, stress both at home and at work, poor financial situation, and misfortunes) also have a significant role in stress-related health disorders, CSDs included, and occupational stress assessment is recommended to be included into prevention programs implemented at industrial enterprises [5–9]. High CSDs prevalence among working population in Siberia was established to be related to wide spread of such psychosocial risk factors as high anxiety, depression, and sleeping disorders [10]. Significant contribution by vital exhaustion, anxiety and depression symptoms was detected in patients at Bern University Hospital who suffered from acute coronary syndrome or myocardial infarction; most of them needed psychological counseling [11]. Besides, according to data provided by the American Heart Association, depression with anxiety is recommended to be included into risk factors of acute cardiovascular disorders [12].

Meta-analysis was performed to examine health and psychological state of Chinese workers; it revealed that depression and anxiety were associated with a risk of developing CSDs [13]. Depression, together with anxiety, results in mortality risks growing by 77 %, including mortality due to CSDs [15]. Complex studies focusing on psychoemotional and personal peculiarities of patients with cardiovascular pathology proved their significance; these studies were performed to provide an opportunity to improve activities aimed at correction of psychological risk factors causing ischemic heart disease (IHD) and its consequences as well as at reducing their negative impacts [16, 17]. At present psychological support is included into corporate labor protection programs provided for workers employed in many dangerous industries [18].

According to WHO experts' opinion (WHO, Fact sheet of mental health, 2015) and "The strategy for creating healthy lifestyle among population, prevention and control over non-communicable diseases up to 2025"[2] approved by the RF Government, an activity program was developed with its aim being to preserve workers' mental health in order to achieve stable labor productivity and long period of employment [19].

Given all that, it is vital to provide up-to-date diagnostics of workers' psycho-vegetative state. A set of activities aimed at revealing

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[1] O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Respublike Tatarstan v 2019 godu: Gosudarstvennyi doklad [On sanitary-epidemiologic welfare of the population in Tatarstan in 2019: The State Report]. Kazan, Rospotrebnadzor Regional office in Tatarstan, 2020, 356 p. Available at: http://16.rospotrebnadzor.ru/c/document_library/get_file?uuid=e952e8fb-d3f5-467a-a301-f3b082a9b477&groupId=10156 (July 21, 2021) (in Russian).

[2] Ob utverzhdenii Strategii formirovaniya zdorovogo obraza zhizni naseleniya, profilaktiki i kontrolya neinfektsionnykh zabolevanii na period do 2025 goda: Prikaz Ministerstva zdravookhraneniya RF ot 15 yanvarya 2020 g. № 8 [On approval of The strategy for creating healthy lifestyle among population, prevention and control over non-communicable diseases up to 2025: The Order by the RF Public Healthcare Ministry dated January 15, 2020 No. 8]. *Garant: information and legal portal.* Available at: https://www.garant.ru/products/ipo/prime/doc/73421912/ (July 03, 2021) (in Russian).

early signs of diseases and a procedure for providing periodical medical examinations (PME) for various occupational groups are stipulated in multiple legal documents: The Order by the RF Public Healthcare Ministry issued on January 28, 2021 No. 29-n "On approval of the procedure for performing preliminary and periodical medical examinations of workers stipulated in the Part 4, Clause 213 in the RF Labor Code, a list of medical contraindications to accomplishing works with harmful and (or) hazardous occupational factors as well as works that can be accomplished only after obligatory preliminary and periodical medical examinations provided for workers"; the RF Federal Law issued on November 21, 2011 No. 323-FZ "On basics of protecting citizens' health in the Russian Federation" as well as standards for rendering medical aid and clinical recommendations[3]. Among other things, a worker is obliged to have obligatory psychiatric examination taking into account provisions stipulated by the RF Law issued on July 02, 1992 No. 3185-1 "On psychiatric aid and guarantee of citizens' rights protection when rendering it"[4].

A psychiatrist who participates in PME is responsible for establishing any possible psychiatric contraindication to occupational activities. However, bearing in mind the aforementioned importance of psychological adaptation when a psychosomatic pathology is developing, it seems advisable to perform a complex assessment of a worker's mental state focusing on mental functions that have etiopathogenetic significance for psychosomatic pathologies. Obtained data are consistent with information about structure and intensity of workers' somatic pathology applied to create a set of examination procedures and further analysis of relations between mental functions and age, working experience, functional and organic signs of a somatic pathology. Thus, it is possible to create a clinical and psychovegetative phenotype of a worker who deals with intense labor [20], to develop and recommend prevention activities and principles of early somatic pathology diagnostics for determining risk groups.

Our research aim was to establish what factors may induce hypertension based on examining changes in psycho-vegetative status, biochemical and functional parameters of the cardiovascular system in underground workers of middle and older age.

Materials and methods. We examined 60 men who performed their work tasks underground (the test group, $n = 60$, aged 46.8 ± 2.0, working experience equal to 22.0 ± 2.4 years); they all gave their written informed consent to be examined. The reference group was made up of 49 workers who didn't deal with underground labor (their age was 43.6 ± 3.8 and working experience, 16.6 ± 1.6 years). To examine workers' health depending on their age, all patients in the test group were divided into two sub-groups using age classification recommended by the WHO; according to it, people younger than 45 are considered young and people aged 45–60 are considered middle-aged. Sub-group I ($n = 20$) was made up of workers aged 38.45 ± 2.95 with their working experi-

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[3] Ob utverzhdenii Poryadka provedeniya obyazatel'nykh predvaritel'nykh i periodicheskikh meditsinskikh osmotrov rabotnikov, predusmotrennykh chast'yu chetvertoi stat'i 213 Trudovogo kodeksa Rossiiskoi Federatsii, perechnya meditsinskikh protivopokazanii k osushchestvleniyu rabot s vrednymi i (ili) opasnymi proizvodstvennymi faktorami, a takzhe rabotam, pri vypolnenii kotorykh provodyatsya obyazatel'nye predvaritel'nye i periodicheskie meditsinskie osmotry: Prikaz Minzdrava Rossii ot 28.01.2021 № 29n [On approval of the procedure for performing preliminary and periodical medical examinations of workers stipulated in the Part 4, Clause 213 in the RF Labor Code, a list of medical contraindications to accomplishing works with harmful and (or) hazardous occupational factors as well as works that can be accomplished only after obligatory preliminary and periodical medical examinations provided for workers: The Order by the RF Public Healthcare Ministry dated January 28, 2021 No. 29n]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_375353/ (July 23, 2021) (in Russian); Ob osnovakh okhrany zdorov'ya grazhdan v Rossiiskoi Federatsii: Federal'nyi zakon № 323-FZ ot 21.11.2011 [On basics of protecting citizens' health in the Russian Federation: The Federal Law No. 323-FZ issued on November 21, 2011]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_121895/ (July 23, 2021) (in Russian).

[4] O psikhiatricheskoi pomoshchi i garantiyakh prav grazhdan pri ee okazanii: zakon RF № 3185-1 ot 02.07.1992 [On psychiatric aid and guarantee of citizens' rights protection when rendering it: the RF Law No. 3185-1 issued on July 02, 1992]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_4205/ (July 23, 2021) (in Russian).

ence being 12.7 ± 3.0 years; the sub-group II (n = 40) included workers aged 50.90 ± 1.46 with their working experience being 26.7 ± 1.9. The reference group was also divided into two similar sub-groups; 23 workers aged 38.0 ± 2.8 with their working experience being 9.3 ± 1.5 years (workers from the reference group younger than 45); and 26 workers aged 49.2 ± 2.1 with their working experience being 24.0 ± 1.8 years (workers from the reference group older than 45). The groups were comparable as per age, gender, social-communal and occupational conditions; sub-groups I and II in both groups were comparable as per working conditions ($p < 0.05$). Clinical examination was performed at the therapeutic department of the Rospotrebnadzor's Federal Scientific Center for Medical and Preventive Health Risk Management Technologies.

Special assessment of working conditions was performed at workplaces of the major occupational group dealing with underground chromium mining; it revealed that equivalent noise varied from 65.3–70.9 dBA to 108.2–114.9 dBA at miners' workplaces (drift miners, blast-hole drillers, and drilling unit operators, hazard category 3.4). Local vibration at workplaces was higher than maximum permissible level (MPL is fixed at 126 dB) and reached 135 dB and overall vibration was 127 dB (MPL is fixed at 115 dB; hazard category 3.3). Physical loads and frequent necessity to keep an uncomfortable (forced) posture also gave grounds for assigning working conditions of this occupational group into hazard category 3.3. Particulate matter (dusts) concentrations in workplace air corresponded to hazard category 3.1 at workplaces of drift miners, blast-hole drillers, drilling unit operators, and scraper winch operators. Chromium contents didn't exceed 0.002–0.012 mg/m^3 at workplaces; average shift concentration was lower than 0.5 mg/m^3 whereas single MPC fixed in hygienic standards was 1.0 mg/m^3. Overall, working conditions at the examined workplaces were established to be "hazardous" and assigned into hazard categories 3.3–3.4 (Table 1).

Working conditions were hygienically assessed at 34 workplaces of workers from the reference group. The results are given in Table 2.

A periodical medical examination revealed that some workers had elevated blood pressure, higher than 140/90 mm Hg. To put a correct diagnosis, those patients were sent to the therapeutic department of the Rospotrebnadzor's Federal Scientific Center for Medical and Preventive Health Risk Management Technologies. Complex examination performed at an in-patient clinic resulted in "I degree hypertension" diagnosed in 38 patients (63.3 %) from the test group; all of them were middle-aged people (sub-group II).

A clinical interview and questioning were used to identify patients' personality peculiarities. Psycho-vegetative dysfunction was assessed using a set of psychophysiological tests ("NS-Psychotest" computer compels) including "Determination of mental strain by T. Nemchin", 2011

Table 1

Working conditions at workplaces of underground miners from basic occupational groups dealing with chromium ore mining

Occupation	Working conditions category as per their hazard and (or) danger								
	Chemical factor	Aerosols	Noise (Lequiv.)	Vibration (total)	Vibration (local)	Microclimate	Labor hardness	Labor intensity	Overall assessment
Miner	2	3.1	2	–	–	3.3	3.2	1	3.3
Drift miner	2	3.1	3.4	3.2	3.3	3.3	3.3	1	3.4
Timber-man	2	3.1	3.2	–	3.2	3.3	3.2	1	3.3
Blast-hole driller	2	3.1	3.4	3.2	3.3	3.3	3.3	1	3.4
Scraper winch operator	2	3.1	3.3.	3.1	3.1	3.3	3.3	1	3.4
Drilling unit operator	2	3.1	3.4	2	2	3.3	3.2	1	3.4

Table 2

Working conditions at surface workplaces of basic occupational groups dealing with chromium ore mining

Occupation	Working conditions category as per their hazard and (or) danger								
	Chemical factor	Aerosols	Noise (Lequiv.)	Vibration (total)	Vibration (local)	Microclimate	Labor hardness	Labor intensity	Overall assessment
Repairman	2	2	3.2	2	2	–	3.1	–	3.2
Conveyer operator	2	2	3.2	2	–	–	3.1	–	3.2
Jigging machine operator	2	2	3.2	2	–	–	3.1	–	3.2
Loader	2	2	2	–	–	–	3.2	–	3.2

(score estimate of mental strain); "Integrative anxiety test" (score estimate). Voluntary attention was analyzed with a test involving use of Shulte – Gorbov tables. Subjective reflection of psycho-vegetative function was assessed using "Intensity of psycho-vegetative syndrome symptoms" questionnaire, score estimates. Clinical examination included ECG, daily BP monitoring, and US of the heart; we also analyzed the results of total blood count and biochemical blood tests (glucose, creatinine, AST, ALT, sodium, potassium, uric acid in blood serum, lipid spectrum, and C-reactive protein). All the results were statistically analyzed using a built-in analysis module in Excel®2016 MSO (© Microsoft, 2016), and "Stat2015", an author's package of applied electronic tables (© V.S. Shelud'ko, 2001–2016).

Results and discussion. All patients from the test and reference groups participated in clinical-laboratory and instrumental examinations; the results show that homeostasis indicators were within reference values (Table 3).

Patients' personality peculiarities were determined during a clinical interview; they were circumstantiality, decision-making based on external circumstances and moral and ethical beliefs, orientation at wellbeing and worries about it. Attention function was rather low among underground workers from the test group (69.72 ± 6.03 sec, $p < 0.05$) against the reference group; this level corresponded to peculiarities of long monotonous work under hazardous conditions and necessity to keep high concentration but without any attention switching as a result of workers being adapted to their labor. We determined a significant level of personal anxiety (5.0 ± 0.4 scores, $p < 0.05$) indicating readiness for changes in a situation both at work and in social-communal environment. Long-term exposure to personal anxiety is accompanied with constant tension of mental functions and activation of the sympathetic nervous system. Average level of personal anxiety is due to work-related peculiarities including occupational hazards, risks for workers' life during a shift, worrying about one's health and probable loss of a workplace and a right for early retirement, a risk that social status and financial position might deteriorate. We established average mental strain (42.7 ± 1.5 scores, $p < 0.05$) as well as a greater number of psychosomatic complaints (1.5 ± 0.3 scores, $p < 0.05$) than in the reference group. These peculiarities of patients' mental state are considered mental adaptation to hazardous working conditions and are "a psychological profile" of an underground worker (Table 4).

We analyzed correlations between age, working experience, functional parameters of the cardiovascular system, blood test results and psycho-vegetative indicators. A correlation was established between working experience and mental strain ($r = 0.301$, $p = 0.0192$); between depleted attention function and level of creatinine ($r = 0.310$, $p = 0.0160$); between average SBP and pulse BP ($r = 0.755$, $p = 0.000$), atherogenic index and interventricular septum thickness (IST) ($r = 0.407$, $p = 0.0013$), atherogenic index and total cholesterol ($r = 0.651$, $p = 0.000$); interventricular septum thickness and total cholesterol ($r = 0.369$, $p = 0.0037$).

Table 3

Functional changes in the cardiovascular system and clinical-laboratory blood indicators detected in miners

Indicators	Test group (n = 60), $M \pm 2m$	Reference group (n = 49), $M \pm 2m$
Functional changes in the cardiovascular system		
Average SBP, mm Hg	131.20 ± 2.10	128.81 ± 2.21
Pulse BP, mm Hg	46.17 ± 1.88	46.23 ± 2.30
Interventricular septum thickness, cm	0.97 ± 0.06*	0.86 ± 0.07
Clinical-laboratory blood indicators		
Atherogenic index	2.12 ± 0.15*	1.76 ± 0.20
Total cholesterol, mmol/l	5.52 ± 0.37*	4.81 ± 0.29
HDLP, mmol/l	1.78 ± 0.09	1.77 ± 0.10
Uric acid, µmol/l	311.43 ± 13.69*	296.42 ± 19.43
Thrombocytes, $10^9/dm^3$	250.08 ± 13.05	231.19 ± 13.18

N o t e : * means $p < 0.05$, that is, differences from the reference group are statistically significant.

Table 4

Indicators of psycho-vegetative state in workers form the test group

Indicators of psycho-vegetative state	Test group (n = 60), $M \pm 2m$	Reference group (n = 49), $M \pm 2m$
Attention fatigue, sec	69.72 ± 6.03*	40 ± 1.80
Mental strain index (MSI), scores	42.72 ± 1.50*	40.5 ± 1.10
Situational anxiety, scores	1.92 ± 0.40	1.91 ± 0.38
Personal anxiety, scores	5.00 ± 0.39*	4.3 ± 0.21
Psycho-vegetative complaints, scores	1.52 ± 0.28*	0.8 ± 0.10

N o t e : * means $p < 0.05$, that is, differences from the reference group are statistically significant.

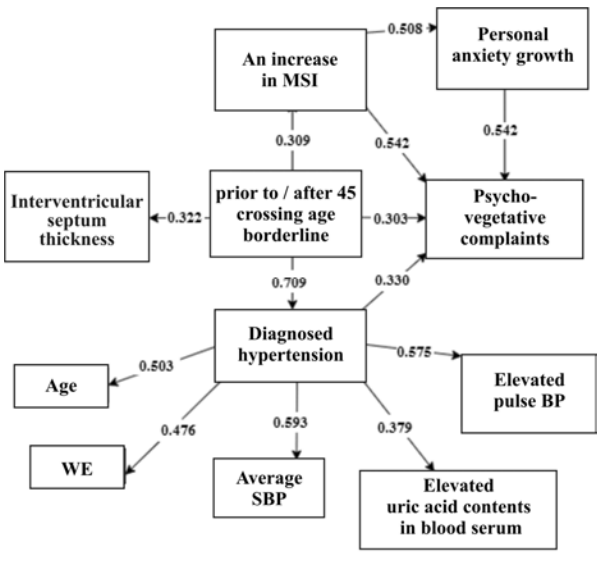

Figure 1. Correlations between functional parameters of the cardiovascular system, blood indicators and psycho-vegetative parameters of workers form the test group

Besides, we established that when an age borderline (45 years) was overcome, it resulted in both greater number of psycho-vegetative complaints and diagnosed hypertension (Figure 1).

These determined correlations gave grounds for assessing risks of deteriorating psycho-vegetative and clinical-functional parameters in patients with hypertension.

Lower attention functions, elevated personal anxiety and a greater number of psychosomatic complains were authentically more frequent in patients with hypertension (OR 7.50, 95 % CI 2.39–23.58; OR 11.06, 95 % CI 4.35–28.10; OR 22.50, 95 % CI 7.09–71.41). We also detected elevated SBP (OR 4.48, 95 % CI 1.80–11.16), pulse BP (OR 3.00, 95 % CI 1.14–7.86), interventricular septum thickness (OR 2.98, 95 % CI 1.26–7.06), atherogenic index (OR 3.20, 95 % CI 1.08–9.50), and uric acid contents in blood serum (OR 3.86, 95 % CI 1.41–10.55) authentically more frequently in such patients. Therefore, patients from the examined groups with diagnosed hypertension are exposed to elevated risks of psycho-vegetative changes such as lower attention functions, greater personal anxiety and a greater number of psycho-vegetative complaints.

Table 5

Results of psychophysiological and clinical examinations in sub-groups I and II

Parameters / indicators	Sub-group I in test group (< 45 years) (n = 20)	Reference group (< 45 years) (n = 23)	p	Sub-group II in test group (> 45 years) (n = 40)	Reference group (> 45 years) (n = 26)	p
Demographic parameters						
Age, years	38.45 ± 2.95	38.00 ± 2.75		50.90 ± 1.46	49.15 ± 1.50	
Working experience, years	12.75 ± 3.02	9.30 ± 1.51		26.68 ± 1.99	23.92 ± 1.27	
Indicators of psycho-vegetative state						
Attention, sec	67.20 ± 6.68*	36.39 ± 2.58	0.0001	70.98 ± 8.44*	39.15 ± 2.12	0.0000
MSI, scores	40.15 ± 1.53*	40.04 ± 1.83	0.0018	44.00 ± 2.01*	41.04 ± 1.48	0.0074
Psycho-vegetative complaints, scores	1.05 ± 0.44*	0.65 ± 0.20	0.0017	1.75 ± 0.33*	0.92 ± 0.24	0.0002
Personal anxiety, scores	4.85 ± 0.61	4.22 ± 0.72	0.3015	5.08 ± 0.50*	4.23 ± 0.62	0.0423
Functional indicators of the cardiovascular system						
SBP, mm Hg	128.45 ± 3.60	126.96 ± 2.90	0.4147	132.58 ± 2.51*	128.81 ± 2.21	0.0441
Pulse BP, mm HG	42.75 ± 2.52	44.43 ± 2.54	0.7326	47.88 ± 2.37	46.23 ± 2.30	0.1993
IST, cm	0.86 ± 0.10	0.84 ± 0.08	0.4465	1.02 ± 0.07*	0.86 ± 0.07	0.0032
Clinical and laboratory homeostasis indicators						
Atherogenic index (IA)	2.04 ± 0.32*	1.83 ± 0.16	0.0067	2.16 ± 0.16*	1.76 ± 0.20	0.0032
HDLP, mmol/l	1.72 ± 0.18*	1.68 ± 0.08	0.0035	1.81 ± 0.10	1.77 ± 0.10	0.3264
AST, U/l	16.20 ± 2.84*	12.52 ± 1.33	0.0292	14.85 ± 1.33*	12.35 ± 1.11	0.0061
ESR, mm/h	8.15 ± 1.71*	5.74 ± 1.24	0.0283	9.48 ± 1.49*	6.31 ± 1.19	0.0056
Total cholesterol, mmol/l	5.03 ± 0.41	4.73 ± 0.29	0.2111	5.77 ± 0.51*	4.81 ± 0.29	0.0021
Creatinine, µmol/l	69.10 ± 6.18	66.96 ± 4.98	0.5059	71.53 ± 6.37*	66.58 ± 4.67	0.0346
Potassium in serum, mmol/l	4.22 ± 0.22	4.10 ± 0.23	0.6669	4.48 ± 0.20*	4.03 ± 0.21	0.0048
Uric acid in serum, µmol/l	300.45 ± 22.28	297.26 ± 22.03	0.8027	316.93 ± 17.19*	296.42 ± 19.43	0.0456
C-reactive protein, mg/l	5.05 ± 1.17	4.18 ± 0.92	0.4560	7.23 ± 1.14*	4.23 ± 0.84	0.0001
Thrombocytes, $10^9/dm^3$	231.30 ± 16.30	226.96 ± 14.76	0.8850	259.48 ± 17.19 *	231.19 ± 13.18	0.0129

Note: * means $p < 0.05$, that is, differences from the reference group are statistically significant.

We analyzed clinical and psycho-vegetative state through comparing two age-sub-groups, I and II, to reveal any adaptation peculiarities (Table 5).

Workers from the test-group, sub-group I had lower attention function, elevated mental strain index with sympathicotonia, and a greater number of psycho-vegetative complaints in comparison with the reference group. We didn't reveal any authentic differences in personal or situational anxiety between the two sub-groups.

Having analyzed parameters of the cardiovascular system, we revealed an ascending trend in average systolic blood pressure (SBP) and in interventricular septum thickness. Total cholesterol and C-reactive protein also tend to be slightly higher.

We analyzed correlations in the sub-group I (Figure 2) to establish there was an apparent one between working experience and mental strain index (r = 0.726, p = 0.0003), an apparent one between mental strain index and a number of psycho-vegetative complaints (r = 0.645, p = 0.0021), a moderate one between age and attention function (r = 0.554, p = 0.011). We didn't establish any correlations between psycho-vegetative indicators and functional changes in the cardiovascular system.

Assessment of risks as per psycho-vegetative and clinical-functional indicators didn't reveal any authentic correlations with diagnosed hypertension in this group.

Therefore, underground miners who are younger than 45 have a specific adaptation clinical-psycho-vegetative phenotype which we label as *"psychologically implemented adaptation phenotype"*. It becomes apparent through lower attention function, increased mental strain index, and a greater number of psycho-vegetative complaints with all these parameters correlating with age and working experience. These results indicate that psycho-vegetative tension is implemented by predominantly psychological mechanisms and is not accompanied with cardiovascular disorders which were not detected in this age group.

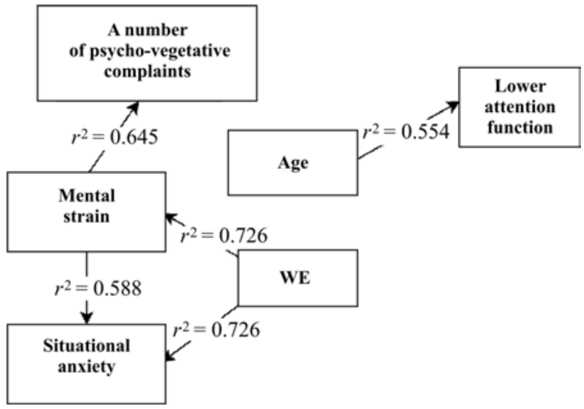

Figure 2. Correlations between age and working experience and psycho-vegetative indicators in workers from sub-group I

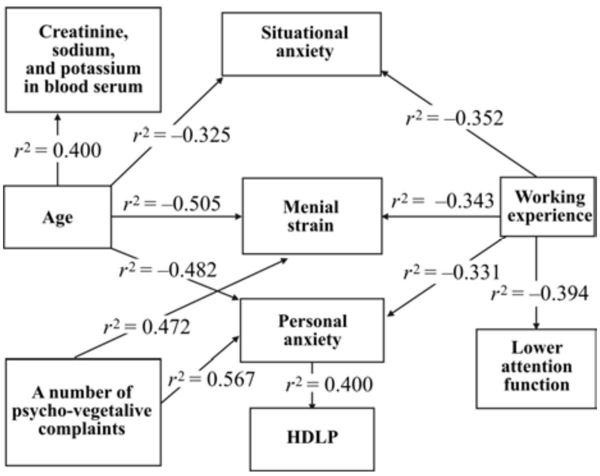

Figure 3. Correlations between age and working experience and psycho-vegetative indicators and laboratory changes in homeostasis in workers from sub-group II

Workers from sub-group II had lower attention function, elevated mental strain index with sympathicotonia, a greater number of psycho-vegetative complaints, and authentically higher personal anxiety. Besides, we detected elevated SBP, growing interventricular septum thickness, elevated atherogenic index and contents of total cholesterol.

Correlation analysis performed in sub-group II revealed the following (Figure 3): a moderate negative correlation between age and mental strain index (r = –0.505, p = 0.0009), age and personal anxiety (r = –0.325, p = 0.026); a moderate negative correlation between age and lower attention function (r = –0.394, p = 0.0119), working experience and mental strain index (r = –0.343, p = 0.0303), working experience and personal (r = –0.331, p = 0.037) as well as situational anxiety (r = –0.352, p = 0.026). Besides, there is moderate correlation between atherogenic index and interventricular septum thickness (invention claim has been submitted). Therefore, there are qualitative changes in psycho-vegetative indicators among workers older than 45; these changes are related to age and working experience and occur against more apparent functional changes in the cardiovascular system and blood indicators. It allows us to determine it as *"adaptation phenotype implemented by psychosomatics"*.

We analyzed risks of deteriorated psycho-vegetative and clinical-functional parameters among patients with hypertension who were older than 45.

Lower attention function and elevated mental strain index were detected authentically more frequently among patients with hypertension (OR 4.98, 95 % CI 1.45–17.07; OR 2.97, 95 % CI 1.07–8.26) but a number of psycho-vegetative complaints was authentically lower (OR 0.17, 95 % CI 0.04–0.85). A risk of changes in psycho-vegetative state among patients with diagnosed hypertension who are older than 45 is different from that among patients without the disease primarily by a decrease in a number of psycho-vegetative complaints thus confirming there is age-related inversion in peculiarities of psycho-vegetative responses.

Therefore, revealed adaptation psycho-vegetative phenotypes show how underground workers adapt psychologically to adverse occupational conditions in different age groups. Workers who are younger have "psychologically implemented adaptation phenotype" with typical elevated mental strain index, a lot of psycho-vegetative complaints, and lower attention function during their first working years. These changes are adaptation in their essence, do not go beyond standard psychological responses and sympathicotonia occurring due to their influence preserves its regulatory function and doesn't induce any changes in the cardiovascular system. As working experience becomes longer, psychological adaptation potential is depleted and workers who are older than 45 have "adaptation phenotype implemented by psychosomatics" which is characterized with lower attention function, elevated mental strain index, a growing number of psycho-vegetative complaints and personal anxiety, elevated SBP, growing interventricular septum thickness, elevated atherogenic index and total cholesterol. As working experience and age grow, there is an inversion of their correlation with psycho-vegetative changes and strain of psychological adaptation functions accumulated with working experience begins to be implemented through psychosomatic mechanisms, sympathicotonia loses its regulatory potential, gets involved into hypertension pathogenesis and makes for its development and creates elevated risks of hypertensive disease.

Conclusion. There are changes in psycho-vegetative status of underground miners combined with certain functional changes in the cardiovascular system and biochemical changes in homeostasis against developing hypertension. Attention function deteriorates, personal anxiety grows, and there is also a growing number of psycho-vegetative complaints (OR 7.50, 95 % CI 2.39–23.58; OR 11.06, 95 % CI 4.35–28.10; OR 22.50, 95 % CI 7.09–71.41). Examination of psycho-vegetative status allows identifying 2 age-dependent phenotypes, "psychologically implemented adaptation phenotype" and "adaptation phenotype implemented by psychosomatics". As working experience and age grow, adaptation psycho-vegetative phenotype transforms together with inversion of correlations with psycho-vegetative indicators against growing functional disorders of the cardiovascular system. Formation of adaptation clinical-psycho-vegetative phenotype in underground miners underlies predicting risks of developing hypertension disease and makes for preventing hypertension in case psychological support is provided (acknowledgment of receipts has been handed in regarding the patent entitled "Method for predicting risks of developing hypertension disease in underground workers", registration No. 2020137973).

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Research article

RISKS OF INCIDENCE OF BREAST CANCER IN A COHORT OF FEMALES OCCUPATIONALLY EXPOSED TO IONIZING RADIATION

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Breast cancer (BrCa) holds the first rank place in morbidity and mortality due to malignant neoplasms among Russian women.

BrCa is a multifactorial disease and ionizing radiation is among factors that cause elevated risks of developing BrCa.

Our research aim was to assess relative risk (RR) of incidence of BrCa among women who were occupationally exposed to chronic ionizing radiation taking into account radiation and non-radiation factors.

RR of incidence of BrCa was analyzed in a cohort of women employed at a nuclear production enterprise, namely Mayak PA, in 1948–1982. 95 % of women started working at the enterprise at their reproductive age. All those women were chronically exposed to ionizing radiation at their workplaces. A mean cumulative breast absorbed dose of external gamma-ray exposure amounted to 0.45 (standard deviation was 0.68) Gy; an average cumulative muscle absorbed dose of internal alpha-particle exposure amounted to 0.003 (0.01) Gy.

According to data taken from "Clinic" medical-dosimetric database, 165 BrCa cases were detected in 157 women of the analyzed cohort (8 women had BrCa in both breasts).

Our analysis involved calculating RR of incidence of BrCa in relation to known non-radiation and radiation factors. Categorical data analysis was performed without age-related and calendar period-related stratification and with them. RR was analyzed based on Poisson regression with AMFIT module in EPICURE software package.

Incidence of BrCa was revealed to be associated with attained age, age of menarche, age of menopause, number of abortions, age of concomitant diseases prior to cancer diagnosis, height, body mass index, age of hiring at the Mayak PA. There was no relationship between BrCa incidence and cumulative doses of occupational chronic external gamma-ray, internal alpha-particle and neutron exposure.

Keywords: *breast cancer, reproductive health, incidence, risk factors, cohort study, women, long-term occupational radiation exposure, Mayak PA.*

Breast cancer (BrCa) is the most widely spread type of cancer among women in both developed and developing countries [1, 2]. And over the last decades there has been a stable growth in incidence of BrCa in most countries all over the world, the Russian Federation (RF) included. BrCa holds the first place in the morbidity pattern for malignant neoplasms (MNs) in the RF female population (21.1 % in 2017). Incidence of BrCa increased by 22 % among women in the RF over 2007–2017 with average annual growth rates of 2.8 % [3, 4].

BrCa is a multifactorial disease. There are several established factors that cause elevated risks of BrCa including age older than 40 years, early menarche (before 12 years of age), late menopause (at age 55 years and later), the first pregnancy terminated by abortion, infertility, age at first birth (30 years and later), breast feeding, reproductive losses, proliferative changes in breast tissues, BrCa in health history of immediate relatives, education, height, body mass index, smoking and some others [2, 5–23].

Breast is well known to be among the most radiosensitive organs [24, 25]. A review issued

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by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) revealed that ionizing radiation (IR) was associated to elevated risks of BrCa [26].

Preston and colleagues [27] analyzed mortality due to BrCa in a combined cohort that included atomic bomb survivors of Hiroshima and Nagasaki (Life Span Study, LSS, Japan) and seven other cohorts comprised of individuals who had undergone radiotherapy for benign neoplasms, communicable diseases and endocrine pathologies. The analysis revealed a linear association of mortality due to BrCa with a radiation dose [28]. Meanwhile, available data on dose-response relationship for BrCa incidence following chronic radiation exposure at low doses are sparse [24, 29]. There are practically no data on effects of known non-radiation factors on incidence of BrCa in cohorts of individuals exposed to IR.

Our research aim was to assess a relative risk (*RR*) of BrCa incidence among females who were occupationally exposed to chronic IR taking into account radiation and non-radiation factors.

Materials and methods. This is a retrospective cohort study. The considered cohort included all females (the total of 5,689) who were employed at the first nuclear enterprise in the former USSR, the Mayak Production Association (PA), in 1948–1982. The cohort members were identified based on occupational histories provided by "The Mayak worker dosimetry system – 2013" (MWDS–2013) [30]. A percentage of workers who were hired at the enterprise prior to 1954 was 51.34 %. The majority of females (95 %) started working at the Mayak PA at their reproductive age (18–45); the average age at the start of employment was 27.32 (standard deviation (*SD*) 7.97) years. As of December 31, 2018, information was available for 95.8 % of females; 3,346 (58.8 %) of them had died (the average attained age was 72.07 years) and 2,103 (37.0 %) were alive (the average age was 75.82 years). The follow-up of the cohort started at the date of hire at one of the main Mayak PA facilities and was ongoing until one of the following dates: date when BrCa was diagnosed; date of death; December 31, 2018 for females who were known to be alive and living in Ozyorsk; date of the last medical record for females who left Ozyorsk for another place of permanent residency (migrants).

Based on data provided by the "Clinic" medical-dosimetric database, 157 females with diagnosed BrCa (malignant neoplasm of breast, C50 in ICD-10) were identified.

Gamma-ray doses from external exposure were available for the whole cohort in the MWDS–2013 [30]. The average duration of employment that involved contacts with gamma-ray sources was 15.6 (10.55) years. The mean cumulative breast absorbed gamma-ray dose from external exposure was 0.45 (0.72) Gy.

We should note that MWDS–2013 does not provide dose estimates for internal radiation exposure of breast but it provides muscle absorbed alpha-particle doses from internal exposure caused by incorporated plutonium. Therefore, in our study we used these doses estimated at the moment of BrCa diagnosis. The mean cumulative muscle absorbed alpha-particle dose from internal exposure due to incorporated plutonium was 0.001 (0.002) Gy.

The analysis estimated the BrCa incidence *RRs* in relation to various non-radiation (attained age, reproductive characteristics, concomitant pathology, height, body mass index (BMI), postmenopausal obesity, BrCa in immediate relatives, education, smoking, alcohol intake, a calendar period of BrCa diagnosis, age and period at hire at the Mayak PA) and radiation factors (external gamma-ray and neutron exposure and internal alpha-particle exposure due to incorporated plutonium).

We performed a categorical data analysis and calculated the BrCa incidence *RRs* for categories of cumulative breast absorbed doses of external gamma-ray exposure (< 0.2 Gy, 0.2–0.5 Gy, 0.5–1.0 Gy, ≥ 1.0 Gy); categories of cumulative muscle absorbed doses of internal alpha-particle exposure (< 0.001 Gy, 0.001–0.005 Gy, ≥ 0.005 Gy); and categories of cumulative muscle absorbed doses of neutron exposure (< 0.0001 Gy, 0.0001–0.0005 Gy, ≥ 0.0005 Gy). Reference groups included workers who were exposed to the lowest doses

(< 0.2 Gy for external gamma-ray exposure; < 0.001 Gy for internal alpha-particle exposure; and < 0.0001 Gy for neutron exposure).

The categorical data analysis that estimated the BrCa incidence *RRs* was performed in two ways: without stratification (Model 1) and with stratification by attained age and calendar period (Model 2).

The association of the BrCa incidence *RR* with internal alpha-particle exposure was analyzed for a subcohort of workers monitored for internal exposure. The association of the BrCa incidence *RR* with neutron exposure was analyzed only for workers who had been occupationally exposed to neutrons.

The *RR* analysis was based on the Poisson's regression and run with AMFIT module of the EPICURE software package [31]. Data were grouped into multidimensional arrays using DATAB module of the EPICURE software package. 95 % confidence intervals (CI) were calculated for *RRs* with maximum likelihood estimation. The results were considered statistically significant at $p < 0.05$.

Results. Malignant neoplasms (Chapter II in ICD-10) accounted for 1.9 % in the pattern of chronic morbidity among females of the study cohort and BrCa held the first place among them (17.6 %).

By December 31, 2018, data were available for all females diagnosed with BrCa: 21 % were alive and 79 % had died. The average age of those who were alive was 80.61 (6.17) years (the median age was 80 years; the minimum age was 67 years, the maximum age was 90 years); the average age of those who had died was 70.96 (12.35) years (the median age was 73.5 years; the minimum age was 28 years; the maximum age was 92 years).

Over the whole follow-up period, 157 females with verified BrCa were identified in the cohort. The average age of BrCa diagnosis was 62.89 (13.10) years (the median age was 65 years; the minimum age was 28 years; the maximum age was 90 years). 8 females had bilateral metachronous BrCa, i.e. BrCa was diagnosed in another breast 6 months later after the first BrCa diagnosis. Therefore, the number of cases identified in 157 females was 165; among them 82 cases (49.7 %) were tumor of a left breast and 83 cases (50.3 %) were tumors of a right breast. 13 females (8.3 %) also had another malignant neoplasm diagnosed prior to BrCa.

Table 1 provides data on BrCa incidence *RRs* in the analyzed cohort by attained age of females.

The *RRs* of BrCa incidence were statistically significantly lower than 1 in all age groups compared to a group of females over 70 year of age (the reference group). The BrCa incidence *RR* increased with increasing attained age.

Table 2 summarizes data on BrCa incidence *RRs* in the analyzed cohort by reproductive characteristics.

The analysis revealed that the BrCa incidence *RR* was elevated in females with age at menarche of 13 years and above and increased with increasing age at menarche; however, the statistically significant *RR* was detected only in females with age at menarche of 18 years and above (Model 1). However, once adjustments for age and calendar period were included in the model, the risk became statistically non-significant.

Table 1

Relative risk of BrCa incidence by attained age

Attained age, years	Number of cases	Person-years of the follow-up / 100,000	Relative risk (95 % confidence interval) (Model 1)	Relative risk (95 % confidence interval) (Model 2)
< 40	9	0.54912	0.07 (0.03, 0.14)	0.13 (0.05, 0.33)
40–49	21	0.36711	0.25 (0.15, 0.40)	0.34 (0.17, 0.65)
50–59	31	0.34663	0.39 (0.25, 0.59)	0.48 (0.28, 0.82)
60–69	39	0.28093	0.60 (0.40, 0.90)	0.68 (0.43, 1.06)
> 70	57	0.24585	1	1

Table 2

Relative risk of BrCa incidence by reproductive characteristics

Characteristic	Number of cases	Person-years of the follow-up / 100,000	Relative risk (95 % confidence interval) (Model 1)	Relative risk (95 % confidence interval) (Model 2)
Age of menarche, years				
< 13	18	0.26422	1	1
14–15	59	0.74931	1.16 (0.70, 2.02)	0.93 (0.56, 1.64)
16–17	42	0.46862	1.32 (0.77, 2.34)	1.09 (0.63, 1.98)
> 18	23	0.17073	1.98 (1.07, 3.71)	1.62 (0.86, 3.11)
Age of menopause, years				
< 44	19	0.1418	1.48 (0.87, 2.41)	1.74 (1.02, 2.82)
45–49	39	0.48423	0.89 (0.60, 1.31)	0.95 (0.64, 1.39)
50–54	71	0.78586	1	1
> 55	9	0.12096	0.82 (0.38, 1.56)	0.82 (0.38, 1.56)
Female infertility (Chapter XIV of ICD-10, N97)				
no	154	1.66065	1	1
yes	3	0.08642	0.37 (0.09, 0.99)	0.34 (0.09, 0.91)
Age at live birth, years				
< 24	88	1.01416	1	1
25–29	45	0.44132	1.18 (0.81, 1.67)	1.14 (0.78, 1.64)
> 30	11	0.12317	1.03 (0.52, 1.84)	1.18 (0.58, 0.21)
The first pregnancy terminated by abortion				
no	135	1.53303	1	1
yes	16	0.20354	0.89 (0.51, 1.45)	0.89 (0.51, 1.45)
Number of births				
1	26	0.34499	1	1
2	90	0.92107	1.30 (0.85, 2.05)	1.11 (0.73, 1.76)
3	25	0.27666	1.20 (0.69, 2.08)	1.01 (0.58, 1.76)
> 4	8	0.12123	0.88 (0.37, 1.85)	0.83 (0.35, 1.79)
Number of abortion				
0	19	0.34073	1	1
1–2	49	0.49395	1.78 (1.07, 3.10)	1.55 (0.92, 2.70)
3–5	54	0.55259	1.75 (1.06, 3.03)	1.37 (0.82, 2.38)
> 6	32	0.37803	1.52 (0.87, 2.73)	1.08 (0.61, 1.97)

We detected the statistically significant elevated *RR* of BrCa incidence for females who had menopause at age below 45.

The BrCa incidence *RR* was statistically significantly lower among females with diagnosed infertility in comparison with those without infertility. However, one should be very careful when interpreting this result since only 3 females (1.91 %) with diagnosed infertility were identified in the analyzed cohort.

We detected the elevated, though statistically non-significant, BrCa incidence *RR* for females who had given birth to the first child at age above 25 years. The BrCa incidence *RR* was below 1 in females who had terminated their first pregnancy by abortion compared to females who had taken pregnancies to terms but the detected risk was statistically non-significant.

The analysis of BrCa incidence in relation to a number of births revealed the elevated (though statistically non-significant) *RR* in females with 2 or 3 births in health histories compared to those with only one birth. Moreover, the BrCa incidence *RR* was lower (though statistically non-significantly) in females with 4 or more births.

Females who had several abortions demonstrated the elevated BrCa incidence *RR* (significant when estimated with Model 1) compared to females without reproductive losses.

Table 3 summarizes data on BrCa incidence *RRs* in the analyzed cohort in relation to a concomitant pathology.

The analysis revealed the statistically significant elevated *RR* of BrCa incidence in females with benign mammary dysplasia, benign neoplasms of breast and leiomyoma of uterus (Table 3).

The analyses based on Model 1 found statistically significant elevated risks of BrCa in females with diabetes mellitus, hypertensive diseases, and neurotic, stress-related and somatoform disorders. When the risk analysis was run using Model 2, the corresponding *RR* estimates levelled down considerably and the risk became statistically non-significant.

Table 4 summarizes *RRs* of BrCa incidence in the analyzed cohort in relation to non-radiation factors.

The analysis revealed the statistically significant elevated *RR* of BrCa incidence in females who were higher than 170 cm compared to those whose height was 150–170 cm. In addition, the elevated (though statistically non-significant) risk of BrCa incidence was detected in females with BMI > 25 kg/m^2 and with post-menopausal obesity ($p < 0.05$ with Model 1).

The BrCa incidence *RR* was elevated ($p > 0.05$) in females whose immediate relatives were diagnosed with BrCa.

The reduced *RR* of BrCa incidence ($p < 0.05$) was detected in females with higher education compared to those without higher education (based on Model 1).

The BrCa incidence *RR* was elevated, though statistically non-significant, in females who had ever smoked. The BrCa incidence *RR* was reduced among alcohol abusers but there were only 2 females in this category with alcohol drinking habit and this result should be interpreted very carefully (due to the insufficient statistical power).

Table 5 provides BrCa incidence *RRs* in the analyzed cohort in relation to a calendar period of BrCa diagnosis and non-radiation occupational factors.

The analysis based on Model 1 revealed BrCa incidence *RRs* below 1 ($p < 0.05$) in all categories of calendar period of BrCa diagnosis (except for 2006–2008) compared to 1991–2005 period. No statistically significant association was observed for BrCa incidence with a period of hire at the Mayak PA. Meanwhile, the elevated *RR* of BrCa incidence was detected in females hired at the Mayak PA at age above 30 years compare to those hired at age between 20 and 30 years.

Table 3

Relative risk of BrCa incidence in relation to a concomitant pathology

Factor	Number of cases	Person-years of the follow-up / 100,000	Relative risk (95 % confidence interval) (Model 1)	Relative risk (95 % confidence interval) (Model 2)
Benign mammary dysplasia (N60 in ICD-10)				
no	140	1.71181	1	1
yes	17	0.03468	5.99 (3.49, 9.62)	3.90 (2.24, 6.36)
Benign neoplasms of breast (D24 in ICD-10)				
no	140	1.71459	1	1
yes	17	0.0319	6.53 (3.80, 10.48)	4.64 (2.70, 7.48)
Leiomyoma of uterus (D25 in ICD-10)				
no	118	1.452	1	1
yes	39	0.29564	1.62 (1.12, 2.31)	0.96 (0.65, 1.38)
Type 1 and 2 diabetes mellitus (E10–E11 in ICD-10)				
no	144	1.7168	1	1
yes	13	0.07285	2.13 (1.15, 3.60)	1.00 (0.53, 1.71)
Hypertensive diseases (I10–I15 in ICD-10)				
no	67	1.26266	1	1
yes	90	0.52698	3.22 (2.35, 4.43)	1.29 (0.88, 1.91)
Neurotic, stress-related and somatoform disorders (F40–F48 in ICD-10)				
no	52	0.84505	1	1
yes	105	0.9446	1.81 (1.30, 2.54)	1.02 (0.73, 1.44)

Table 4

Relative risks of BrCa incidence in relation to non-radiation factors

Factor	Number of cases	Person-years of the follow-up / 100,000	Relative risk (95 % confidence interval) (Model 1)	Relative risk (95 % confidence interval) (Model 2)
Height, cm				
< 150	5	0.09305	0.64 (0.23, 1.40)	0.65 (0.23, 1.43)
150–170	130	1.54558	1	1
> 170	9	0.05153	2.08 (0.98, 3.85)	2.64 (1.24, 4.91)
BMI (kg/m^2)				
< 18.5	14	0.25033	0.53 (0.28, 0.96)	0.57 (0.3, 1.03)
18.5–24.9	39	0.3723	1	1
≥ 25	46	0.34947	1.26 (0.82, 1.93)	1.25 (0.82, 1.93)
Postmenopausal obesity (E66 in ICD-10)				
no	119	1.5677	1	1
yes	38	0.22194	2.26 (1.55, 3.22)	0.92 (0.61, 1.36)
BrCa in immediate relatives				
no	104	0.71004	1	1
yes	5	0.02405	1.42 (0.50, 3.14)	1.58 (0.56, 3.5)
Education				
not higher	140	1.50888	1	1
higher	11	0.21895	0.54 (0.28, 0.95)	0.68 (0.35, 1.20)
Smoking				
never smoked	144	1.66776	1	1
has been a smoker	9	0.09867	1.06 (0.5, 1.95)	1.34 (0.63, 2.50)
Alcohol intake				
never drank	85	0.92939	1	1
a moderate drinker	66	0.74429	0.97 (0.70, 1.34)	0.87 (0.62, 1.22)
alcohol abuser	2	0.07328	0.30 (0.05, 0.94)	0.38 (0.06, 1.20)

Table 5

Relative risks of BrCa incidence in relation to a calendar period of BrCa diagnosis and non-radiation occupational factors

Factor	Number of cases	Person-years of the follow-up / 100,000	Relative risk (95 % confidence interval) (Model 1)	Relative risk (95 % confidence interval) (Model 2)
Calendar period of BrCa diagnosis, years				
< 1960	2	0.25467	0.06 (0.01, 0.18)	0.49 (0.07, 2.04)
1961–1975	16	0.40781	0.27 (0.15, 0.46)	0.82 (0.40, 1.64)
1976–1990	38	0.50502	0.52 (0.35, 0.78)	0.90 (0.56, 1.43)
1991–2005	60	0.41812	1	1
2006–2018	41	0.20403	1.4 (0.94, 2.08)	1.12 (0.72, 1.73)
Period of hire at the Mayak PA, years				
1948–1953	67	0.80503	1	1
1954–1958	19	0.23603	0.97 (0.57, 1.58)	0.97 (0.57, 1.58)
1959–1982	71	0.74859	1.14 (0.82, 1.59)	1.14 (0.82, 1.59)
Age at hire, years				
< 20	19	0.32094	0.77 (0.45, 1.24)	0.82 (0.47, 1.36)
20–30	73	0.94314	1	1
> 30	65	0.52556	1.60 (1.14, 2.23)	1.30 (0.91, 1.86)

Table 6

Relative risk of BrCa incidence in relation to cumulative breast absorbed gamma-ray dose of external exposure

	Cumulative dose of external gamma-ray exposure, Gy			
	< 0.2	0.2–0.5	0.5–1.0	> 1.00
Number of cases	91	26	18	22
Person-years of follow-up / 100,000	0.96002	0.2781	0.20983	0.27402
Relative risk (95 % confidence interval) (Model 1)	1	0.99 (0.63, 1.50)	0.91 (0.53, 1.46)	0.85 (0.52, 1.32)
Relative risk (95 % confidence interval) (Model 2)	1	0.89 (0.56, 1.37)	0.88 (0.51, 1.46)	0.81 (0.49, 1.31)

Table 7

Relative risk of of BrCa incidence in relation to cumulative breast absorbed dose of neutron exposure

	Cumulative dose of neutron exposure, Gy			
	0	< 0.0001	0.0001–0.0005	> 0.0005
Number of cases	137	8	6	6
Person-years of the follow-up / 100,000	1.56911	0.04058	0.05842	0.05842
Relative risk (95 % confidence interval) (Model 1)	–	1	0.52 (0.17, 1.50)	1.27 (0.50, 2.63)
Relative risk (95 % confidence interval) (Model 2)	–	1	0.49 (0.16, 1.41)	0.49 (0.16, 1.41)

Table 8

Relative risk of BrCa incidence in relation to cumulative muscle absorbed alpha-particle dose of internal exposure

	Cumulative dose of internal alpha-particle exposure, Gy		
	< 0.001	0.001–0.005	> 0.005
Number of cases	82	15	3
Person-years of the follow-up / 100,000	0.934	0.13898	0.04014
Relative risk (95 % confidence interval) (Model 1)	1	1.23 (0.68, 2.07)	0.85 (0.21, 2.27)
Relative risk (95 % confidence interval) (Model 2)	1	0.75 (0.41, 1.29)	0.57 (0.14, 1.55)

Tables 6–8 summarize *RRs* of BrCa incidence in the analyzed cohort in relation to cumulative doses of occupational radiation exposure.

The analysis did not reveal an association of BrCa incidence with either cumulative breast absorbed gamma-ray dose of external exposure, neutron dose or alpha-particle dose of internal exposure.

Discussion. The results of the study demonstrated that BrCa incidence in the cohort of female nuclear workers employed at the Mayak PA was associated with many non-radiation factors and the results were mostly in line with those obtained in other studies [2, 5, 6, 8, 12, 14–22, 32].

For example, the risk of BrCa incidence increased with increasing attained age what could be expected [2, 5, 6] and was consistent with observations of many other studies.

In contrast to a number of studies reporting that early age at menarche (before 13 years) increased risks of BrCa [8–10], we detected the statistically significant elevated risk of BrCa incidence in females with age at menarche 18 years and older (based on Model 1). With inclusion of additional adjustments for age and calendar period in the model (Model 2), the risk remained elevated but became statistically non-significant. We also detected the elevated risk of BrCa in females of the study cohort who had menopause at age below 45 years while some other studies [9, 11] revealed that late menopause (at age above 55) increased BrCa risks.

The study demonstrated the elevated risk of BrCa incidence in females with late age at first birth (above 25 years) and this agreed well with results observed in some other studies [6, 9, 10, 13].

The BrCa incidence *RR* was lower in those females of the analyzed cohort who had four or more births ($p < 0.05$) and this was consistent with the results of a meta-analysis [14] and a number of other studies [8] that demonstrated decreased risks of BrCa with increasing number of pregnancies and births.

We revealed the elevated risk of BrCa incidence in females of the study cohort who terminated their pregnancies by abortion and this agreed with other research results reporting that three or more abortions led to a considerable increase in risks of BrCa [15, 16].

This study demonstrated the elevated risk of BrCa incidence in females with fibrocystic breast disease and benign neoplasms of breast registered prior to BrCa in health histories and this agreed well with results of other studies [6, 17, 18].

We revealed the statistically significant elevated risk of BrCa incidence in females of the study cohort who had a concomitant pathology (leiomyoma of uterus, diabetes mellitus, hypertensive diseases, or neurotic disorders) prior to BrCa and this was consistent with results of other studies [5, 15, 16, 18–20]. Meanwhile, we should note that the risks became non-significant when we used the model that included additional adjustments for attained age and calendar period (Model 2). This result was most likely observed due to insufficient statistical power of the additional analyses but this needs further investigation.

The present analysis revealed a relationship between incidence of BrCa and height and BMI and this agreed with results of other studies [5, 15, 16]. Thus, the follow-up of females aged 30–69 years (approximately 570,000) during 6–18 years revealed that tall women in all age groups were at high risks of BrCa [21]. Overweight is another risk factor of BrCa since the imbalance of extra-ovarian estrogens produced in fat tissues during the reproductive period results in elevated risks of BrCa [26]. According to a number of studies, the present one included, postmenopausal obesity is an established factor that increases the risk of BrCa [5, 6, 8, 12, 15, 18, 22].

The present study revealed elevated risks of BrCa for females having immediate relatives with BrCa and this agreed well with other studies that provided evidence to 6–7 times higher risks of BrCa in females whose genetic relatives had BrCa [5, 6].

A number of studies have revealed a positive statistically significant correlation between alcohol intake (even moderate) and risks of BrCa incidence [6]. However, similar to an earlier study [32], we did not find any evidence that could prove this; it was probably due to the insufficient statistical power of the analysis with only two females assigned to the category of 'alcohol abuse' in the analyzed cohort. In contrast, the analysis revealed the elevated risks of BrCa incidence associated with smoking and this agreed well with results of other studies demonstrating the BrCa incidence *RR* of 2.3 for smoking females even with many other factors taken into account [16].

BrCa incidence in females of the study cohort was not associated with cumulative breast absorbed gamma-ray dose of external exposure, cumulative muscle absorbed alpha-particle dose of internal exposure, or cumulative breast absorbed neutron dose.

Conclusion. The results of the presented cohort study that considered female nuclear workers who had been chronically exposed to IR suggested that BrCa incidence was associated with many non-radiation factors (attained age, age at menarche, age at menopause, number of abortions, concomitant diseases prior to BrCa (fibrocystic breast disease, benign neoplasms of breast, leiomyoma of uterus, diabetes mellitus, hypertensive diseases, stress and neurotic disorders, postmenopausal obesity), height, BMI, age at hire at the Mayak PA) and was not associated with occupational radiation exposure. Meanwhile, we revealed the risk estimate close to 1 with the upper limit of the confidence interval being higher than 1 by 30–50 %. Since the statistical power of the performed analyses was not high, the observed findings should not be considered as conclusive. The follow-up of the cohort of Mayak PA female workers is ongoing and in future an excess relative risk of BrCa incidence per unit breast absorbed radiation dose and a lifetime risk of BrCa incidence will be estimated considering the extended follow-up period and the updated information on members of the cohort.

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Research article

ANALYZING RISKS OF OCCUPATIONAL INJURIES IN BASIC INDUSTRIES

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Our research aim was to analyze occupational injuries in basic industries in Irkutsk region.

Materials and methods. Occupational injuries (OI) in basic industries were analyzed using data from statistical reports issued in 2010–2019. To analyze OI in dynamics, we calculated relative values of OI and applied linear regression and Shewhart charts. Normalized intensity indicators method was used to reveal different probability of injuries in various industries as well as to predict OI risks.

Results. Analysis of OI in dynamics indicates that there is a stable descending trend in a number of injuries. However, in spite of this apparent descending trend, OI values are stably by 1.3–3.0 times higher in some industries than on average in the region. The highest frequency coefficient (FC) for occupational injuries was detected in wood processing where it was equal to 5.35 [2.90–7.71] per 1,000 workers; the indicator varied within 1.00–2.93 per 1,000 workers in other industries. Shewhart chart for FC indicates that systems of occupational health and safety management are not efficient enough in all the analyzed industries since FC exceeds the upper limit in some years. We established that severity of occupational injuries tended to grow in wood processing (C_s = +3.23; 5.33 %), metallurgy (C_s = +0.94; 1.26 %), land transport (C_s = +2.42; 4.39 %), and aircraft production (C_s = +0.59; 1.68 %). The greatest number of fatal OI was detected in mining, construction, and agriculture as a share of fatal OI in the overall structure of occupational injuries amounted to 22.0 %, 19.2 %, and 11.7 % in these brunches accordingly. A probability that an injury becomes fatal is also the highest in them, 11.7 %, 9.0 %, and 6.0 % accordingly. "Wood processing and production of wood articles", "Aircraft production", and "Construction" are among industries where risks of occupational injuries are the most probable.

Key words: *occupational injuries, risk, workers, industries, occupational health and safety.*

Irkutsk region is an area with a lot of operating industries. There are metallurgic enterprises, wood processing plants, aircraft production, mining, coal mining, and some other brunches where more than 500 thousand people are employed [1]. Prevention of occupational injuries is vital since such injuries result in a decrease in working population and higher social expenses [2, 3], and also lead to mortality among working population which has been proven in multiple epidemiological studies [4–8]. It is especially important to analyze levels of occupational injuries since they are determined by existing working conditions and labor safety and changes in them are immediate after any changes in these conditions. Besides, levels of occupational injuries are an important indicator useful for assessing workers' health, working conditions, and labor protection [9]; they can be the most significant criterion in occupational risk assessment and, consequently, are absolutely necessary in labor protection management and for developing efficient preventive activities [10]. We should note that at present the state policy on labor protection is in transition to a risk-oriented model based on prevention since it allows saving or reducing costs related to unfavorable working conditions [11, 12]. There is rather high wear and tear of production equipment in many industries, technological standards are rather poor and modernization is slow as new safe up-to-date technologies and equipment are not being implemented fast enough; capital

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construction and preventive repair of industrial buildings, constrictions, machinery and equipment has also been declining in volumes [1, 13]. There are not enough data available in literature on occupational injuries analyzed as per different industries [3, 4, 14, 15]. Given the structure of production in Irkutsk region with prevailing industries where occupational injuries are likely to occur, it seems necessary to analyze levels and dynamics of occupational injuries in the leading brunches operating in the region.

Our research aim was to analyze occupational injuries in basic industries in Irkutsk region.

Materials and methods. Occupational injuries (OI) were analyzed using data taken from Statistical Report Form No. 7 "Data on occupational injuries and diseases" and Appendix to Form No. 7 "Data on distribution of a number of people who were injured in occupational accidents as per major types of such accidents and their causes" issued by the Federal State Statistic Service in 2010–2019[1]. We considered basic industries that operated in Irkutsk region, notably "Agriculture, hunting, and forestry", "Wood processing and production of wood articles", "Metallurgy", "Production of aircrafts, including spacecrafts", "Production, supply, and distribution of electricity", "Construction", "Land transport", "Public healthcare", "Mining"[2]. We analyzed the following data: average number of workers; a number of injured workers who were unable to work for 1 day or longer; a number of fatal injuries; a number of person-days of temporary disability among injured people who were unable to work for 1 day or long and in case of fatal injuries; a number of injured people with partial disability who were moved from their workplace to another one for 1 working day or longer. Relative OI values were calculated: a coefficient of occupational injuries frequency (C_f); a coefficient of occupational injuries severity (C_s); a coefficient showing losses of working hours (C_l); a coefficient of fatal occupational injuries frequency (C_{fatal}); a coefficient of summarized labor losses (C_{sum}); and also indicator S [16] that was a ratio of a total number of occupational injuries to a number of fatal occupational injuries. The last indicator is the most objective one showing how safe a specific production is. We applied statistic Shewhart charts in our analysis[3]. Normalized intensity indicator method was applied to reveal industries with different risks levels as well as to predict risks of occupational injuries [17]. A level of OI risk in an industry (R) was calculated as per the following formula:

$$R = \mathrm{NII_{in}} \cdot C,$$

where $\mathrm{NII_{in}}$ is a normalized intensity indicator for a given industry, C is a weight coefficient; $\mathrm{NII_{in}}$ = intensity indicator for an industry / regional intensity indicator, $C = \max \mathrm{NII_{in}} / \min \mathrm{NII_{in}}$.

All data were statistically analyzed using Microsoft Office 2003. Linear regression analysis was applied to analyze OI dynamics. Research results are given as extensive (%) and intensive (per 1,000 workers) values, average values, minimum and maximum values in different years over the examined period.

Results and discussion. Analysis of OI dynamics over the examined period indicates there is a stable descending trend in a number of occupational injuries, both in Irkutsk region

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[1] Usloviya truda [Working conditions]. *The Federal State Statistic Service*. Available at: https://rosstat.gov.ru/working_conditions (February 03, 2021) (in Russian).

[2] Obshcherossiiskii klassifikator vidov ekonomicheskoi deyatel'nosti (OKVED 2) OK 029-2014 (KDES Red. 2): prinyat i vveden v deistvie prikazom Federal'nogo agentstva po tekhnicheskomu regulirovaniyu i metrologii ot 31 yanvarya 2014 g. N 14-st (s izmeneniyami i dopolneniyami) [Russian National Classifier of Economic Activities (RNCEA 2) RC 029-2014 (Edition 2): approved on and implemented by the Federal Agency on Technical Regulation and Metrology on January 31, 2014 No. 14-st (with alterations and addenda)]. *GARANT database*. Available at: https://base.garant.ru/70650726/ (April 08, 2021) (in Russian).

[3] GOST R ISO 7870-2-2015. Natsional'nyi standart Rossiiskoi Federatsii. Statisticheskie metody. Kontrol'nye karty. Chast' 2. Kontrol'nye karty Shukharta (data vvedeniya: 12.01.2016) [GOST R ISO 7870-2-2015. The National Standard of the Russian Federation. Statistical procedures. Control charts. Part 2. Shewhart charts (introduced on January 12, 2016)]. *TEKHEKSPERT*. Available at: http://docs.cntd.ru/document/1200124585 (March 25, 2021) (in Russian).

overall and in some industries as well: in wood processing (from 6.14 to 4.27 per 1,000 workers, $y = –0.3382x + 7.2073$, $R^2 = 0.6067$); agriculture (from 3.74 to 2.46 per 1,000 workers, $y = –0.2582x + 4.352$, $R^2 = 0.7737$); metallurgy (from 2.08 to 1.23 per 1,000 workers, $y = –0.1169x + 1.92$, $R^2 = 0.5865$); and mining (from 2.82 to 2.19 per 1,000 workers, $y = –0.1156x + 3.002$, $R^2 = 0.7252$) (Figure 1). But OI dynamics revealed that OI rates were rather unstable in some industries; it is true for production, supply, and distribution of electricity ($y = –0.0045x + 1.0267$, $R^2 = 0.0036$); land transport ($y = –0.1022x + 1.832$, $R^2 = 0.4684$); aircraft production ($y = –0.1591x + 3.418$, $R^2 = 0.2453$); construction ($y = 0.0516x + 1.984$, $R^2 = 0.0378$); and public healthcare ($y = 0.0049x + 1.16$, $R^2 = 0.005$).

However, despite this appearing descending trend, OI rates are still by 1.3–3.0 times higher in some industries than on average in the region and this gives an indirect indication that working conditions are hazardous there and workers are not provided with sufficient protection. Some authors also mention a drastic decrease in rates of occupational injuries and state there are several reasons for that including influence by a risk-oriented approach in organizing state control (surveillance) [11], declining number of workers employed in industries with high risks [2], and hiding data on occupational accidents [18].

A share of occupational injuries for women employed in analyzed industries on average amounts to 21.0 [3.2–66.7] %; for men, 79.0 [33.4–96.8] %; it is most likely due to male workers prevailing in industries where injuries are more probable [19].

Relative values calculated for occupational industries were a coefficient of occupational injuries frequency (C_f); a coefficient of occupational injuries severity (C_s); a coefficient of summarized labor losses (C_{sum}); and a coefficient showing losses of working hours (C_l). They are given in Table 1.

The highest coefficient of occupational injuries frequency was detected in wood processing, 5.35 [2.90–7.71] per 1,000 workers. In other industries, this coefficient varied within 1.00–2.93 per 1,000 workers. An average rate of change in C_f turned out to be negative practically in all analyzed industries, except construction; on one hand, it indicates there is a descending trend in frequency of occupational injuries but, on the other hand, it might be due to mild or average injuries not being included into reports. Annually C_f goes down by 5.49 % on average. We built a Shewhart chart that included the upper and lower limits of coefficients showing frequency and severity of

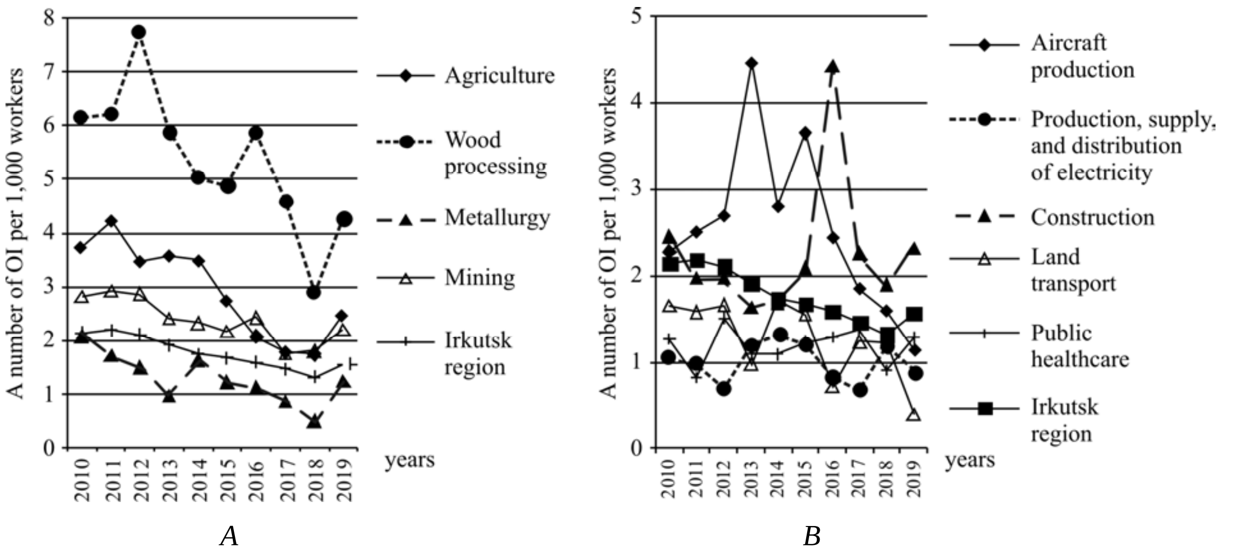

Figure 1. Rates of occupational injuries in basic industries in Irkutsk region in 2010–2019 (per 1,000 workers) taken in dynamic; industries with stable dynamic are shown in part *A*; with unstable, in part *B*

Table 1

Average long-term rates of occupational injuries in basic industries in Irkutsk region in 2010–2019 (per 1,000 workers), M [min–max]

Industries	Occupational injuries			
	Coefficient of occupational injuries frequency (C_f)	Coefficient of occupational injures severity (C_s)	Coefficient of working hours losses (C_l)	Coefficient of summarized losses (C_{sum})
Agriculture, hunting, and forestry	2.93 [1.74–4.21]	59.23 [34.12–78.51]	167.92 [74.8–294.6]	1,252.9
Wood processing and production of wood articles	5.35 [2.90–7.71]	60.94 [36.72–85.13]	295.79 [251.4–398.7]	2,157.3
Metallurgy	1.28 [0.49–2.08]	75.12 [35.66–92.30]	91.25 [38.2–179.1]	299.6
Production of aircrafts, including spacecrafts	2.55 [1.13–4.47]	35.35 [20.37–56.89]	82.46 [38.7–137.3]	528.5
Production, supply, and distribution of electricity	1.00 [0.68–1.34]	62.64 [34.81–118.23]	59.22 [32.3–121.8]	310.8
Construction	2.27 [1.63–4.42]	61.52 [47.04–80.0]	126.29 [73.4–140.7]	1,200.9
Land transport	1.27 [0.38–1.70]	55.21 [38.09–102.14]	61.44 [39.6–93.9]	404.8
Public healthcare	1.20 [0.82–1.38]	41.14 [27.30–61.68]	47.74 [28.4–78.2]	168.3
Mining	2.37 [1.75–2.91]	77.39 [37.68–214.54]	171.34 [58.8–527.4]	1,850.3

Table 2

Calculated limits of changes in coefficients of occupational injuries frequency and severity in basic industries

Industries	Coefficient of occupational injuries frequency		Coefficient of occupational injuries severity	
	Lower limit	Upper limit	Lower limit	Upper limit
Agriculture, hunting, and forestry	2.29	3.57	49.58	68.86
Wood processing and production of wood articles	4.43	6.15	50.53	70.71
Metallurgy	0.94	1.61	60.89	89.34
Production of aircrafts, including spacecrafts	1.85	3.23	26.55	44.15
Production, supply, and distribution of electricity	0.84	1.17	45.34	79.94
Construction	1.69	2.84	53.38	69.62
Land transport	0.95	1.59	42.32	68.07
Public healthcare	1.05	1.37	33.59	48.68
Mining	2.07	2.66	38.29	116.49

occupational injuries (Table 2). The chart allowed establishing that C_f was higher than the upper limit in some years; hence, occupational safety management systems are not efficient enough in all analyzed industries.

The coefficient of occupational injuries severity, with its indirect indicator being a number of days of disability, was calculated for the examined industries. The highest average long-term coefficient of occupational injuries severity (C_s) was detected in mining and metallurgy; the lowest one, in public healthcare and in aircraft production. Calculation of average rate of change in C_s indicates that occupational injuries tend to become more severe in wood processing (C_s = +3.23; 5.33 %), metallurgy (C_s = +0.94; 1.26 %), land transport (C_s = +2.42; 4.39 %), and aircraft production (C_s = +0.59; 1.68 %). An average rate of change in C_s turned out to be negative in other analyzed industries and it indicates there is a descending trend in severity of occupational injuries.

A decrease in frequency of occupational injuries in some industries highlighted by the relevant coefficient taken in dynamics contradicts to values calculated for the coefficient of occupational injuries severity and growing

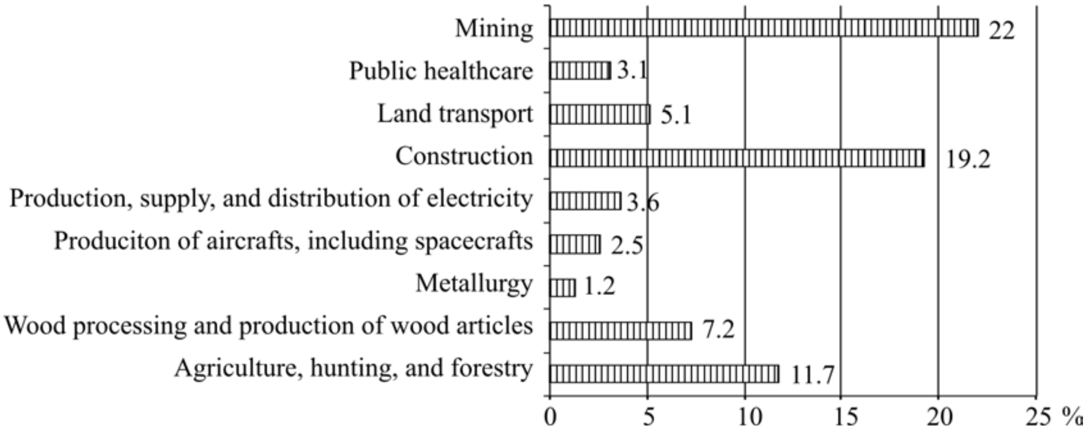

Figure 2. A share of fatal injuries per industries in the overall structure of fatal injuries in Irkutsk region in 2010–2019, %

specific share of fatal injuries; it is probably due to not all injuries being taken into account (only the most severe injuries and fatal injuries are registered).

Average long-term number of fatal injuries varied from 0.02 to 0.31 cases per 1,000 workers in basic industries in Irkutsk region over the examined period. The highest share of fatal injuries in the overall structure of such accidents in Irkutsk region is detected in mining (22.0 %), construction (19.2 %), and agriculture (11.7 %) (Figure 2).

Indicator *S* also shows that a probability of a fatal injury is the highest in these industries, 11.7, 9.0 and 6.0 accordingly; in some authors' opinion [13–15, 21–23], it requires more efforts on providing safe and harmless working conditions. Besides, experts note that only 45–65 % of overall requirements to labor protection are satisfied [14].

Fatal OI rates amount to 0.06–0.41 per 1,000 workers for men and 0.0–0.10 per 1,000 workers among women in all analyzed industries. According to ILO estimates, overall, men account for approximately 80 % of all fatal occupational injuries worldwide [2].

We also analyzed occupational injuries in different industries as per the coefficient showing losses of working hours (C_l); the analysis revealed the highest C_l value in wood processing and the lowest, in public healthcare.

We calculated the coefficient of summarized labor losses (C_{sum}) and revealed that the first rank place belonged to "Wood processing and production of wood articles"; the second one, "Mining"; the third one, "Agriculture, hunting, and forestry"; the fourth one, "Construction"; other industries, given in the descending order, were "Aircraft production", "Land transport", "Production, supply, and distribution of electricity", "Metallurgy", and "Public healthcare".

Risk rates for OI (*R*) in basic industries are given in Table 3.

We should note that a situation seems rather ambiguous in some industries. Thus, OI risk seems to be the lowest in mining although the coefficient of occupational injuries frequency calculated for the industry is comparable to those calculated for aircraft production and construction with OI risks being substantially higher in these industries. In our opinion, it is due, first of all, to average annual fluctuations in parameters that are taken as a basis for OI risk calculation and also, probably, due to deliberate hiding of occupational injuries.

Table 3

Risks of occupational injuries in basic industries in Irkutsk region

Industries	OI risk
Agriculture, hunting, and forestry	2.710
Wood processing and production of wood articles	5.008
Metallurgy	1.846
Production of aircrafts including spacecrafts	4.643
Production, supply, and distribution of electricity	1.611
Construction	4.313
Land transport	2.832
Public healthcare	1.739
Mining	1.693

Table 4

Estimation table for risks of occupational injuries in the analyzed industries

Risk groups	Fluctuation range	Industries
I – the group with favorable forecast (the lowest probability)	1.61–2.74	Agriculture, hunting, and forestry
		Metallurgy
		Production, supply, and distribution of electricity
		Public healthcare
		Mining
II – the group that requires attention (average probability)	2.75–3.87	Land transport
III – the group with unfavorable forecast (the highest probability)	3.88–5.00	Wood processing and production of wood articles
		Production of aircrafts including spacecrafts
		Construction

We assessed OI risks using normalized intensity indicators method and it allowed us to rank the analyzed industries as per several risk groups: favorable forecast, requiring attention, and unfavorable forecast (Table 4).

According to calculated fluctuation ranges, the group with favorable forecast included the following industries: "Agriculture, hunting, and forestry", "Metallurgy", "Production, supply, and distribution of electricity", "Public healthcare", "Mining". "Land transport" was an industry that required attention. Industries where probability of occupational injuries was the highest included "Wood processing and production of wood articles", "Production of aircrafts, including spacecrafts", and "Construction".

Conclusions. Therefore, our analysis revealed multidirectional basic trends in OI in industries operating in Irkutsk region. The situation is especially unfavorable in wood processing and production of wood articles, construction, mining, and agriculture. Although not all actual injuries are included into official statistics [16, 18, 23], our research results indicate that a serious approach is required to preventing occupational injuries. Besides, bearing in mind that rates of occupational injuries tend to change [24] and there can be significant annual fluctuations due to sudden and severe occupational accidents, it is necessary to develop targeted and systemic prevention activities and relevant policies in the sphere of workers' health protection. Prevention of potentially hazardous situations, risk assessment and management of occupational injuries should become top priorities in any such policy.

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Research article

ANALYZING RISKS OF INCIDENCE OF TICK-BORNE ENCEPHALITIS IN AREAS WITH DIFFERENT CLIMATIC AND GEOGRAPHICAL CONDITIONS

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Ticks are natural reservoirs and vectors of a virus that is an infectious agent of tick-borne encephalitis, a communicable disease with great medical and social significance. Tick-borne encephalitis (TBE) is widely spread in Arkhangelsk region (AR) located in the Arctic zone in Russia where substantial climatic changes are taking place at the moment.

Our research involved examining spatial and temporal distribution of numbers of people bitten by ticks, a number of people bitten by ticks per 100 thousand, a number of TBE cases and TBE incidence in districts and settlements in AR. We calculated relative risks of TBE incidence among people bitten by ticks in AR from 1980 to 2019.

We analyzed dynamics of indicators showing numbers of people bitten by ticks per 100 thousand and TBE incidence among people living in Arkhangelsk region. The analysis revealed that a number of bitten people grew slowly in 1980–1990, then there was an exponential growth in 1990–2010, and then the trend stabilized in 2010–2019. Dynamics of TBE incidence was completely in line with changes in number of bitten people up to 2014 but there was a substantial drop in TBE incidence after that.

Spatial distribution of numbers of bitten people and TBE incidence revealed that average number of bitten people amounted to 25.1 per 100 thousand in the northern districts in 1980–2019 and was statistically significantly lower than in the central and southern districts ($p < 0.001$). Average long-term incidence was the highest (7.9 per 100 thousand) in the southern districts in comparison with the central (3.0 per 100 thousand; $p < 0.001$) and northern ones (0.7 per 100 thousand; $p < 0.001$). Maximum relative risks of TBE incidence was detected in the southern districts in 1990–1999 (38.8) in comparison with the northern ones.

We made an assumption about probable reasons for declining TBE incidence in Arkhangelsk region detected over the last years given the growing numbers of bitten people.

Key words: *ticks, tick-borne encephalitis, relative risk, Arkhangelsk region.*

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Ticks are an important medical issue. These blood-sucking arthropods are not only vectors of various infectious agents, for example, viruses of tick-borne encephalitis, tick borreliosis, human monocytic erlichiosis and granulocytic anaplasmosis, but also reservoirs of several pathogens [1, 2][1]. Each tick bite should be considered potentially dangerous for a bitten person's health; it should be seen as potential contagion with mixed infections[2].Meanwhile, a number of tick attacks constantly grows in the Russian Federation (RF). In 2018 it increased by 12.6 % against average rates detected in 2013–2017 and reached 502,794 cases [3]. Tick-borne encephalitis (TBE) is the most socially significant issue in the RF among all tick-borne infections. In 2018 1,508 cases of the disease were registered in the RF and 153 out of them were among children younger than 14. TBE was detected in 46 RF regions and the incidence rate amounted to 1.3 per 100,000 population; the disease developed after a tick bite in 98 % of cases. 22 TBE cases had a lethal outcome; lethality amounted to 0.7 [3].

Previously we established that TBE incidence rates in the Arkhangelsk region (AR) and the RF in general had opposite trends. There was a considerable growth in the indicator in the AR which, in our opinion, was to a great extent due to expansion of territories where TBE cases were detected; on the contrary, in the RF there was an apparent descending trend starting from 90ties last century[1].

Our research aim was to reveal the latest trends regarding changes in habitats of *I. Persulcatus* and dynamics of TBE incidence and also to describe relative risks of TBE incidence among people bitten by ticks in the AR.

Materials and methods. We took data from the federal statistical forms No. 1 and 2 "Data on infectious and parasitic diseases" and also used the results of operative seasonal monitoring over TBE provided by Rospotrebnadzor Regional Office in the Arkhangelsk region.

We analyzed data on a number of people living in different districts in the region who were bitten by ticks in 1980–2020. Each case was confirmed by an official document stating a date and a place of a bite (Report form No. 058/u entitled "An emergency notification about infectious disease, parasitic disease, food poisoning, an unusual reaction to vaccination, or post-vaccination complications). When analyzing these data, we calculated a number of people bitten by ticks during one year per 100 thousand people living on a given administrative territory. We also calculated TBE incidence (a number of TBE cases during one year per 100 thousand people) in the AR in 1980–2020. TBE was diagnosed based on clinical and epidemiologic data and, as a rule, was confirmed by serological diagnostic techniques (from 84.1 % cases in 2008 to 100 % cases in 2020).

To compare a number of bitten people and TBE incidence in different years, the whole observation period was divided into equal time periods, 10 years each (a decade): the 1st one, from 1980 to 1989 ; the 2nd, from 1990 to 1999; the 3rd, from 2000 to 2009; the 4th, from 2010 to 2019. Official statistical data on population in the AR were taken from Rosstat official web-site[3].

We applied one-way analysis of variance with the Bonferroni correction to reveal differences in a number of bitten people and TBE incidence between the districts located in the southern, central, and northern zones. We calculated relative risks (*RR*) and 95 % confidence intervals (95 % *CI*) to compare

[1] Tokarevich N.K., Stoyanova N.A., Gracheva L.I., Trifonova G.F., Tronin A.A., Shumilina G.M., Glushkova L.I., Galimov R.R. [et al.]. Infektsii, peredayushchiesya iksodovymi kleshchami, v Severo-Zapadnom federal'nom okruge Rossii. Analiticheskii obzor [Tick-borne infections in the Northwestern Federal District in Russia. Analytical review]. St. Petersburg, Feniks, 2008, 120 p. (in Russian).

[2] Korenberg E.I., Pomelova V.G., Osin N.S. Prirodno-ochagovye infektsii, peredayushchiesya iksodovymi kleshchami [Tick-borne natural foci infections]. In: A.L. Gintsburg, V.N. Zlobin eds. Moscow, OOO Kommentarii Publ., 2013, 464 p. (in Russian).

[3] The Federal State Statistics Service: official web-site. Available at: http://www.gks.ru/ (June 12, 2021) (in Russian).

TBE incidence rates in different zones as per decades. Critical level of statistical significance (*p*) was taken as equal to 0.05. All the data were statistically analyzed with SPSS 28 software package.

Geographical background. The AR is located in the north of the European part in the RF in a zone that borders the Arctic. The region includes 19 districts and 6 cities and its total area amounts to 330.1 thousand square kilometers (without the Nenets Autonomous Area and polar islands). We divided the whole region territory into three conditional zones, northern, central, and southern, to provide better visualization of changes in territorial distribution of people bitten by ticks and registered TBE cases (Figure 1). There were substantial differences between these three zones regarding ecological and epidemiological situation associated with this infection. Overall area covered with forests didn't change significantly over the analyzed period in the AR and amounted to 23 million hectares in 2019[4].

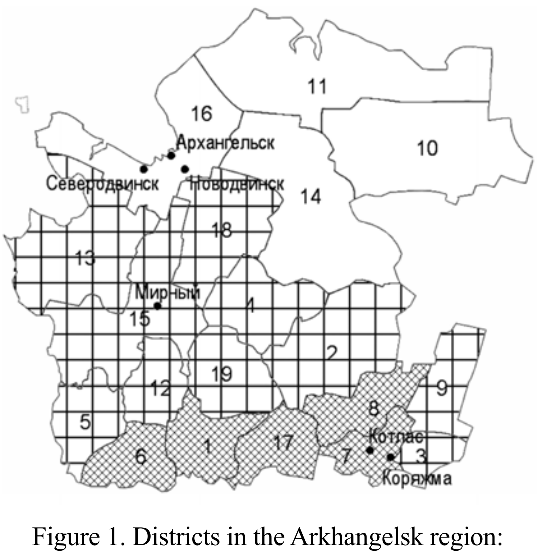

Figure 1. Districts in the Arkhangelsk region:
1 – Velskiy, *2* – Verkhnetoemskiy, *3* – Vilegodskiy,
4 – Vinogradovskiy, *5* – Kargopolskiy, *6* – Konoshskiy,
7 – Kotlasskiy, *8* – Krasnoborskiy, *9* – Lenskiy,
10 – Leshukonskiy, *11* – Mezenskiy, *12* – Nyandomskiy,
13 – Onezhskiy, *14* – Pinezhskiy, *15* – Plesetskiy,
16 – Primorskiy, *17* – Ust'yanskiy,
18 – Kholmogorskiy, *19* – Shenkurskiy

Ixodes persulcatus prevails in the AR (more than 99 %) and this species is a major source of TBE virus spread among people [4].

Results. ***Territorial and spatial distribution of people bitten by ticks in the region.*** Overall, 122,470 people living in the AR were bitten by ticks over the analyzed period. A number of tick bites grew constantly. Thus, it amounted to 2,840 in 1980–1989; 15,030, in 1990–1999; 38,820 in 2000–2009; and 64,780 in 2010–2019. Average numbers of bitten people – bitten people[10] grew by 22.8 times over a period from 2010 to 2019 against 1980-1989. Overall, there were no statistically significant differences in numbers of bitten people in the southern and central zones (540.9 and 356.5 per 100 thousand people) during 40 years of observation ($p = 0.159$). An average number of bitten people in the districts located in the northern zone amounted to 25.1 per 100 thousand people in 1980–2019 and was statistically significantly lower than in the southern and central zone ($p < 0.001$).

In 1980–1989 bitten people, as a rule, lived in the southern zone in the AR. People living in the Velskiy and Kotlasskiy districts in the southern zone and the Krasnoborskiy and Nyandomskiy districts in the central zones were the most frequently bitten by ticks. There were only sporadic tick bites registered in other administrative districts in the central zone and there were no tick bites registered in that time period in the northern zone. Numbers of people bitten by ticks in the AR taken in dynamics and their spatial distribution are given in Table 1 and Figure 2.

There was an apparent growth in a number of bitten people in most districts in the AR over the analyzed period. In the 4th decade in the observation period people were bitten by these blood-sucking arthropods in almost all districts in the region including the northern zone. Very few cases when people applied for medical aid due to tick bites were registered

[4] O sostoyanii i ispol'zovanii zemel' v Rossiiskoi Federatsii v 2019 godu: gosudarstvennyi (natsional'nyi) doklad [On the situation and use of lands in the Russian Federationin 2019: The State (National) report]. *The Federal Service for State Registration, Cadastre and Cartography*. Moscow, 2020. Available at: https://rosreestr.gov.ru/upload/Doc/16-upr/%D0%94%D0%BE%D0%BA%D0%BB%D0%B0%D0%B4%20%20%D0%B4%D0%BB%D1%8F%20%D0%B4%D0%B8%D1%81%D0%BA%D0%B0%2011.12.pdf (June 12, 2021) (in Russian).

Table 1

Distribution of people in the AR bitten by ticks as per decades and administrative districts in 1980–2019 (bitten people[10])

Districts	Zones	Decades			
		1st (1980–1989)	2nd (1990–1999)	3rd (2000–2009)	4th (2010–2019)
Velskiy	southern	46	244	653	942
Verkhnetoemskiy	southern	16	7	159	234
Vilegodskiy	southern	2	6	60	168
Vinogradovskiy	central	3	40	162	285
Kargopolskiy	central	22	59	135	304
Konoshskiy	southern	17	76	304	417
Kotlasskiy	southern	41	327	296	296
Krasnoborskiy	central	45	163	264	338
Lenskiy	central	2	6	64	125
Leshukonskiy	northern	0	0	1	3
Mezenskiy	northern	0	0	0	1
Nyandomskiy	central	16	38	218	414
Onezhskiy	central	3	12	99	242
Pinezhskiy	northern	0	0	6	25
Plesetskiy	central	4	20	139	274
Primorskiy	northern	0	0	3	13
Ust'yanskiy	southern	7	14	263	488
Kholmogorskiy	central	1	10	78	171
Shenkurskiy	central	5	11	174	316
Arkhangelsk	northern	0	11	83	271
Kotlas	southern	41	276	464	539
Novodvinsk	northern	0	0	12	32
Severodvinsk	northern	0	8	58	204
Mirniy	central	1	8	10	51
Koryazhma	southern	12	125	280	331
Arkhangelsk region		284	1,503	3,982	6,478

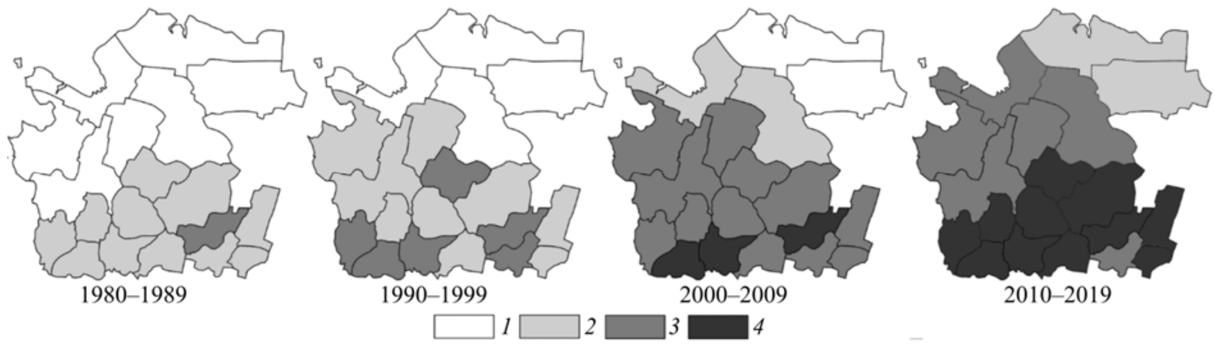

Figure 2. Territorial distribution of people in the AR bitten by ticks in 1980–2019 per 100,000 population: 1) < 10; 2) 10–100; 3) 100–1,000; 4) > 1,000

only in the Leshukonskiy and Mezenskiy districts. A number of bitten people grew more significantly in all other districts in the northern zone. For example, in the Pinezhskiy district there were no registered tick bites prior to 1999; in 2000–2009 a number of bitten people[10] amounted to 6; and it was already equal to 25 in 2010–2019. Relatively high numbers of bitten people[10] in Arkhangelsk and Severodvinsk, cities located in the northern zone, were probably to a great extent due to intense migration of people who lived in these cities to other districts in the AR and even beyond the region. However, a considerable growth in a number of bitten people[10] was registered in the Primorskiy district where these two cities were located.

Incidence of tick-borne encephalitis. 1,582 TBE cases were registered in the AR over the analyzed 40-year period. This infection was diagnosed only in 14 people during the whole 1st decade. A significant rise in incidence was detected starting from 1990 and to 2013. Maximum incidence rates were detected in 2009 and 2013 and amounted to 9.9 and 8.7 disease cases per 100,000 population accordingly. Then there was a significant decrease in a number of patients and the rate was 24 or 2.2 per 100,000 population in 2020. On the contrary, a number of people bitten by ticks grew over that period (Figure 3).

Spatial characteristics of TBE incidence rates revealed that average annual long-term incidence was the highest in the southern zone (7.9 per 100,000 population) against the central (3.0 per 100,000 population; $p < 0.001$) and northern zone (0.7 per 100,000 population; $p < 0.001$).

Average number of people with TBE grew by almost 50 times in 2000–2009 against 1980–1989 (Table 2).

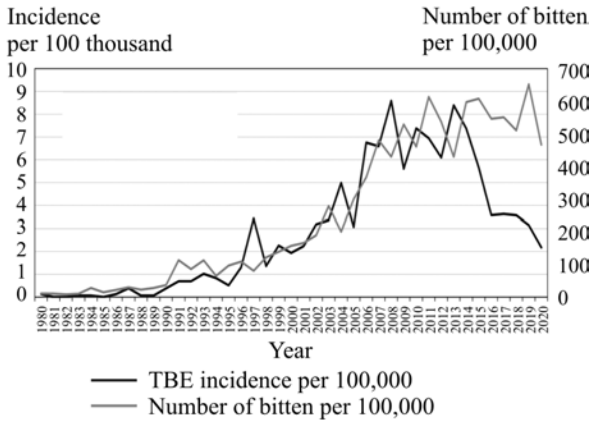

Figure 3. Dynamics of TBE incidence rates and numbers of bitten people in the Arkhangelsk region, (number of bitten people[10])

Table 2

Distribution of patients with TBE as per administrative districts and decades (average number)

Districts	Zones	Decades			
		1st (1980–1989)	2nd (1990–1999)	3rd (2000–2009)	4th (2010–2019)
Velskiy	southern	0.10	2.40	20.50	13,50
Verkhnetoemskiy	southern	0.00	0.00	1.90	3,40
Vilegodskiy	southern	0.00	0.40	0.00	0,20
Vinogradovskiy	central	0.00	0.00	0.00	1,30
Kargopolskiy	central	0.20	0.10	2.89	2,10
Konoshskiy	southern	0.10	1.10	7.11	5,50
Kotlasskiy	southern	0.30	4.50	4.80	2,00
Krasnoborskiy	central	0.40	1.40	3.10	2,50
Lenskiy	central	0.00	0.00	0.70	0,60
Leshukonskiy	northern	0.00	0.00	0.00	0,00
Mezenskiy	northern	0.00	0.00	0.00	0,00
Nyandomskiy	central	0.00	0.30	1.80	4,10
Onezhskiy	central	0.00	0.30	0.70	0,50
Pinezhskiy	northern	0.00	0.00	0.10	0,10
Plesetskiy	central	0.00	0.00	1.00	0,90
Primorskiy	northern	0.00	0.00	0.20	0,10
Ust'yanskiy	southern	0.00	0.00	2.40	3,30
Kholmogorskiy	central	0.00	0.20	0.30	0,30
Shenkurskiy	central	0.00	0.00	4.80	6,50
Arkhangelsk	northern	0.10	1.00	3.80	6,60
Kotlas	southern	0.00	4.10	7.50	4,40
Novodvinsk	northern	0.00	0.00	0.50	0,30
Severodvinsk	northern	0.20	0.30	1.40	4,30
Mirniy	central	0.00	0.00	0.00	0,10
Koryazhma	southern	0.00	4.60	5.20	3,80
Arkhangelsk region		1.40	20.70	69.70	66.40

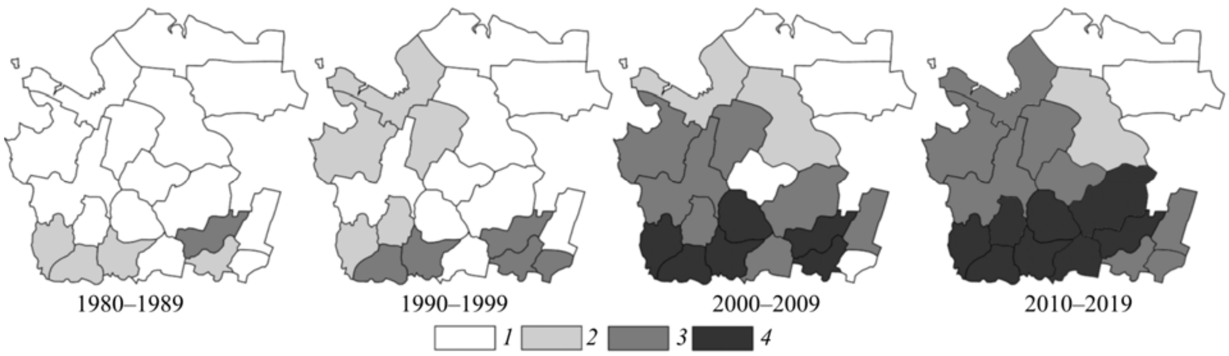

Figure 4. TBE incidence rates in AO, cases/100,000 population: 1) 0.0–0.09; 2) 0.1–0.9; 3) 1.0–4.9; 4) > 5.0

Table 3

Relative risk of TBE incidence as per three zones in the Arkhangelsk region

Decades	Indicator	Zones		
		Northern	Southern	Central
1980–1989	*RR*	Reference zone	2.1	2.2
	95 % *CI*		0.1–34.0	0.1–35.9
1990–1999	*RR*	Reference zone	38.8	4.6
	95 % *CI*		5.2–292.0	0.42–51.4
2000–2009	*RR*	Reference zone	18.5	6.1
	95 % *CI*		7.9–43.1	2.4–15.6
2010–2019	*RR*	Reference zone	6.9	4.6
	95 % *CI*		3.5–13.6	2.2–9.7

And if over the 1st decade TBE was registered only in 7 administrative districts in the AR (the Velskiy, Kargopolskiy, Konoshskiy, and Kotlasskiy districts located in the southern zone, the Krasnoborskiy district in the central zone and Arkhangelsk and Severodvinsk in the northern zone), then in the 4th one the infection was registered in the whole region, excluding districts located in the northern zone, the Leshukonskiy and Mezenskiy (Figure 4).

We didn't find any differences in TBE incidence rates between the zones in the AR in the 1st decade. In the 2nd decade relative risk of TBE incidence reached its maximum in the southern zone and amounted to 38.8 against the northern zone; TBE incidence in the central zone didn't have any statistically significant differences from that detected in the northern on (Table 3).

Relative risks were high in the 3rd decade in the districts located in the southern and central zones (18.5 and 6.1 accordingly) in comparison with the northern zone. Relative risks of TBE incidence went down in the 4th decade both in the districts located in the southern zone (*RR* = 6.9) and in the central one (*RR* = 4.6) and this indicated that TBE occurred in the districts located in the northern zone.

Discussion. Contemporary prevailing tick species, including *Ixodes persulcatus* Sch. 1930, probably occurred as far back as at the end of Pliocene or the beginning of Holocene [5]. Such long evolution helped ticks adapt to a lot of territories with variable natural and climatic conditions and to parasitize on practically all orders of land mammals as well as on many species of birds and reptiles. They usually feed on mammals or birds that are the most widely spread in a given ecosystem[5].

Over the last decades there have been considerable changes in biotic components in zones located in the northern European part of Russia; for example, forest zones were detected to move farther to the north. Changes in flora have considerable influence on fauna and the latter reacts quite dynamically to any changes in climatic conditions. Wild mammals migrate onto northern territories. Rodents and insect-eaters are a source of food for tick larvae and nymphs thus infecting them with TBE virus. Large mammals bitten by these bloodsucking arthropods exert substantial impacts

[5] Balashov Yu.S. Parazitizm kleshchei i nasekomykh na nazemnykh pozvonochnykh [Tick parasitism on land vertebrates]. St. Petersburg, Nauka, 2009, 357 p. (in Russian).

on contamination in population of vectors increasing a number of congested female ticks who carry the virus and efficiency of transovarial transmission of the pathogen. 12 new bird species were registered in taiga zones in the western part of the Russian plain in the last quarter of the 20th century; they hadn't been ever detected on those territories before [6]. Migrating birds bitten by ticks can carry TBE virus onto new territories [7, 8].

A considerable growth in a number of people bitten by ticks was registered over the analyzed period in Arkhangelsk region; this was true not only for the southern zone where there were only sporadic cases of tick bites detected in 80ties last century but also in the northern zone where previously people didn't get bitten by these blood sucking arthropods at all. This substantial growth in a number of bitten people can to a certain extent be due to people applying for medical aid more often since they are now much better aware of dangerous consequences tick bites might have.

But at the same time data on registered cases of tick bites and TBE cases on new territories in the AR where this infection was not ever registered in the past indicate that ticks infected with TBE virus have spread farther onto northern territories. Previously, the northern border of tick habitat was located further to the south in the western part of the AR, approximately at the 62nd parallel; as for the eastern part of the region, it reached the northern latitude at which Shangala and Kizem settlements were located [9]. In our opinion, during a 40-year period of observations over ticks their northward migration amounted to not less than 200 kilometers from southern districts in the AR. In 2019 two more districts, namely Pinezhskiy and Primorskiy, were added to the list of areas that were endemic as per TBE[6]. Similar processes occur on neighboring territories, for example in the Komi Republic [10] and Karelia [11]. Ticks migrated mostly due to a substantial rise in both average annual temperatures and a sum of "effective" temperatures that created natural conditions favorable for *Ixodes persulcatus* and made for longer periods of their activity [12]. Socioeconomic factors may as well contribute into growing numbers of people bitten by ticks [10].

Tick migration onto new territories and, consequently, TBE occurrence in areas that were previously free from this infection are described in many countries where *I. ricinus* prevails [13–16]. The present work has a significant distinction from many others cited in it since it has been accomplished in the region where *I. persulcatus* prevails completely. This tick species differs greatly from *I. ricinus* as per its biological properties; for example, it is much more resistant to cold, therefore, its habitat can be located farther to the north. Moreover, *I. persulcatus* contamination with TBE virus is usually significantly higher than *I. ricinus* contamination [17][7].

Although there has been a certain decrease in TBE incidence in the AR, tick-borne infections are still a vital medical issue in the region. First, a significant share of TBE virus (35 %) in ticks caught in the Komi Republic, a neighboring region to the AR, belongs to the Far East genotype which has high lethality [18]. Secondly, *I. persulcatus* that prevail in the AR are contaminated not only with TBE virus but also with other pathogens with no specific prevention means against them available at the moment[8]. Third, a considerable

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[6] O perechne endemichnykh territorii po kleshchevomu virusnomu entsefalitu v 2019 godu: Pis'mo Rospotrebnadzora ot 31.01.2020 № 02/1305-2020-32 [On the list of territories that are endemic as per tick-borne encephalitis in 2019: The Letter by Rospotrebnadzor dated January 31, 2020 No. 02/1305-2020-32].The Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing. Available at: https://www.rospotrebnadzor.ru/upload/iblock/365/o-perechne-endemichnykh-terr.-po-kve-v-2019-g.-31.01.2020.pdf (June 15, 2021) (in Russian).

[7] Balashov Yu.S. Iksodovye kleshchi – parazity i perenoschiki infektsii [Ticks as parasites and infection vectors]. St. Petersburg, Nauka, 1998, 287 p. (in Russian).

[8] Ob itogakh sezona aktivnosti kleshchei v 2021 godu [On the results of the tick activity season in 2021]. The Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing. Available at: http://29.rospotrebnadzor.ru/c/journal/view_article_content?groupId=10156&articleId=902166&version=1.0 (June 13, 2021) (in Russian).

share of local natives who have never been bitten by ticks before can be more susceptible to tick-borne infections than people living in southern districts in the AR [19].

Analysis of changes in a number of bitten people[10] taken in dynamics revealed a slow rise in 1980–1990 followed by an exponential growth in 1990–2010. The same drastic increase was detected in the Komi Republic, the neighboring region. In 2010–2020 the trend stabilized in the Komi Republic and there were only slight changes in a number of bitten people over time. The character of such distribution is probably determined by air temperature, a basic abiotic factor that influences *I. persulcatus* ecology [10].

An apparent decrease in TBE incidence in the AR registered over the last years against growing number of people bitten by ticks is to a large extent due to greater volumes of specific prevention aimed at fighting against the infection.

Thus, a number of vaccinated people in the AR grew by 3.6 times from 6,699 in 2005 to 23,933 in 2015; in 2015 almost 30 % of bitten people were provided with emergency seroprevention with immunoglobulin [4]. Growing natural immunization among population may be another reason for this decrease in TBE incidence. From 1980 to 2020 more than 127 thousand people were bitten by ticks and it amounted to 12 % of the total population in the region. Seroprevalence regarding TBE virus exceeds 20 % among people living in southern districts in the AR [4].

Detected migration of ticks and growing TBE incidence in northern districts in the AR can be typical for other regions with similar natural and climatic conditions. However, we should bear in mind that when we try to detect factors influencing TBE incidence, attention should be paid to decreasing numbers of TBE cases in Russia as a whole. In our opinion, it is quite possible to assume that incidence rates are influenced by biocoenotic regularities that haven't been studies profoundly yet; these regularities determine cyclic changes in intensity of epizootic processes in natural foci.

Conclusion. Therefore, we analyzed a number of bitten people and TBE incidence taken in dynamics over a long period. The analysis revealed that there was ongoing expansion of *I. persulcatus* into northern districts in the AR and this caused TBE incidence on those territories that were previously free from this infection. From 1980 to 2014 a number of people bitten by ticks grew constantly; there was a synchronous growth in TBE incidence. Over the last years TBE incidence declined substantially and a number of bitten people also stabilized. Ticks spread onto northern territories gives grounds for examining them to detect contamination not only with TBE virus but also with other "tick" pathogens; it is also necessary to examine seroprevalence among population living in these districts regarding "tick" infectious agents in order to make preventive activities more efficient.

Our research indicates there is growing risk of TBE contagion in the northern districts in the AR due to ticks migrating northward. Besides, people living on northern territories that haven't been endemic so far haven't encountered tick-borne infections yet; they are not obliged to get vaccinated against TBE and hence they are exposed to elevated risks in case they are bitten by ticks. The accomplished analysis substantiates the necessity to make managerial decisions on organizing epidemiologic and epizootological monitoring on territories that have previously been free from ticks; it is also essential to provide specific and non-specific prevention against TBE and pother tick-borne infections for people living there.

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

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Research article

EFFICIENCY OF DISINSECTION AND DERATIZATION AIMED AT REDUCING EPIDEMIOLOGIC RISKS IN GORNO-ALTAISKIY HIGH-MOUNTAIN NATURAL PLAGUE FOCUS

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Our research aim was to estimate efficiency of emergency disinsection and deratization that were accomplished to reduce risks of diseases among population in Gorno-Altaiskiy high-mountain natural plague focus.

The research was performed in 2016–2021 in Gorno-Altaiskiy high-mountain plague focus which is the northern part of Sailygem cross-border natural focus located both in Russia and Mongolia. Zoological, epizootologic, epidemiological and statistical research procedures as well as GIS-tools were applied to collect and analyze research data.

Epidemiologic surveillance over plague in the focus has been accomplished since 1961. Prior to 2011 only rhamnosopositive strains of the plague microbe with selective virulence were found here, belonging to the Central Asian subspecies Yersinia pestis altaica, circulating mainly in the population of the Ochotona pallassi. Given that, the focus was believed to have low epidemic potential. Since 2012 highly virulent strains of the basic plague microbe Yersinia pestis ssp. pestis started to occur in populations of Marmota baibacina and other carriers. As a result, starting from that period of time, epidemiologic status of the focus changed and it led to 3 cases of bubonic plague among humans in 2014–2016. Disinsection and deratization remained the major components in anti-epidemic activities aimed at non-specific plague prevention. In 2016–2021 fields disinsection covered a total square equal to 162.7 km^2; disinsection in settlements, 127.3 thousand m^2; deratization in settlements, 461.7 thousand m^2. An approach involving disinsection only on land spots that were considered epidemically hazardous was first implemented; such land spots were around livestock breeders' camps located within boundaries of detected epizooties. Efficiency of fields disinsection amounted to 94.6; disinsection in settlements, 100 %; deratization in settlements, 88.0 %. Population of plague vectors and carriers was controlled bearing in mind environmental aspects in regulating numbers of animals and compliance with environmental protection requirements.

Deratization and disinsection, together with other activities aimed at plague prevention, provide epidemiologic welfare in the focus and reduce its epizootic activity.

***Key words:** plague, natural focus, plague vectors and carriers, risk factors, risk groups, risk time, risk territory, disinsection, deratization, epidemiologic welfare.*

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Plague is still among the most dangerous natural foci diseases and is widely spread in the North and South America, Africa, and Eurasia [1–5]. According to the valid International Health Regulations (2005) plague is a socially significant and extremely dangerous infection that requires international control [6–11]. In 2000–2020 plague outbreaks were detected on 5 continents in 20 countries worldwide with a total number of cases being 28,082 and 2,504 (8.9 %) out of them were lethal ones [12–13].

In Russia, CIS member states, Mongolia and China natural plague foci that occur in mountain natural habitats of marmots and gophers have become more active over the last decade. Given that growing activity, there have been sporadic cases of bubonic plague among humans caused by dressing carcasses of hunted marmots [14–22][1]. In Russia three cases were registered in 2014–2016 in the Gorno-Altaiskiy high mountain natural plague focus which is the northern part of Saylugem cross-border natural plague focus [23, 24].

In the Russian Federation and the CIS countries epidemiologic surveillance in natural plague foci involves epizootologic monitoring with its results giving grounds for planning and implementing prevention activities. In case an epidemic situation is deteriorating, strategies and tactics of surveillance over the dangerous infection are adjusted bearing in mind that all studies are epidemiologically oriented and aimed at preventing plague outbreaks [25]. In 2014–2021 a whole (integrated) set of anti-epidemic and prevention activities has been implemented in the Gorno-Altaiskiy high mountain, Tuvinskiy mountain, and Tien Shan high mountain natural plague foci. This set includes epizootologic examinations, epidemiologic monitoring, security and restrictive measures, sanitary-technical activities, informing and educational work with population, as well as disinfection in epidemic foci and on epizootic territories [26–28]. Insecticide and rodenticide treatments are the most radical measures aimed at inhibiting and eliminating epizooties. Reducing a number of carriers and vectors down to levels which put an end to an epizootic process allows minimizing risks of infection spread among people and provides epidemiologic welfare of population regarding this dangerous disease.

At present numbers of marmots are rapidly recovering and these animals are known to be basic plague carriers in mountain foci [18, 29][1]. This fur-bearing animal is traditionally hunted by locals. Despite marmot hunting is strictly prohibited in natural plague foci, local population hunt them all the same as a source of meat and fat which is usually used as a therapeutic mean. At present it is recommended to cease hunting this valuable and protected species since it will help inhibit plague epizooties in marmot habitats. As experience shows, ecological peculiarities of marmots related to their eating habits, places of living, and spatial-ethological features can't secure any reduction in their numbers without significant expenditure on organizing and accomplishing their extermination. Any attempts to regulate rodents' numbers without taking their population peculiarities into account are inefficient and ungrounded [30].

At present the greatest effects in inhibiting epizooties in plague foci are produced by eliminating fleas since these insects are specific vectors and keepers of the plague microbe. To do that, variable techniques are used including powder-based or wet disinsection or impregnation of materials with phosphor organic chemicals, pyrethroids, or phenylpyrazole [26, 31–33]. Their pulicide effects persist for 2–4 months; up to 6 months in some cases; and as it has been reported in some observations, even up to 3 years, probably, due to violated biocenosis in burrows. In case burrow holes of rodents or lagomorphs are to be treated with powder-like compounds, the most efficient way is to apply deep dusting with air blowers (motor dusters) or aerosol treatment using cold foggers.

[1] Abdel Z.Zh. Natural plague foci in the Tien Shan mountains in Kazakhstan and Kirgizia. Almaty, KNZKZI Publ., 2019, 168 p.

Emergency plague prevention in its natural foci is planned and implemented based on a systemic approach to contents of all applied activities. Only their integrated set can provide sustainable anti-epidemic effects. At the same time disinsection and deratization remain the most radical measures aimed at inhibiting and eliminating plague epizooties thus reducing risks of the infection spread among people [23].

Our research aim was to estimate efficiency of emergency disinsection and deratization that were accomplished to reduce risks of contagion among population in Gorno-Altaiskiy high-mountain natural plague focus.

Materials and methods. The research was accomplished in 2016–2021 in the Gorno-Altaiskiy high-mountain natural plague focus with its square being equal to 11,681 km^2. The focus is located within administrative boundaries of Kosh-Agachskiy district in Altai Republic (the Russian Federation). It is the northern part of Saylugem cross-border natural focus located both in Russia and Mongolia with its total square being 28,597 km^2. Over the last 5 years experts have examined 9,286 small mammals as typical plague carriers and 70,025 blood-sucking ectoparasites including fleas (57,919), lice, ticks and gamasite mites as primary and secondary plague vectors in the Gorno-Altaiskiy high-mountain natural plague focus. Overall, 146,665 burrows have been examined to detect fleas in them; all these burrows belonged to grey marmots (*Marmota baibacina*), Mongolian and Daurian pika (*Ochotona palassii* and *Ochotona dauurica*), and long-tailed (Siberian) souslik (*Spermophilus undulatus*). Also, 77 animal nests have been dug out.

Epidemic complications related to bubonic plague cases among people required restructuring the whole system of epidemiologic surveillance in the focus and its status changed after detecting highly virulent strains of the basic plague microbe [23, 34]. Given the existing situation, insecticide and rodenticide treatments increased in volumes and their tactics also changed. A new approach involved using small mobile teams (made up of 5 people) who worked on land spots with the highest epidemiologic risks around livestock breeders' camps located in epizootic areas. In one day such a team is able to accomplish barrier disinfection around 6–10 livestock breeder' camps located in mountains.

The Altai Plague Control Station got assistance in a period when the epidemiologic situation as per plague could deteriorate (from May to September) as 10–12 experts came there from the "Microbe" Russian Research Anti-Plague Institute (Saratov), Irkutsk Research Anti-Plague Institute and Stavropol Anti-Plague Institute [24, 28]. Experts from the prevention departments of the Center for Hygiene and Epidemiology in Altai Republic and Rospotrebnadzor Regional Office in Altai Republic took part in examining settlements and extermination activities in them. All the works were accomplished in accordance with the documents including "The Complex program of activities performed by Rospotrebnadzor and aimed at improving the epidemiologic situation in the Gorno-Altaiskiy high-mountain natural plague focus in Kosh-Agachskiy district of Altai Republic", "The activity program (roadmap) aimed at reducing risks of epidemiological complications in the Gorno-Altaiskiy high-mountain natural plague focus for 2019–2023" approved by the Order by the Altai Republic Government No. 2-r dated January 11, 2019, "The Program of disinsection and deratization in the Gorno-Altaiskiy high-mountain natural plague focus", and operation plans made up by the Altai Plague Control Station in 2016–2021.

Data were collected and analyzed using zoological, epizootological, epidemiological, and statistical procedures as well as GIS-tools [20]. The latter were applied when managerial decisions were being taken based on "Management of restoration activities in the Gorno-Altaiskiy high-mountain natural plague focus" interactive electronic map.

Results and discussion. From 1961 to 2021 only the plague microbe belonging to the Central Asian sub-species *Yersiniapestis* ssp. *Altaica* was detected in the Gorno-Altaiskiy high-mountain natural plague focus in Kosh-

Agachskiy district of Altai Republic. The microbe circulated in habitats of Mongolian (*Ochotona pallassii*) and Daurian (*O. daurica*) pika, long-tailed (Siberian) souslik (*Spermophilus undulatus*), and flat-headed vole (*Alticola strelzowi*). These plague microbe strains are highly virulent for white mice but weakly or even anti-virulent for guinea pigs [2]. Given that, the epidemic potential of the focus was considered to be low regardless of its permanent epizootic activity: plague was not registered among people for 50 years. In 2012 a strain of the highly virulent basic plague microbe *Y. pestiss* ssp. *pestis* was detected in the focus for the first time in a carcass of a long-tail souslik. Over the next few years this strain started to be detected regularly in grey marmots (*Marmota baibacina*) and long-tailed sousliks (*Spermophilus undulatus*) as well as in a wide range of fleas and other ectoparasites [18, 31]. Overall, in 1961–2021 2,601 cultures of the plague microbe were isolated in the focus; 2,438 out of them belonged to the Altai subspecies and 163 to the basic one (160 strains were detected in the field and 3 were isolated in clinics).

Epizootologic monitoring established there were seasonal and yearly changes in numbers of plague carriers including such background rodents and lagomorphs as grey marmots, Mongolian and Daurian pika, long-tailed souslik and flat-headed vole. At present marmot populations are rather dense and biotopes inhabited by this rodent have become larger. A number of occupied burrows varies from 0.3 to 2.0 per 1 hectare or 0.8 on average per 1 hectare. Numbers and habitats of Mongolian pika and long-tailed souslik are rather stable: average density of pika colonies amounts to 4.8 per 1 hectare in spring and 6.7 per 1 hectare in autumn; souslik population density is 3.8 and 5.7 animals per 1 hectare in spring and autumn accordingly. Average long-term number of flat-headed vole that lives in rock outcrops and scatterings in mountain ranges all around Chutskaya steppe on average amounts to 11.25 % in spring and 29.7 % in autumn if measured as per a number of entrapped animals.

A number of synanthropic rodents remains low. House mouse (*Mus musculus*) prevails in 11 large settlements in the focus; an average share of animals entrapped in mashers amounts to 2.6 in spring and to 3.3 in autumn. Flat-headed vole is easily found in buildings within high mountain livestock breeders' camps; its numbers vary from 4.0 % in spring to 7.1 % of entrapped animals in autumn. A lot of such camps are surrounded by habitats with a lot of various species living there including marmots, sousliks, and pikas.

Fleas that live in the focus and participate in the plague microbe circulation belong to 54 species and subspecies; 29 out of them were registered in 2016–2021. 17 species are mass ones and they are fleas typical for marmot, souslik, pika and vole. Indices of abundance (IA) of ectoparasites in animals' fur are quite stable over time and amount to 0.7 insects on grey marmot; 2.0, long-tailed souslik; 7.7, Mongolian pika; 1.9, flat-headed vole. In 2016–2020 IA for fleas amounted to 0.16 ± 0.03 insects on average in burrow holes. At present an overall number of fleas prevailing on Mongolian pika amounts to 190 insects per 1 hectare in spring and grows twice in autumn up to 390 insects per 1 hectare. *Oropsylla silantiewi* fleas prevail on grey marmots; *Amphalius runatus*, *Ctenophyllus hirticrus*, *Frontopsylla hetera*, *Paradoxopsyllus scorodumovi*, *P. scalonae*, *P. dashidorzhii*, *P. hesperius kalabukhovi*, *Amphipsylla primaris* and *Rhadinopsylla dahurica*, on pika and in its colonies; *Citellophilus tesquorum*, *Oropsylla alaskensis*, on long-tailed souslik.

Most cultures of the plague microbe belonging to the Altai subspecies were isolated from pikas and fleas that were specific for them; cultures of the basic plague microbe were isolated from grey marmots and long-tailed sousliks and their ectoparasites (94 %). The plague microbe of the Altai subspecies circulates at heights varying from 1,800 to 2,600 meters above the sea level; the basic plague microbe, 2,200–2,700 meters. Habitats of *Y. p. altaica* и *Y. p. Pestis* are overlapped on the major part of the focus territory.

Factors, contingents, time, and risky territories in terms of possible contagion with plague among population were analyzed thoroughly and analysis results were estimated to give grounds for building up a map showing levels of epidemiological hazard (risk) of plague contagion in the focus. The map is checked up and, if necessary, adjusted every year (Figure 1). This cartographic basis is used in planning and implementing examinations and prevention activities thus making them more targeted.

The Gorno-Altaiskiy high mountain natural plague focus is unique due to two independent adjacent plague foci occurring on its territory that are different as per their biocoenotic and spatial structure. The plague microbe of Altai subspecies is established to circulate in three meso-foci, Ulandrykskiy, Tarkhatinskiy and Kuraiskiy ones, which are territorially and functionally linked to Mongolian pika populations of the same name [34]. An area where epizootic events caused by *Y. p.* ssp *altaica* were detected amounts to 2,317.2 km^2 and it coincides with the Mongolian pika habitat completely. Results of several studies indicate that the aforementioned foci are relatively independent in their functioning [16, 35].

An area where *Y. p. pestis* was established to circulate in 2021 amounts to 2,015.7 km^2 whereas the whole habitat of grey marmot amounts to 4,120 km^2. It can be considered as a future opportunity for the highly virulent subspecies to spread over larger areas in this focus. There is a partial overlap in the focus regarding epizootic events caused by two different subspecies of the plague microbe since strains of them both are detected on an area being equal to 950.0 km^2. Therefore, the total area here plague epizooties are detected amounts to 3,383.0 km^2 or 29.0 % of the whole focus (Figure 2).

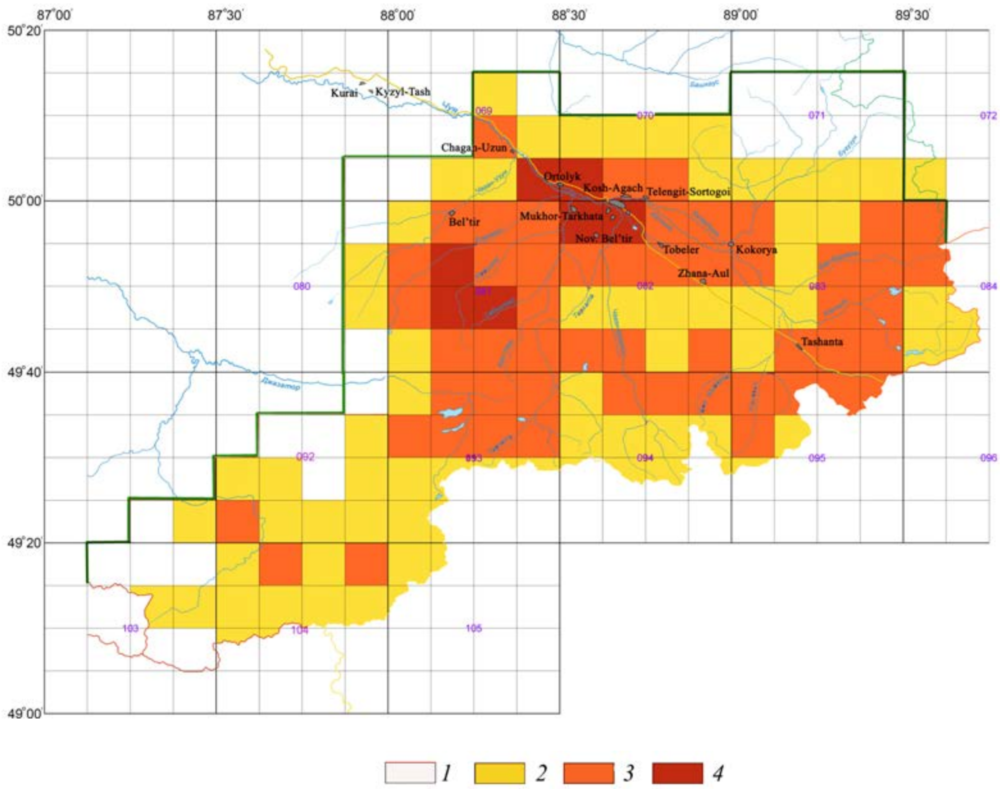

Figure 1. Levels of epidemiologic risks in the Gorno-Altaiskiy high mountain natural plague focus
1 is low; ***2***, moderate; ***3***, high; ***4***, extremely high

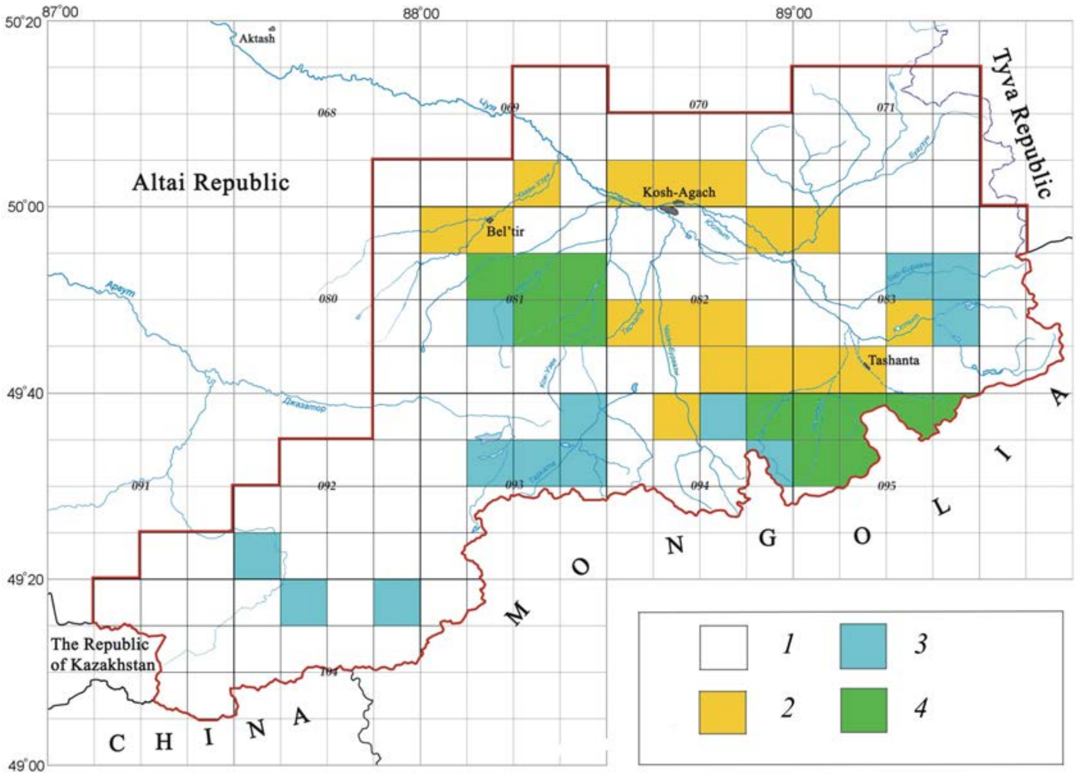

Figure 2. Places where plague cultures were isolated in the Gorno-Altaiskiy high mountain focus Sectors: ***1*** means cultures were not isolated; ***2***, only *Y. p. ssp. altaica* strains; ***3***, only *Y. p. ssp. pestis* strains; ***4***, both strains were isolated

Disinsection and deratization remained primary anti-epidemic activities. Reducing numbers of plague carriers and vectors down to levels at which an epizootic process stops provides epidemiologic safety regarding this dangerous infection. Growing volumes of operative insecticide and rodenticide activities that were relevant to the existing situation with plague were provided by attracting additional resources from anti-plague institutions in Russia.

We should note that seasonal schedules of livestock breeders' roaming were taken into account when volumes and places of field disinfections were determined. It was obligatory to treat all livestock breeders' camps located on land spots that were epizootic as per plague as it was detected in previous seasons or through operative field examinations. Major part of these barrier treatments was accomplished in May and this allowed reducing numbers of fleas and preventing development of plague epizooties around summer camps before a great number of people settled in them for a season.

Deratization and disinsection in settlements was basically accomplished by experts from the Department for preventive disinsection of the Center for Hygiene and Epidemiology in Altai Republic. Home mouse (*Mus musculus*) is the only synanthropic rodent living in large settlements in the focus. All buildings in livestock breeders' camps located in highlands are inhibited by flat-headed vole. Occasionally Mongolian pika or Campbell's dwarf hamster can also be found there. Regular monitoring allowed establishing that numbers of home mouse and its fleas were very low in settlements. Given that, in case there are indications that some extermination procedures are necessary, as a rule, rodents and ectoparasites are not detected after deratization and disinsection. Since these activities have been highly efficient so far, the result is lower epizootic activity in the focus as a number of isolated cultures belonging to the highly virulent basic subspecies has been decreasing (Table). These activities, together with other preventive measures, gave an opportunity to provide epidemiologic welfare as per plague in the Gorno-Altaiskiy high mountain natural plague focus. Since 2017 and up to now there have been no plague cases registered among people.

From 2016 to 2021 the overall square of field disinsection in the Gorno-Altaiskiy high mountain focus amounted to 140.9 km^2; disinsection in settlements, 117.7 thousand meters^2; deratization in settlements, 393.2 thousand meters^2. Field deratization wasn't either planned or accomplished in the focus since it was considered inefficient to exterminate marmots in order to inhibit epizooties as well as due to the necessity to protect this valuable commercial species. Annually from 46 to 132 livestock breeders' camps as well as border stations were examined on epizootic areas. Disinsection was accomplished around each camp in multi-species settlements of pika, marmot, and souslik on a square varying from 0.3 to 1.0 km^2 as per results of epizootologic monitoring over territories that were endemic as per plague and depending on a lay of land. Density of burrows in multi-species animal settlements varied from 11 to 84 with its average value being 22.1 ± 3.2 per 1 hectare. Index of abundance (IA) for burrow fleas varied from 0.116 ± 0.02 to 0.197 ± ± 0.03 in different years around livestock breeders' camps on epizootic territories. IA for fleas fell from 0.007 to 0.003 after insecticide effects expired. On average, 5.5 kg of insecticide dust were spent on one camp. Treatment was accomplished by dusting burrow holes or deep dusting with TWISTER knapsack dusters and CIFARELLI motor (petroleum-driven) air blowers.

Deratization took place only in large settlements and livestock breeders' camps in the focus as well as in building at border stations. Given that house mice prevailed in settlements and flat-headed voles prevailed in buildings in highland livestock breeders' camps, it was quite efficient to use rodenticide baits in animas' shelters (burrows, cracks, containers, cellars, etc.).

Ready-made baits based on the second-generation anticoagulants were used as rodenticides to perform deratization in settlements in the Gorno-Altaiskiy high mountain natural plague focus; the examples are paraffin blocks "Blokada", "Brodifan" and "Zernotsin-blok" (based on 0.005 % *bromadiolone* and *brodifacoum*). Field disinsection was performed by using dust mixtures "Kaprin-F" (0.04 % *fenvalerate* + 4.0 % *boric acid*), "Fas-dubl'" (0.02 % *zete cipermetrina* + 0.01 % *fenvalerate*) and "Zelenyi dom" (0.2 % *ccipermetrina* + 0.2 % *sumithion*) based on synthetic pyrethroids and phosphor organic compounds. Wet disinsection in settlements was performed by using concentrated emulsion of "Fufanon-super" phosphor organic compound (44–57 % *malathione*).

Table

Epizootic activity, efficiency of deratization and disinsection in the Gorno-Altaiskiy high mountain natural plague focus in 2016–2021

Year	Number of isolated *Y. p. pestis*	Square of epizooties, km^2	Field disinsection		Deratization in settlements		Disinsection in settlements	
			km^2	eff., %	th. m^2	eff., %	th. m^2	eff., %
2016	65	930.6	30.4	86.0	102.9	81.1	72.8	100.0
2017	49	925.0	43.5	96.7	99.1	82.9	13.9	100.0
2018	11	670.4	32.7	94.5	77.7	80.5	12.9	100.0
2019	8	418.1	32.0	97.4	39.0	83.7	7.4	100.0
2020	5*	503.4**	2.3	–	74.5	100.0	10.7	100.0
2021	5	415.2	26.3	98.5	68.5	100.0	9.6	100.0
Total	138	3,383.0	167.2	94.6	461.7	88.0	127.3	100.0

Note: * means 3 out of 5 plague microbe strains were isolated on hard-to-reach spots in Ukok highlands which were not examined in 2016–2019; ** means square of epizooties in Ukok highlands is also included and amounts to 252.7 km^2.

Factors of epidemiologic risks related to plague contagion are to a great extent determined by epizootic activity of a natural focus. At present species structure, numbers, and specific distribution of vectors and carriers in the Gorno-Altaiskiy high mountain natural plague focus make for persistent circulation of the highly virulent basic plague microbe subspecies. It is either rather difficult or not advisable to exterminate small rodents that are plague carriers in natural biotopes given their environmental peculiarities [36]. Thus, grey marmot and pika are grass-eating animals and given that it seems rather inefficient to use ready-made traditional rodenticide baits. Besides, it is prohibited to exterminate grey marmots as they are a valuable commercial species and are protected by environmental legislation. Deratization is to be accomplished only in settlements where it is necessary to completely exterminate synanthropic and hemisynanthropic rodents. The up-to-date concept of disinsection and deratization in plague foci involves focusing on insecticide treatments against fleas in human settlements as well as in natural biotopes where basic plague carriers live. When a number of fleas as plague microbe vectors and keepers is reduced, it helps break an epizootic chain and, consequently, inhibit or eliminate an epizooty. Risks for people to get infected with plague are also reduced or prevented completely and it is exactly the main goal that epidemiologic surveillance over plague is to achieve.

Selecting a procedure for accounting numbers of fleas as plague vectors is a major task that has to be solved when assessing efficiency of accomplished insecticide treatments. Fleas that live on burrowing animals migrate rather poorly from depths to holes in highlands in the focus. At the same time all animal settlements located around and within livestock breeders' camps are mixed colonies with grey marmots, pikas, and sousliks living there; insects can be collected in such animal settlements during the whole season (from May to September) using a flannel band (or a hose).

Pulicide efficiency was estimated as per results of insecticide treatments accomplished in May–June around livestock breeders' camps; the estimation was based on flea abundance at burrow holes of plague carriers and indicated that efficiency amounted to 94.6 % on average in the focus varying from 86.0 to 97.7 % in different years. Indices of abundance for burrow flea went down by 20–40 times on different areas. To obtain correct data on efficiency of insecticide treatments against burrow fleas, experts performed simultaneous examinations on treated (test) land spots around livestock breeders' camps and on untreated (reference) ones. The examinations proved accomplished insecticide activities to be highly efficient. Test land spots around livestock breeders' camps were repeatedly examined in July and August to reveal that insecticide effects on fleas at burrow holes persisted for up to three months (observation periods). We should note that examinations also revealed either total absence of fleas or very low numbers of them in burrow holes on most land spots around livestock breeders' camps that were treated in the previous year. However, this fact can be due to not only persisting effects of applied insecticides one year after but also be a consequence of flea taxocenes recovering rather slowly by fleas penetrating from neighboring untreated areas given that insects were highly tessellated and highland biocenoses were relatively isolated.

Apart from providing satisfactory pulicide effects, we should also bear in mind that accomplished insecticide treatments also may have anti-epidemic and anti-epizootic effects. In 2017–2021 there have been no plague cases registered among people in the Gorno-Altaiskiy high mountain focus. Over the same period epizootic territories and a number of isolated cultures have also been going down.

Conclusions. Epidemiological anamnesis with data on people getting infected with plague in the Gorno-Altaiskiy high mountain natural plague focus is clear evidence that all cases when people got infected with bubonic plague were caused by dressing carcasses of sick marmots that were illegally hunted. Given that, informing and educational work with population becomes very important and people should be aware of prevention activities against the dangerous infection; control over restrictions imposed on people's visits to epizootic areas is another vital issue. But at the same time a major task to be solved is to inhibit and eliminate plague epizooties in carriers' settlements including grey marmot, Mongolian pika and long-tailed souslik. It will allow reducing a probability that people would get infected on epizootic areas. Insecticide treatments performed on such areas as well as deratization within settlements and around them makes the focus territory healthier and, together with other prevention activities, reduces a number of possible contacts between people and infected animals.

Field disinsection as well as disinsection and deratization in settlements were proven to have high anti-epizootic efficiency; given that, volumes and territories to be treated were increased when emergency anti-plague activities were planned and implemented in order to make them relevant to the existing situation. In this relation, traditional experience accumulated by Rospotrebnadzor was applied involving providing additional resources of anti-plague stations and institutes in emergency situations.

A decrease in numbers of fleas as basic plague microbe vectors and keepers in natural biotopes resulted in inhibiting epizooties development in settlements of basic plague carriers (grey marmots, sousliks and pikas) and reducing risks of people getting infected in the focus. Deratization and disinsection in settlements provide eliminating rodents and their fleas (plague microbe carriers and vectors) in settlements and livestock breeders' camps. A set of prevention activities accomplished in 2017–2021 allowed providing epidemiologic welfare of population and reducing epizootic activity in the Gorno-Altaiskiy high mountain natural plague focus.

Unique experience in planning, organizing, and implementing a set of prevention activities in the Gorno-Altaiskiy high mountain natural plague focus should be examined and recommended to be applied in other natural plague foci in Russia and neighboring countries.

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Research article

STROKE AND STROKE RISK FACTORS AS DISEASE BURDEN

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Stroke is the most common cause of disability and death in the world. Cardiovascular disease rates increase with age (10.9 % for people aged 20–30 years and 85.3 % for people older than 80 years). Coronary heart diseases is the leading cause of deaths attributable to cardiovascular diseases in the United States, followed by stroke, high BP, HF, diseases of the arteries, and other cardiovascular diseases. The report on the global burden of neurological disorders has shown that hemorrhagic stroke accounted for 35.7 % in it, and ischemic stroke, 22.4 %. Seven indicators are important and strategic to prevent cardiovascular disorders; they include healthy diet, sufficient physical activity, smokingstatius, BMI, cholesterol level, blood pressure, and glucose in blood on a fasting stomach. These indicators are associated with healthy behavior (diet quality, PA, smoking, BMI) which are as important as health factors (blood cholesterol, BP, blood glucose). There is a strong protective association between ideal cardiovascular health indicators and many clinical and preclinical conditions including premature all-cause mortality, stroke, CVD mortality, ischemic heart disease mortality, HF, deep venous thromboembolism, and pulmonary embolism. Atrial fibrillation, metabolic syndrome, renal failure, and sleep apnea are important risk factors which are modifiable and treatable. Air pollution has been reported as an increasing and very important risk factor for stroke. COVID-19 has been reported as another new stroke risk factor during the pandemic. Future targets must include each cardiovascular health indicator to decrease stroke risk burden and stroke risk.

Key words: *stroke, cardiovascular diseases, health indicators, risk factors, disease burden.*

Neurological diseases account for 10.2 % of global loss in health, cause 16.8 % of global deaths, and 9.4 million people in the world lose their lives every year because of neurologic diseases. Stroke is the most common cause of disability. The striking facts show that every 40 seconds someone in the United States has a stroke and someone dies of one approximately every 4 minutes.

Stroke death rate decreases with the improvement in acute stroke treatment and widely usage of stroke units. According to the AHA statistics (2018) the 10 leading causes of death are heart disease (No. 1), cancer (No. 2), chronic lower respiratory diseases (No. 3), unintentional injuries (No. 4), stroke (No. 5), Alzheimer disease (No. 6), Diabetes Mellitus (No. 7), influenza and pneumonia (No. 8), kidney disease (No. 9), suicide (No. 10). There is also an important changes in ICD 11 (stroke listed under the brain disorders) and this important step may support more accurate statistics for stroke prevelance and incidence [1].

High body mass index, high fasting plasma glucose, and smoking are the first, second, and third leading years lived with disability and injury risk factors in the United States in both 1990 and 2019, whereas smoking dropped from first to third leading years lived with disability and injury risk factor during this time period. Smoking and high systolic BP remained the first and second leading years of life lost risk factors in the United States in both 1990 and 2019. High systolic BP and smoking are the first and second leading years of life lost risk factors

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globally in 2019. High fasting plasma glucose and high body mass index were the first and second leading years lived with disability and injury risk factors globally in 2019. The recent data show that cardiovascular disease rates increase with age (10.9 % for 20–30 ages and 85.3 % for older 80 ages). Coronary hearth diseases (43.8 %) is the leading cause of deaths attributable to cardiovascular diseases in the United States, followed by stroke (16.8 %), high BP (9.4 %), HF (9.0 %), diseases of the arteries (3.1 %), and other cardiovascular diseases (17.9 %).

Between 1990 and 2010, ischemic stroke mortality decreased 37 % in high-income countries and 14 % in low and middle-income countries. Hemorrhagic stroke mortality decreased 38 % in high-income countries and 23 % in low- and middle-income countries. The report on the global burden of neurological disorders showed that burden consists of 35.7 % hemorrhagic stroke, 22.4 % ischemic stroke, 12.7 % migraine, 9.9 % epilepsy, 6.4 % dementias, 1.1 % Parkinson diseases, 1.0 % tension headache other 10.2 % [2–5].

Risk Factors for Stroke. AHA-Health Metrics were defined to follow health risk and management of this parameters. Seven Health Metrics which are important and strategic to prevent cardiovascular disorders; Healthy diet pattern, sufficient physical activity, smoking, BMI, cholesterol level, blood pressure, fasting blood glucose. These metrics include also health behaviours (diet quality, PA, smoking, BMI) which are as important as health factors (blood cholesterol, BP, blood glucose).

There are strong protective association between ideal cardiovascular health metrics and many clinical and preclinical conditions including premature all-cause mortality, stroke, CVD mortality, ischemic heart disease mortality, HF, carotid arterial wall stiffness, coronary artery calcium progression, impaired physical function, cognitive decline, depression, end-stage renal disease, chronic obstructive pulmonary disease, deep venous thromboembolism, and pulmonary embolism [5].

High blood pressure. It was reported that there are 3.47 billion adults worldwide with systolic BP of 110 to 115 mmHg or higher in 2015. The death rate attributable to high BP increased by 10.5 %, and the actual number of deaths attributable to high BP rose by 37.5 % from 2005 to 2015.

Smoking and tobacco use. According to the AHA statistics, the prevalence of current smoking in the United States in 2015 was 15.1 % for adults and 4.2 % for adolescents. Despite all efforts to reduce, tobacco use remains the leading cause of preventable death in the United States and globally. It was estimated to account for 7.2 million deaths worldwide in 2015. Recently, there has been a rapid increase in e-cigarette use especially among adolescents. Cigarette smoking is known as an independent risk factor for both ischemic stroke and SAH. Current smokers have a 2 to 4 times increased risk of stroke compared with nonsmokers or those who have quit for > 10 years lowering CVD risk. Another ignored risk factor is secondhand smoke which is as harmful as smoking. Nonsmokers who are exposed to secondhand smoke at home or at work increase their risk of developing CHD by 25 % to 30 %. Exposure to secondhand smoke; increases the risk of stroke by 20 % to 30 %, associated with increased mortality after a stroke.

Physical inactivity. Physical inactivity is the fourth-leading risk factor for global death, responsible for 1 to 2 million deaths annually. It was reported that only 21.5 % of American adults achieve adequate leisure-time aerobic and muscle-strengthening activities to meet the physical activity guidelines. The prevalence of adolescents meeting the aerobic physical activity guidelines is 27.1 %.

Nutrition. Nutrition has been reported as a leading risk factor for stroke and other cardiovascular disorders. 45.4 % of US deaths caused by heart disease, stroke, and type 2 diabetes mellitus (DM) (cardiometabolic mortality) were attributable to poor dietary habits.

The top contributing poor dietary factors were reported as; High sodium intake, low levels of nuts and seeds, high intake of processed meats, low consumption of seafood omega-3 fats, low intake of vegetables, low intake of fruits, and high consumption of sugar-sweetened beverages [6].

Obesity and overweight. Obesity is a very common health problem in the world. It has been reached a very risky level for every ages including children. There are important results from a meta-analysis from 2016 which suggests that CVD risk was higher (relative risk, 1.45) in obese individuals without metabolic syndrome than in metabolically healthy normal-weight participants, which suggests that obesity is a risk factor even in the absence of high blood pressure, high cholesterol, and DM [3].

High blood cholesterol and other lipids. An estimated 28.5 million adults ≥ 20 years of age have serum total cholesterol levels ≥ 240 mg/dL, with a prevalence of 11.9 %. 21 % of youths 6 to 19 years of age have at least 1 abnormal cholesterol measure. 56.0 million (48.6 %) US adults ≥ 40 years of age are eligible for statin therapy based on the 2013 American College of Cardiology / AHA guidelines [7].

Diabetes mellitus. Diabetes mellitus rate increases with the increase of obesity, unhealthy diet. In 2015, an estimated 5.2 million deaths globally were attributed to DM. The prevalence of diagnosed DM was estimated to range from 5.6 % to 20.4 %, and the prevalence of undiagnosed DM ranged from 3.2 % to 6.8 %.

Atrial fibrillation. Atrial fibrillation is an increasing risk factor with age. Multiple lines of evidence have increased awareness of the burden of unrecognized AF. In individuals without a history of AF with recent pacemaker or defibrillator implantation, subclinical atrial tachyarrhythmias were detected in 10.1 % of patients.

Subclinical atrial tachyarrhythmias were associated with a 5.6-fold higher risk of clinical AF and ≈ 13 % of ischemic strokes or embolism.

Sleep apnea. A modifiable risk factor sleep apnea must be taken into consideration. The prevalence of sleep-disordered breathing, defined as an AHI ≥ 5, has been estimated to be 34 % for men and 17 % for women aged 30 to 70 years. Obstructive sleep apnea causes increase in stroke especially in men [8].

Metabolic syndrome. The prevalence of metabolic syndrome was 17 % among people < 40 years old, 29.7 % for people 40 to 49 years old, 37.5 % among those 50 to 59 years old, and > 44 % among people ≥ 60 years of age.

The prevalence of metabolic syndrome was higher among females (34.4 %) than males (29 %) and increased with advancing age.

Of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks analysed in GBD 2013. It was assessed risk–outcome pairs (17 risks and stroke-related DALYs) that met explicit evidence criteria for 188 countries [9].

Top risk factors ranked by number of DALYs attributable to stroke for both sexes combined in 21 regions in 2013 DALY= disability-adjusted life-year (Figure 1) [10–12].

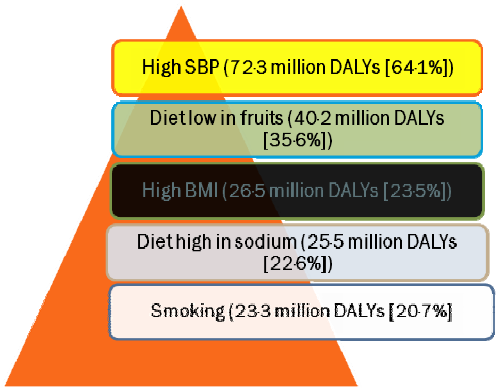

Figure 1. The five leading risk factors for DALYs (GBD 2016 – Feigin et al. [13])

Air pollution. A new and very important risk factors were environmental factors (air pollution and lead exposure; 33.4 %, 95 % CI 32.4–34.3) were the second and third largest contributors to DALYs [14].

Globally, 29.2 % (95 % CI 28.2–29.6) of the burden of stroke was attributed to air pollution. It has been reported that air pollution has emerged as a significant contributor to global stroke burden, especially in low income and middle-income countries, and therefore reducing exposure to air pollution should be one of the main priorities to reduce stroke burden in these countries.

Eating habits and life styles change with the change of demographics and economic levels. Globally, there were a significant increase in the stroke-related DALYs associated with high BMI low physical activity, high fasting plasma glucose high SBP, diet high in sugar-sweetened beverages, high total cholesterol, ambient particulate matter pollution of aerodynamic diameter less than 2.5 μm ($PM_{2.5}$), alcohol use, diet high in sodium, diet low in vegetables, and smoking. It can be concluded that if these trends continue the differences will be increase as dependent of countries income levels. Especially diet high in sodium is an important marker which is able to affect other risk factors [6, 14].

A promising result is a reality which shows that more than 90 % of the stroke burden is attributable to modifiable risk factors, and achieving control of behavioural and metabolic risk factors could avert more than three-quarters of the global stroke burden.

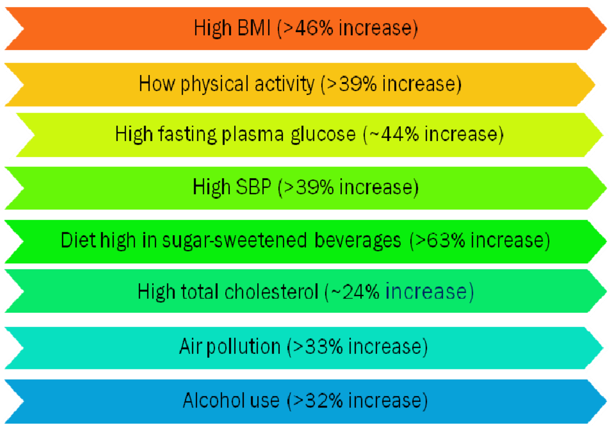

Figure 2. Increase in the stroke-related DALYs and risk factors (1990–2013) (GBD 2016 – Feigin et al. [13])

The COVID-19 pandemic is an additional ongoing threat for this widespread and important group of diseases. While the field is rapidly emerging, our current knowledge on the role of COVID-19 in stroke is increasing. Evidence suggests that infected patients may develop significant coagulopathy which leads to thromboembolic complications like stroke, peripheral artery thrombosis, deep vein thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, and venous sinus thrombosis. Histopathologic analysis of the ischemic brain of a COVID-19 patient revealed hypoxic neurons, significant edema from the underlying ischemic insult, fibrin thrombi in small vessels, and fibroid necrosis of the vascular wall without any signs of vasculature inflammation. The authors suggested that the cerebrovascular thromboembolic events in COVID-19 infection may be related to acquired hypercoagulability and coagulation cascade activation due to the release of inflammatory markers and cytokines, rather than virus-induced vasculitis. Microthrombi within the vessels were more consistent with a systemic inflammatory response-mediated mechanism, probably related to elevated serum inflammatory markers such as D-dimer and fibrinogen [15, 16].

Lockdown periods can cause a hesitation among patients to admit themselves to hospitals for routine care of chronic diseases, or for acute health care such as stroke, which is a time-dependent condition and irregularity for routine checkups for risk factor prevention.

To prevent these proven risk factors and to decrease burden of stroke ESO published an action plan for 2030 [17]. To reduce effect of stroke in public health and to increase supports by health authorities and politicians, this was an important strategy. General targets and item specific targets were defined. General target for 2030 was defined to reduce the absolute number of strokes in Europe by 10 % and to treat 90 % or more of all patients with stroke in Europe in a dedicated stroke unit as the first level of care. The national awareness and action was important and national societies were motivated to have national plans for stroke encompassing the entire chain of care from primary prevention to life after stroke.

Targets for primary prevention. Achieving universal access in Europe to primary preventive treatments based on improved and more personalised risk prediction, having blood pressure detected and controlled in 80 % of persons with hypertension.

Secondary prevention: The statistical data show that secondary prevention as important as primary prevention to reduce stroke burden. Secondary preventionIncluding secondary prevention in national stroke plans with follow-up in primary / community care, ensuring that at least 90 % of the stroke population is seen by a stroke specialist and have access to secondary prevention management (investigation and treatment), ensuring access to key preventative strategies: lifestyle advice, antihypertensives, lipid lowering agents, antiplatelets, anticoagulants, oral hypoglycaemic agents and insulin, carotid endarterectomy, and PFO closure.

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Research article

ASSESSING FUNCTIONAL STATE OF THE BODY WHEN WEARING A REUSABLE PROTECTIVE SUIT TO MINIMIZE RISKS OF CONTAGION AMONG MEDICAL PERSONNEL

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Personal protective equipment has become the last line of protection for medical personnel during the pandemic of the new coronavirus infection since it allows minimizing risks of biological contagion. Given the existing staffing shortage, medical workers have to spend from 4 to 12 hours a day in the "red zone" where they necessarily wear personal protective equipment. Protective clothing is known to produce negative effects on functional state of the body and personnel's working capacities. Assessment of up-to-date protective suits will allow developing recommendations on their suitable application bearing in mind a balance between necessary protection, providing favorable ergonomics, and reducing risks of adverse effects on functional state and working capacities.

Our research aim was to hygienically assess health risks for medical workers who had to wear reusable protective suits.

Our research object was a reusable suit made from polyether fabric with polyurethane membrane coating and antistatic threads. We performed an experiment aimed at evaluating thermal state of the body, psychophysiological state, and responses by the volunteers' cardiorespiratory system in laboratory conditions during an 8 hour working shift under controlled microclimate. Participants in the experiment were questioned in order to assess suits' ergonomics.

Heat exchange dynamics and amount of changes in thermal physiological parameters caused by wearing a protective suit determined heat contents of volunteers' bodies that conformed to optimal standard values. Data on psychophysiological and mental state taken in research dynamics didn't have any statistically significant changes. Gas exchange indicators naturally grew during the "load" phase; however, there were no significant changes detected in any phase in the research.

Hygienic assessment of the thermal state, functional state of the cardiovascular and respiratory systems, and psychophysiological indicators confirmed that wearing a protective suit was quite safe and didn't involve any health risks for volunteers.

***Key words**: personal protective equipment, health risk, thermal state of the body, functional state of the body, gas exchange, psychophysiological indicators.*

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On March 11, 2020 the World Health Organization (WHO) declared the beginning of a new coronavirus infection pandemic which involved the necessity to provide additional beds in hospitals for treating patients with it. Staffing shortages resulted in greater loads on medical personnel who were engaged in treating people with the infection regardless of their specialty or a position [1, 2]. Given that the new infection was assigned into the second group of pathogenicity (according to the classification accepted in the Russian Federation) and there were scarce data on how this new infection was transmitted, wearing personal protective equipment (PPE) was considered obligatory for minimizing risks of biological contagion [3, 4]. Since there was apparent staffing shortage in medical organizations, medical workers had to spend from 4 to 12 hours a day working in protective suits in "red zones" [5–8].

Most materials PPE is made from have low air and vapor permeability and this creates favorable conditions for the body getting overheated even under optimal air temperature [9–12]. According to recommendations given by the WHO and Rospotrebnadzor[1] medical personnel exposed to risks of contagion should use PPE that protects from biological agents, similar to anti-plague ones [13]. Such suits provide reliable protection; however, medical workers complain about certain discomfort they have to face when wearing them and also mention poorer functional state of the body and lower working capacities associated with disrupted heat exchange and unsatisfactory ergonomic properties of protective suits [14–17]. Medical personnel's work during the pandemic often had to be done under high air temperature, especially in summer, and it aggravated adverse effects produced by PPE and led to elevated risks of overheating [18, 19].

There is a wide range of protective suits available at the moment; they are manufactured from different materials and produce different effects on the body. This requires evaluating their impacts on functional state of the body as well as on mental and physical working capacities of medical personnel.

Our research aim was to hygienically assess health risks for medical workers due to wearing reusable protective suits.

The research involved solving the following tasks:

1. To examine heat indicators of volunteers who had to wear a protective suit for 8 hours in a stationary laboratory.
2. To examine volunteers' mental and psychophysiological indicators.
3. To examine responses by the cardiorespiratory system to working in a protective suit.
4. To evaluate ergonomic properties of a protective suit through questioning.

Materials and methods. Six practically healthy male volunteers took part in the research. They were aged from 36 to 45 years, their average body weight was 85.9 ± 16.4 kg; average height, 176 ± 4.7 cm.

The research program was approved by the local ethical committee of the State Scientific Test Research Institute of Military Medicine of the RF Ministry of Defense.

We evaluated functional state of the volunteers who wore a reusable protective site made from a polyether fabric with polyurethane membrane coating and antistatic thread (hereinafter called the suit). The suit consisted of overalls and shoe covers. The volunteers also wore two pairs of surgical nitrile gloves on each hand, safety goggles, and FFP2 type respirator (KN95). Cotton underwear was put on beneath the suit (boxers and a long-sleeve T-shirt) and it was the same for all volunteers; they also put on cotton socks and sneakers.

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A suit for each volunteer was carefully selected from 6 options with different sizes depending on a person's weight and height. The suits were worn uninterruptedly for 8 hours (a typical working shift). The volunteers didn't eat or drink water during the experiment.

The experiment was accomplished in a laboratory at air temperature being 25.4 ± 0.1 ºC; air humidity, 33.9 ± 1.1 %; air speed, 0.2 ± 0.1 m/sec.

The experiment involved using the following equipment:

1. KMTP-01 kit for monitoring over thermal and physiological indicators of the body ("Spetzmedtekhnika" LLC, Saint Petersburg) applied to measure temperature and heat flow within a temperature range from 0 ºC to 50 ºC (measuring inaccuracy was ± 0.05 ºC).

2. "MES-200" meteometer ("NPP "Ellektrostandard" Ltd, Saint Petersburg) to register microclimatic conditions.

3. "TVM-150" electronic scales with measuring accuracy up to 50 grams ("Massa-K" PLC, Saint Petersburg), and "V1-15" electronic scales with measuring accuracy 2–5 grams depending on a range necessary for measuring weights of examined samples ("Massa-K" PLC, Saint Petersburg); these devices were applied to determine the volunteers' body weight and weights of different pieces included into the protective equipment set.

The experiment involved determining and evaluating the following:

– whether it was possible for the volunteers to wear suits (both at rest and under mild physical loads) under air temperature being 25.0 ºC and average air humidity not exceeding 80 % for 8 hours without any risks for their health;

– dynamics of heat exchange and heat state of the body;

– intensity and efficiency of moisture losses;

– microclimatic conditions at a workplace (air temperature, relative air humidity, and air speed).

The experiment involved measuring and registering the following indicators:

– rectal temperature (Tr);

– skin temperature on 11 body parts selected for examination (Ts);

– heat flow density on 11 body parts selected for examination (HFD);

– how heat was felt by the volunteers, overall and locally;

– the volunteers' body weight without the suit and accessories;

– a mass of each piece included into the overall PPE set.

All the aforementioned thermal and physiological indicators as well as microclimatic conditions were determined prior to the experiment (background values), after each 30 minutes during the experiment and at the end of it. The volunteers' body weight and masses of PPE pieces were determined prior to and after the experiment. The volunteers were thoroughly examined after the experiment to detect any possible skin irritation.

Integral indicators of the volunteers' heat state were calculated based on measuring results; these indicators included average weighted skin temperature (AWST), average body temperature (ABT), average weighted heat flow (AWHF), total heat losses, and a change in heat content in the body (ΔQ). Sweat evaporation efficiency was calculated and considered an integral characteristic of PPE hygienic properties that influenced heat exchange in the body.

Volunteers had mild physical loads for 5 minutes at the beginning of each hour (walking on a treadmill at a speed equal to 5 km/hour without any rise of the running belt) with indicators of gas exchange being registered during it. To do that, we used *"MetaLyzer 3B"* system for spiroergometry and gas analysis (Cortex, Germany) and *T-2100* treadmill compatible with the spiroergometry system (General electric, USA).

Responses by the cardiorespiratory system (CRS) were evaluated at 9 time points: 1, 2, 3, 4, 5, 6, 7, 8 and 9 hours after taking the suit off.

We analyzed primary (lung ventilation (LV), partial pressure of oxygen and carbon dioxide during inhalation and exhalation, heart rate (HR), respiratory rate (RR), lung volume (RLV)) and derived indicators (oxygen volume (VO_2), carbon dioxide volume (VCO_2), respiratory quotient (RQ), lung volume (LV), metabolic intensity (MI)).

The volunteers had moderate intellectual loads during time periods free from registering indicators of their functional state (20–30 minutes during each hour in the experiment). These intellectual loads involved several psychodiagnostic tests (a comprehensive personality test and a 16-factor personality inventory) and this allowed us to model occupational activities performed by medical personnel in "red zones".

Each hour we took blood pressure and performed psychophysiological tests (simple visuomotor reaction time (SVMRT), complex visuomotor reaction time (CVMRT) and determined volunteers' activity, mood, and wellbeing with "CAM" questionnaire (cenesthesia, activity and mood). Psychophysiological indicators were assessed using "*NS-Psychotest*" software and hardware complex ("Neurosoft", Ivanovo, Russia).

After the experiment was over, each volunteer took part in a poll by filling in a specifically designed questionnaire; it was done to analyze how comfortable the suit was for wearing it and working in it as well as to evaluate subjective feelings regarding health and heat during the experiment.

The results were statistically analyzed using STATISTICA for Windows applied software package, Version 10.0. We applied Wilcoxon's T-test to determine authenticity of differences between two samplings of pair measurements; correlations between variables in a dependent sample were determined with the Spearman correlation coefficient (rxy) at the significance level being 95 % ($p \leq 0.05$). In case values of an indicator were distributed normally, we took a simple mean (*M*), statistical error of the mean (*m*) and standard deviation (*SD*) to describe averaged values. In case this distribution wasn't normal, averaged values were described with median (*Me*), and the 1st (*Q1*) and the 3rd (*Q3*) quartiles were applied to describe spread in values. We applied one-factor dispersion analysis to examine indicators of gas exchange.

Results and discussion. Table 1 provides data on dynamics of heat indicators measured for the volunteers who had to spend 8 hours in the suit.

Our assessment of the heat state revealed that rectal temperature grew slightly (by 0.2 ºC on average) in all volunteers by the end of the experiment under the experimental conditions described above. Overall, the volunteers subjectively assessed their state as "feeling warm". We should note that this self-assessment was given by several volunteers only under physical loads and just after them during first 3–4 hours in the experiment. When the volunteers were at rest, they evaluated their overall feeling of heat as "comfortable". This fact is proven by objective data since there were no rises in rectal temperature during that period or they didn't exceed 0.1 ºC. As a result, the ultimate levels of rectal temperature at the end of the experiment conformed to permissible physiological standards for a person who was in a state of relative rest (37.2 ± 0.5 ºC) and optimal values for easy physical labor (37.4 ± 0.2 ºC).

Overall slight heating of the body is confirmed with dynamics of temperature measured at some surfaces of the volunteers' bodies which were selected for analysis as well as with volume of "dry" heat emission (mostly by convention or radiation, and to a lesser extent by conduction) on these surfaces.

We detected certain differences in dynamics of thermal physiological indicators on various surfaces of the body. The greatest skin temperature rise (from 2.8 to 3.4 ºC) was detected on the body, except from the area near the shoulder blades where this rise didn't exceed 1.4 ºC. Heat emission from the chest, stomach and waist surface on average amounted to 22.1–25.0 Wt/m^2 during the experiment. The same indicator measured on the back surface of the chest was objectively higher and amounted to 30.8 Wt/m^2; this fact to a certain extent can explain a smaller temperature rise on this area in comparison with other surfaces on the body.

Dynamics of skin temperature and heat emission on feet were comparable to values obtained for the body. The greatest temperature rise and the lowest heat emission were detected on feet. By the end of the experiment skin temperature grew by 3.8 ºC and reached

Table 1

Heat indicators taken in dynamics

Examined indicators	Values ($M \pm m$)		
	initial ($n = 6$)	ultimate ($n = 6$)	average ($n = 6$)
Air temperature, ºC	25.0 ± 0.2	25.2 ± 0.1	25.4 ± 0.1
Relative air humidity, %	35.2 ± 1.6	34.1 ± 1.2	33.9 ± 1.1
Air speed, m/sec	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
Body temperature (rectal), ºC	37.3 ± 0.1	37.5 ± 0.1	37.4 ± 0.1
AWST, ºC	31.9 ± 0.4	34.2 ± 0.1	33.8 ± 0.1
Overall feeling of heat, scores	0	+1.0	
ABT, ºC	35.7 ± 0.1	36.8 ± 0.1	36.6 ± 0.1
AWHF, Wt/m^2	43.5 ± 2.3	35.3 ± 1.6	36.4 ± 0.8
Forehead skin temperature, ºC	32.2 ± 0.7	34.1 ± 0.3	33.6 ± 0.3
Heat flow density (HFD) on the forehead surface, Wt/m^2	86.5 ± 9.3	61.3 ± 6.4	65.2 ± 2.9
Chest skin temperature, ºC	32.2 ± 0.8	35.0 ± 0.2	34.5 ± 0.2
HFD on the chest surface, Wt/m^2	19.5 ± 3.5	23.7 ± 2.2	22.1 ± 2.7
Skin temperature near the shoulder blade, ºC	31.9 ± 0.6	33.3 ± 0.2	33.1 ± 0.3
HFD near the shoulder blade, Wt/m^2	28.2 ± 6.8	36.2 ± 2.8	30.8 ± 2.6
Stomach skin temperature, ºC	31.7 ± 0.6	35.1 ± 0.2	34.4 ± 0.2
HFD near the stomach, Wt/m^2	25.7 ± 4.3	20.8 ± 5.1	25.0 ± 2.9
Waist skin temperature, ºC	30.7 ± 0.5	33.5 ± 0.3	33.0 ± 0.2
HFD near the waist, Wt/m^2	16.2 ± 2.5	22.8 ± 2.2	23.9 ± 1.0
Shoulder skin temperature, ºC	31.9 ± 0.3	34.0 ± 0.5	33.6 ± 0.4
HFD on the shoulder surface, Wt/m^2	38.8 ± 2.2	38.2 ± 3.3	35.1 ± 1.9
Hand skin temperature, ºC	31.7 ± 0.8	34.2 ± 0.2	34.2 ± 0.2
HFD on the hand surface, Wt/m^2	67.2 ± 5.7	62.5 ± 5.0	60.8 ± 1.6
Thigh skin temperature, ºC	31.5 ± 0.3	33.6 ± 0.2	33.1 ± 0.2
HFD on the thigh surface, Wt/m^2	45.8 ± 3.8	34.2 ± 2.6	39.5 ± 2.2
Shin skin temperature, ºC	32.7 ± 0.3	34.4 ± 0.3	34.1 ± 0.2
HFD on the shin surface, Wt/m^2	64.7 ± 4.0	40.8 ± 2.6	39.8 ± 2.1
Sole skin temperature, ºC	32.6 ± 0.2	35.4 ± 0.2	35.3 ± 0.3
HFD on the sole surface, Wt/m^2	50.2 ± 9.1	24.2 ± 1.8	25.8 ± 1.5
Foot skin temperature, ºC	32.0 ± 0.3	35.8 ± 0.3	35.6 ± 0.3
HFD on the foot surface, Wt/m^2	27.2 ± 4.0	16.5 ± 1.6	21.5 ± 3.5

35.8 ºC on them but the ultimate heat emission amounted to only 16.5 Wt/m^2; this was due to greater heat insulating properties of clothing on this part of the body. Meanwhile, a temperature rise on soles wasn't so intense and amounted to 2.8 ºC with heat emission being a bit higher, 25.8 Wt/m^2 on average.

A rise in skin temperature on the upper and lower extremities, excluding their distal sections (hand and feet) was objectively lower in comparison with the same indicators measured on the body. Thus, by the end of the experiment skin temperature on the thigh and shoulder didn't rise by more than 2.1 ºC against its initial values and by more than 1.7 ºC on the shin. Heat emission on these body surfaces was within 35.1–39.8 Wt/m^2. We should note that a temperature rise was more apparent on hand skin (2.5 ºC) together with rather high heat flow density in this surface (60.8 Wt/m^2). On one hand, this is due to poor heat insulating properties of surgical gloves and absence of inert air layer between their inner surface and skin and, on the other hand, due to practically absent efficient sweat evaporation producing cooling effects on this surface.

Since the suit hood was not fit tightly with the face and didn't cover the forehead completely we can't consider data on heat exchange on this body surface to be truly informative. Nevertheless, a rise in forehead skin temperature amounted to 1.9 ºC against the initial level together with rather high heat emission being equal to 65.2 Wt/m^2.

Apart from dynamics of temperatures measured on various body surfaces, we should mention certain indicators that describe how efficiently sweat was removed from the skin surface into upper layers of the clothing and also how efficiently it evaporated.

We established that intensity of sweat excretion amounted to 111.5 g/hour on average in the volunteers wearing the suit. On average, pieces of the overall PPE set held 40.8 g of sweat and this indicated its evaporation was quite efficient and amounted to 95.5 %. As a result, heat losses due to sweat evaporation amounted to 34.4 Wt/m^2 for a person wearing the suit.

Dynamics of body temperature regimes, "dry" heat emission and heat emission due to sweat evaporation determined character and volumes of changes in integral heat indicators determined for the volunteer's bodies.

By the end of the experiment an average rise in AWST amounted to 2.3 ºC, mostly due to rises in temperatures on the body and distal sections in the extremities. But the ultimate value of this indicator (34.2 ºC) conforms to permissible heat state of the body when easy physical labor is performed (33.0 ± 2.0 ºC) and optimal values detected for the body at rest or activities performed by operators (33.5 ± 1.0 ºC). Dynamics of rectal temperature and AWST determined changes in the integral indicator of the body temperature regime, ABT. Its value grew by 1.1 ºC over the 8-hour period and this indicated there was only slight strain of thermal regulation mechanisms in the volunteers' bodies and that heat exchange with the environment was quite balanced. This is also confirmed by the character and volumes of overall heat losses by the body. Thus, on average 36.4 Wt/m^2 of heat was emitted from the volunteers' bodies by convection and radiation, and, as it was described above, 34.4 Wt/m^2 were emitted by sweat evaporation, that is, practically the same volume. Therefore, total heat losses amounted to 70.8 Wt/m^2.

Overall, heat exchange dynamics and values of changes in thermal physiological indicators determined excessive heat contents in volunteers' bodies to be equal to 5.6 Wt/m^2 and this was within optimal standard values (from –16.0 to +16.0 Wt/m^2).

Changes in the volunteers' psychophysiological indicators were examined during uninterrupted use of the suit based on concepts about multi-level morphological and functional organization of the human body.

Data analysis didn't reveal any statistically authentic changes in the volunteers' psychophysiological and mental indicators (except from a number of mistakes in SVMRT test); given that, all dynamics of the examined processes is described as certain trends. Statistical significance might be absent due to several reasons, for example, too small a sampling, variability of values obtained for the analyzed indicators, and absence of significant data dynamics.

Having compared SVMRT and CVMRT, we revealed some fluctuations within reference ranges without any apparent regular correlation with microclimatic conditions and cycles involving physical and intellectual loads (Tables 2 and 3)

Table 2

Dynamics of volunteers' simple visuomotor reaction time

No.	Background, msec	Load, msec							
		1st hour	2nd hour	3rd hour	4th hour	5th hour	6th hour	7th hour	8th hour
1	209.4	199.1	234.23	241.53	268.43	237.17	232.11	242.936	230.74
2	235.28	237.84	239.54	243.59	237.5	236.51	248.01	234.97	256.77
3	202.04	191.54	198.69	201.09	195.3	199.1	202.04	191.94	198.54
4	273.74	256.64	303.1	274.19	274.24	277.57	275.79	288.76	266.77
5	205.19	201.53	221.57	220.44	230.27	213.64	205.09	211.93	223.33
6	216.76	201.12	208.8	221.66	221.34	219.24	223.97	234.41	211.54

Table 3

Dynamics of volunteers' complex visuomotor reaction time

No.	Background, msec	Load, msec							
		1st hour	2nd hour	3rd hour	4th hour	5th hour	6th hour	7th hour	8th hour
1	346.31	380.75	438.99	504.87	418.01	408.98	417.97	399.06	351.28
2	403.45	419.93	372.24	388.2	345.64	421.37	360.93	334.84	326
3	344.51	357.87	353.59	332.35	339.49	337.4	311.47	306.87	288
4	415.9	424.5	428.48	445.93	424.84	434.38	417.64	426.97	439.64
5	411.76	398.64	414.17	411.57	464.58	412.13	423.24	426.94	398.04
6	376.92	357.16	379.45	406.48	364.91	369.13	379.89	376.89	370.58

Average SVMRT tended to grow by the end of the experiment against its initial values (216.76 [209.4; 235.86] and 236.63 [233.5; 245.71] msec accordingly, $p < 0.08$) but there were no significant differences in CVMRT (Figure 1).

All volunteers made by 1 mistake more in SVMRT test after the experiment was over (0 [0; 0] and 1 [1; 1] mistake accordingly, $p < 0.04$) and this might be due to either certain fatigue or "mental demobilization" occurring when the experiment was over.

We also performed a test that allowed the volunteers to give subjective evaluation of their state (Cenesthesia, Activity, and Mood – CAM test); the test revealed that all three indicators went down slightly within reference ranges. But still, after all the tests were over, there was certain discord in the indicators since cenesthesia and activity went down (5.95 [5.9; 6.0] and 5.7 [5.4; 5.8] scores accordingly, $p < 0.08$) but the mood didn't. This indicates that the volunteers were only physiologically tired and doesn't mean that the overall depression of the central nervous system occurred in comparison with its initial state (Figure 2).

In our opinion, subjectively assessed better mood after the experiment ended was primarily due to all the trials being over and the volunteers being able to relax.

Test results obtained for the 1st volunteer made the greatest contribution to negative dynamics of activity since there was a drop in this indicator detected during the 4th and 8th hour; it was the most probably due to initial anthropometric and physiological peculiarities of this volunteer (Table 4).

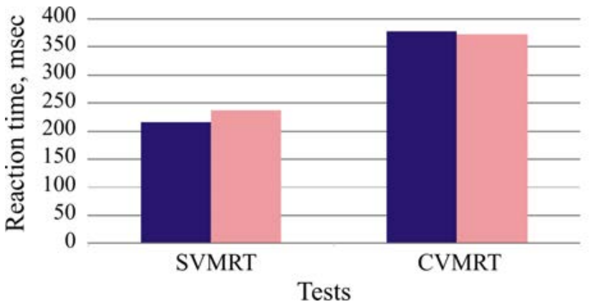


Figure 1. Average (*Me*) SVMRT and CVMRT test results of the volunteers prior to and after the experiment (n = 6): the blue column shows values prior to the experiment and the red column after it

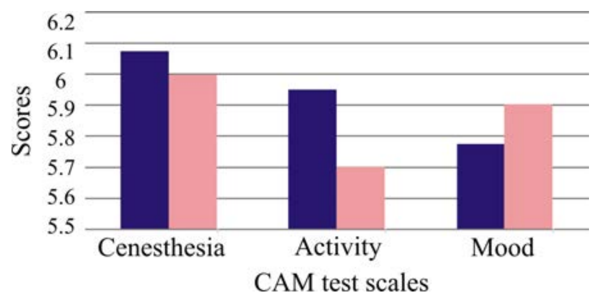


Figure 2. Average indicators (*Me*) measured with CAM test in the volunteers prior to and after the experiment (n = 6): the blue column shows values prior to the experiment and the red column after it

Table 4

Dynamics of indicators determined as per Activity scale in CAM

No.	Back-ground, scores	Load, scores							
		1st hour	2nd hour	3rd hour	4th hour	5th hour	6th hour	7th hour	8th hour
1	6	5.5	5.5	5.7	4.7	5.4	5.6	5.5	4.7
2	6	6.2	6	6	6	6.1	5.8	5.7	5.9
3	6	5.6	5.6	6.1	6	6	5.9	5.7	5.6
4	6.2	6	5.8	5.8	5.5	5.3	5.8	5.7	5.4
5	5.7	5.8	5.8	5.9	5.8	5.8	5.8	5.8	5.8
6	5.9	6	5.7	6.1	5.9	5.6	5.9	5.6	5.9

Therefore, we examined changes in objective psychophysiological and subjective psychological indicators of the volunteers in the experiment aimed at evaluating a probability to wear the suit uninterruptedly for several hours. Our examination allows us to conclude that there were no statistically significant changes in indicators of the volunteers' psychophysiological and mental state and they all varied within reference ranges. Subjective feeling of high spirits against poorer cenesthesia and activity as well as a growing number of mistakes in SVMRT test were due to "mental demobilization" after all the experimental trials were over.

Figure 3 provides the results of gas exchange (VO_2, VCO_2) indicators. We analyzed data obtained in all phases in the experiment including rest, loads, and recovery.

Gas exchange indicators in volunteers naturally grew during the load phase; however, there were no significant changes detected in either experimental phase during 8 hours of wearing the suit. CRS indicators including heart rate, respiratory rate, lung volume, and minute ventilation also grew naturally only when a volunteer was walking on the treadmill; however, they didn't change during 8 hours of wearing the suit. The great dispersion of the values is due to different anthropometric data and initial levels of the volunteers' physical working capacities (Figure 4).

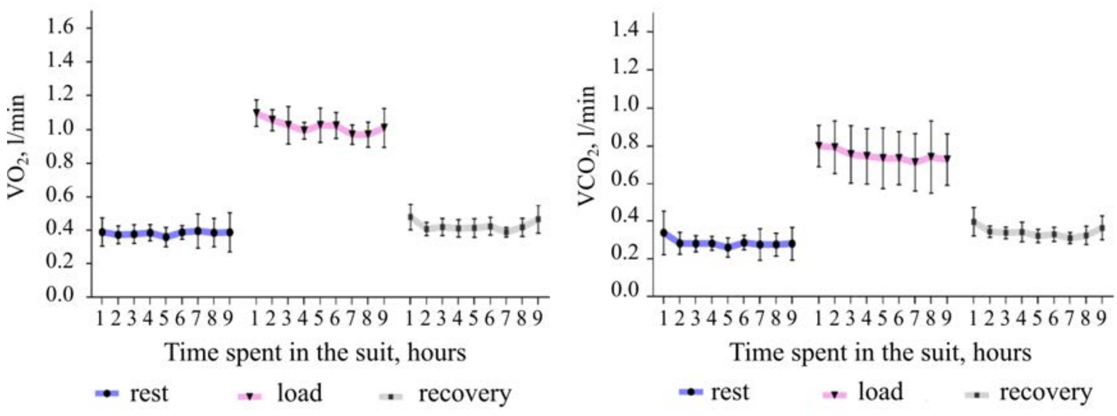
Statistical analysis didn't reveal any significant influence exerted by wearing the suit on indicators of gas exchange and the cardiorespiratory system both at rest and under mild physical loads.

Ergonomic properties of the suit were assessed by a poll performed among the volunteers. Our specifically designed questionnaire was made up of 50 questions regarding the suit ergonomics and the overall estimate was made by summing up the scores. Each positive answer gave 1 score; each negative one, 0 scores; 0.5 scores were given if a volunteer found it difficult to answer this particular question. Overall assessment of the ergonomic properties had the following grades:

- ♦ *good* was 40–50 scores;
- ♦ *satisfactory* was 30–40 scores;
- ♦ *unsatisfactory* was less than 30 scores.

Average score estimate amounted to 43 scores and this meant that the ergonomic properties of the suit conformed to the assessment grade "good".

We also asked the volunteers about their feeling of heat and their answers allowed concluding that subjective estimates corresponded to objective data obtained in the research. Subjective feelings of heat were described by the volunteers as "warm" or "comfortable" and none of them told they were feeling "hot" under the air temperature being 25 ºC during the experiment. The ergonomic properties of the suit didn't prevent the volunteers from accomplishing their tasks.



A *B*

Figure 3. Dynamics of changes in gas exchange indicators depending on time spent wearing the suit: *A* is for VO_2; *B* is for VCO_2

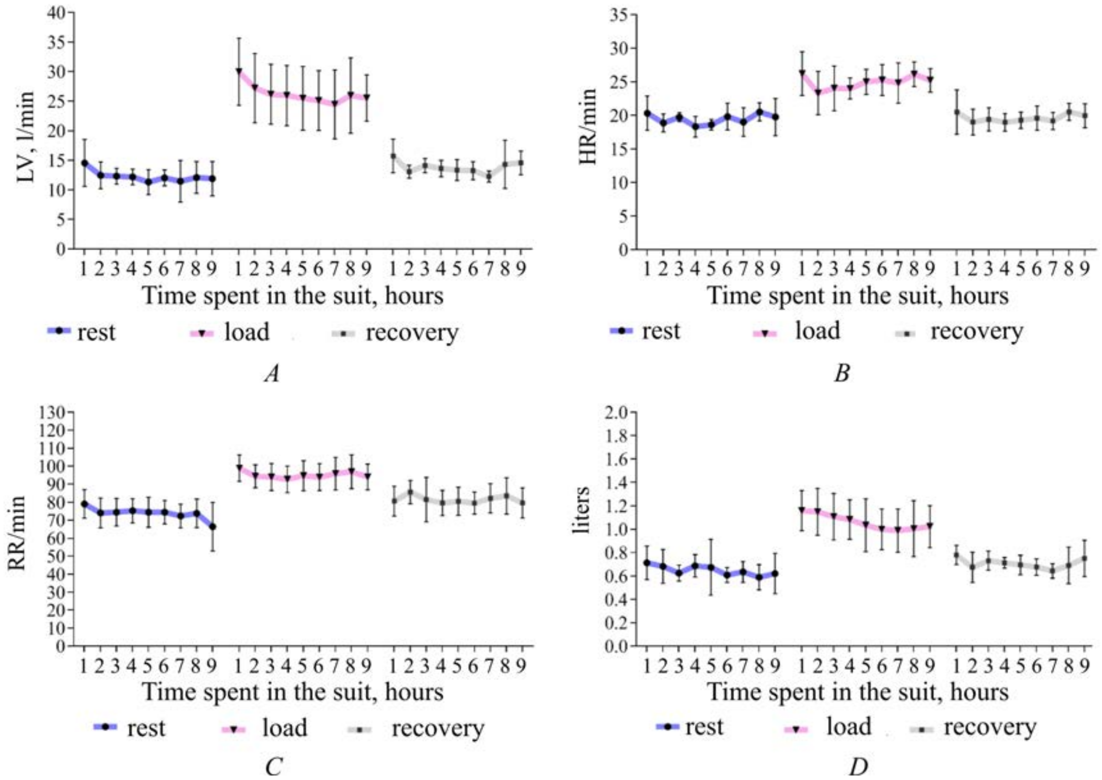


Figure 4. Changes in CRS indicators in dynamics depending on time spent in the suit:
A is for LV; *B* is for HR; *C* is for RR; *D* is for minute ventilation

Therefore, we performed the experiment to assess the heat state of the body taking into account functional state of the cardiovascular and respiratory systems as well as psychophysiological parameters at rest and under mild physical loads. Our experiment involved wearing the protective suit for 8 hours under air temperature being 25.0 ºC; it allowed confirming that it was safe for the volunteers to wear the suit for this amount of time since we didn't detect any health risks for them associated with wearing it or performing their tasks in it.

Conclusion:

1. Use of the suit under the air temperature being 25 ºC and mild physical loads provides adequate heat exchange and doesn't create any risks of overheating.

2. Data on psychophysiological and mental state of the volunteers taken in dynamics didn't have any statistically significant changes and varied within reference ranges. This indicates that there were no adverse effects produced on psychophysiological and mental functions of the volunteers who performed their tasks wearing the suit. Negative dynamics of subjective indicators evaluating cenesthesia, activity, and mood was caused by fatigue and was not associated with overall depression of the central nervous system. Subjective feeling of high spirits against poorer cenesthesia and activity as well as a growing number of mistakes in the simple visuomotor reaction time test were due to developing "mental demobilization" after all the experimental trials were over.

3. We didn't reveal any significant changes in indicators of the cardiorespiratory system depending on time spent in the suit. These data indicate that no adverse effects were produced on the cardiorespiratory system during the 8-hour experiment.

4. Use of the suit didn't result in violated ergonomics.

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

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Research article

ON REVEALING RISK GROUPS REGARDING EMOTIONAL BURN-OUT SYNDROME AMONG MEDICAL WORKERS DURING THE COVID-19 PANDEMIC

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Medical workers have become a most affected population group during the pandemic of the new coronavirus infection (COVID-19). They were the first to start fighting against an unknown infection and at that stage their psychoemotional state determined not only correct evaluations of a situation but also relevant planning regarding control over it.

Our research aim was to study the peculiarities of reacting to stress of medical organizations in an emergency epidemic situation in order to reveal potential risk groups for developing emotional burnout syndrome.

We applied our own author's anonymous online poll available at Google platform to examine psychoemotional state of medical workers. The poll had a built-in "Scale of perceived stress-10" that included two sub-scales; one of them measured a subjectively perceived level of the situation strain and the other, the amounts of efforts made by medical workers to overcome it. The poll was performed in November–December 2020; overall, 638 medical workers took part in it. They were of different age and sex and had different positions and working experience.

We established great variability in individual levels of overstrain as per the stress perception sub-scale ($Ex < 0$; $Ex = –0.59$) with more "low" than "high" values as per this sub-scale ($As > 0$; $As = 5.66$). Having analyzed variability of values as per the stress overcoming sub-scale, we revealed that they were homogenous ($Ex > 0$; $Ex = 3.98$) with prevailing "high" values ($As < 0$; $As = –6.97$).

Medical workers with their working experience being shorter than 5 years turned out to be a risk group with the most destructive reactions to long-term affecting stress factors at work and at home during the COVID-19 pandemic. Apart from them, high mental risks were also detected for workers who treated patients with COVID-19 as well as those who had previously had the coronavirus infection.

The research allowed obtaining actual data on psychoemotional state of medical workers during the COVID-19 pandemic and determining potential risk groups regarding developing emotional burnout syndrome. We substantiated the necessity to constantly provide psychological trainings for medical workers with their focus on peculiarities of their reacting during the first meeting with destabilizing factors and with further adjustment of educational programs provided for potential risk groups.

Key words: *COVID-19, pandemic, medical workers, psychoemotional state, stress perception and overcoming, adjustment activities, psychological aid, emotional safety.*

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The pandemic of the new coronavirus infection (COVID-19) caused by SARS-CoV-2 virus, a previously unknown infections agent, has become an unprecedented challenge for the global community. According to official data, as of December 01, 2021 there were more than 250 million registered cases of COVID-19 contagion and more than 5 million deaths caused by the infection [1–4].

The COVID-19 pandemic has resulted in millions of people worldwide feeling fear and anxiety and has influenced their mental health. A lot of people have lost their relatives, faced long-term isolation and economic instability, and are now uncertain about their future. The existing situation has become a severe trial for the global community [5].

Medical workers have been at the front line in fighting this new dangerous infection from the very beginning. They were the first to suffer from it [6–10]. COVID-19 incidence among medical workers has been substantially higher than among other citizens and occupational groups at every stage in the pandemic development. Studies accomplished in May–June 2020 revealed that frequency of contagion reached 14 % among medical workers; 7 % of them had antigen of the infectious agent without any clinical signs of the disease and it was also considerably higher than in population studies [11–13]. Another research work established that COVID-19 prevalence was by 11 times higher among medical workers than among other population groups [14].

Since the beginning of the COVID-19 pandemic medical workers all over the world have been working under extreme physical and emotional loads. Psychoemotional state of medical workers was gravely destabilized by limited resources, long working shifts, sleeping disorders, imbalance between work and private life, as well as occupational risks associated with constant contacts with patients suffering from COVID-19. Several authors mentioned various risk factors that might cause mental disorders among medical workers; the most significant ones were an extreme situation, substantial changes in occupational activities and in overall lifestyle [15], specific clinical course of COVID-19 (fast development of the infection, grave complications, scarce knowledge about the new disease) [16], extreme loads at workplace, sleep becoming shorter and worse [17], a possibility to get infected when treating patients [18], a risk to infect family members or close friends [19], fears of not being properly provided with personal protective equipment (PPE) and expendables [20], physical discomfort related to the necessity to constantly wear PPE [21], isolation and uncertainty about the situation [16, 22].

These changes in occupational activities and everyday life of medical workers not only made them feel anxiety, fear, and anger but also induced acute stress reactions [23]. According to Tan B.Y.Q. and colleagues [24], this atmosphere created favorable conditions for such disorders as post-traumatic stress disorder (PTSD), anxiety and affective disorders that produced negative effects on mental health. Other authors mentioned that during the COVID-19 pandemic medical workers suffered from insomnia, anxiety, more or less apparent depression, and in some cases even certain addictions [25–30]. Most researchers believed that developing post-traumatic stress disorder unavoidably led to irreversible loss of human resources [28–31]. In another work, the authors expressed their deep concern about high frequency of emotional burnout among medical personnel since this could influence the quality of medical aid rendered to patients in case there were no timely remedial activities and mental aid provided for medical workers [32].

Several studies accomplished in different countries mostly focused on examining mental aspects regarding health of medical workers who treated patients in “red zones”. It was shown in one of them that medical workers who had direct contacts with COVID-19 patients suffered from greater anxiety and had symptoms of depression or PTSD more frequently than their colleagues who didn’t work in a “red zone” [33]. Besides, medical workers who treated patients with COVID-19 in a "red zone" not only had to perform their occupational tasks but also had to be able to evaluate negative emotional reactions by patients and react adequately to them; we should bear in mind that they had to do it without any special training in communication, psychology, or psychiatry [34, 35]. Another study concentrated on analyzing peculiarities of stress perception by different occupational groups of workers in a "red zone"; it was shown that middle medical personnel (nurses) who had longer contacts with patients and had to communicate with them more closely than doctors were exposed to higher risks of developing emotional burnout [36]. Also, according to data obtained in the poll by Lee S.M. with colleagues [37], the necessity to use a full set of personal protective equipment became a serious communication barrier for medical workers that made it more difficult for them to communicate with colleagues; this, together with challenges arising in communicating with patients, created even more stressful working conditions.

We should also mention that there have been almost no complex studies focusing on assessing psychoemotional state of medical workers from various occupational groups or non-medical personnel employed by medical organizations although such employees play a no lesser role in implementing various business processes in a medical organization thus helping to render qualitative medical aid to patients.

Given all that, it is becoming truly vital to evaluate psychoemotional state of medical and non-medical personnel at a medical organization during the pandemic of the new coronavirus infection; it is also important to examine prevailing types of emotional reactions during a crisis since it allows developing relevant preventive and rehabilitation programs for personnel employed by a medical organization.

Our research aim was to study the peculiarities of reacting to stress of medical organization in an emergency epidemic situation in order to reveal potential risk groups for developing emotional burnout syndrome.

Materials and methods. The present research involved examining psychoemotional state of personnel employed by medical organizations during the second epidemic rise in COVID-19 incidence bearing in mind peculiarities of stress perception and reacting to stress factors during this crisis. Evaluation of psychoemotional state as well as profound examination of factors that cause stress in medical workers during the pandemic allow obtaining data necessary for developing efficient ways to provide such workers with relevant organizational and psychological aid [16, 32, 38, 39].

We applied *The Perceived Stress Scale-10, "PSS-10"*[1] as our measuring tool; it gave an opportunity to evaluate how much stress, in workers' opinion, occurred in their life during the month previous to the present research. The scale was made from two sub-scales; one of them determined a subjectively perceived level of the situation strain, and the other, the amount of efforts medical and non-medical workers had to make to overcome it.

The perceived stress scale was built into an anonymous online poll created by us and based on a Google platform; the poll was suggested to medical and non-medical workers by corporate mail, such messengers as WhatsApp or Telegram, or it was available on specialized online resources adapted for use by public healthcare workers. The poll was available in November–December 2020; overall, 638 workers employed by medical organizations took part in it. They were of different age and sex, occupied different positions and had different working experience. Their functional responsibilities regarding medical aid rendered to patients with COVID-19 and their infectious health history regarding the disease were also different (Table).

[1] Shkala vosprinimaemogo stressa-10 [The perceived stress scale-10]. Available at: https://therapy.irkutsk.ru/doc/pss.pdf (March 05, 2021) (in Russian).

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Table

Profile of workers employed by medical organizations who took part in the poll

№	Parameter	Absolute	%
Position			
1	Doctor	276	43.3
2	Middle medical personnel (nurses)	150	23.5
3	Administrative worker	51	8.0
4	Non-medical personnel	161	25.2
Sex			
5	Male	102	16.0
6	Female	536	84.0
Working experience, years			
7	Less than 5	192	30.1
8	6–10	109	17.1
9	11–20	145	22.7
10	Longer than 20	192	30.1
Occupational activities are related to treating patients with COVID-19			
11	Yes	263	41.2
12	No	375	58.8
Had COVID-19 prior to answering the poll			
13	Yes	200	31.3
14	No	438	68.7

We applied asymmetry (*As*) and excess (*Ex*) rates as measures of variability to describe distribution of respondents as per analyzed parameters. The results on the sub-scale 1 were interpreted as follows: 0–10 scores meant neutral "green" zone that corresponded to well-balanced psychoemotional state; 11–18 scores meant border "yellow" zone, that is, classic stress perception or a strain zone; 19–30 scores were "red zone", that is, overstrain. Another approach was used to interpret results on the sub-scale 2 (strategy of reacting to stress and overcoming it), namely: 0–12 scores were a "red zone" that corresponded to high sensitivity to stress and no available resources to overcome it in a constructive way; 13–17 scores were a "yellow zone" where workers had limited resources necessary to overcome emotional overstrain; 18–20 scores were a "green one" where workers had the greatest adaptation potential as regards overcoming stress loads.

We built up a multi-cell contingency table to comparatively assess research results obtained for different occupational groups of workers employed by medical organizations. Statistical significance of differences was estimated with Pearson's chi-square and results of post hoc analysis. Differences were considered authentic at $p < 0.05$. Data were statistically analyzed with Google electronic services, Microsoft Office 2013 and IBM SPSS Statistics (Version 26).

Results and discussion. We assessed how medical workers perceived the situation strain using measures of variability; our assessment established certain peculiarities indicating that individual levels of emotional overstrain varied greatly ($Ex < 0$, $Ex = -0.66$) and that "low" values as per this sub-scale prevailed over "high" ones ($As > 0$, $As = 5.42$). This fact indicates that most workers employed by medical organizations were able to perceive stress factors adequately; however, great variability of this indicator means that there were certain differences in stress perception between some occupational groups (Figures 1–5).

Non-constructive scenarios in stress perception ("red zone", 19–30 scores) were detected in 61 (22.1 %) doctors, 18 (12.0 %) nurses, 9 (17.6 %) administrative workers and 33 (20.5 %) non-medical personnel ($\chi^2 = 6.805$, $p = 0.078$). Having analyzed respondents' gender characteristics, we didn't reveal any significant differences in stress perception; 15 males (14.7 %) and 106 females (19.8 %) were in a "red zone" according to this sub-scale (19.8 %) ($\chi^2 = 1.433$, $p = 0.231$).

When it comes to working experience, we established that workers with their working experience being shorter than 5 years had the highest overstrain and perceived stress worse than their colleagues with longer working experience. Non-constructive stress perception (emotional overstrain) was detected in 56 (29.2 %) respondents with working experience being shorter than 5 years; in 23 (21.1 %) respondents with working experience being 6–10 years; 17 (11.7 %) respondents with working experience being 11–20 years; 25 (13.0 %) respondents with working experience exceeding 20 years ($\chi^2 = 22.686$, $p < 0.001$). This fact found further confirmation in post hoc analysis when we compared stress perception by people with working experience being shorter than 5 years, 11–20 years, and longer than 20 years ($p < 0.001$).

Specific procedures involved in rendering aid to patients with the new coronavirus infection turned out to become a significant destabilizing factor for workers employed by medical organizations. Thus, non-constructive stress perception was detected in 62 (23.6 %) workers who treated patients with COVID-19 while they occurred only in 59 (15.7 %) workers who didn't deal with treating such patients ($\chi^2 = 6.184$, $p = 0.013$).

We also established that workers who had previously had COVID-19 tended to perceive stress factors less constructively. Thus, 84 (22.5 %) workers who had had COVID-19 couldn't perceive stress adequately and it was higher than among those without the disease in their health history, 37 (14.0 %) ($\chi^2 = 7.383$, $p = 0.007$).

Analysis of results as per the sub-scale showing resistance to stress involved examining measures of variability in reacting to stress. The analysis revealed that obtained values were rather homogenous ($Ex > 0$, $Ex = 3.98$) with "high" values prevailing over "low" ones ($As < 0$, $As = -6.97$). This indicated that most workers employed by medical organizations tended to have similar scenarios for overcoming stress and were able to react to it constructively in most cases. However, there were people in a "red zone" (lower than 12 scores) due to absence of any capability to overcome stress and too much effort made to resist destabilizing factors (Figures 1–5).

65 (23.6 %) doctors, 32 (21.3 %) nurses, 8 (15.7 %) administrative workers, and 37 (23.0 %) non-medical personnel overcame stress with a lot of overstrain ($\chi^2 = 1.662$, $p = 0.645$). We didn't reveal any gender-related significant differences in efforts made to overcome stress; 18 (17.6 %) males and 124 (23.1 %) females were in a "red zone" according to this sub-scale ($\chi^2 = 1{,}491$, $p = 0{,}222$).

We also established that workers with their working experience being less than 5 years had the greatest difficulty in overcoming stress situations. 56 (29.2 %) respondents from this group mentioned psychoemotional overstrain involved in resisting stress; there were 25 (24.3 %) such workers among those with their working experience being 6–10 years; 29 (20.0 %), 11–20 years; 32 (16.7 %), longer than 20 years ($\chi^2 = 9.221$, $p = 0.026$). Post hoc analysis revealed significant differences between people with their working experience being shorter than 5 years and those with their working experience exceeding 20 years ($p = 0.021$).

We didn't reveal any significant differences in reacting to stress among workers who treated patients with COVID-19 and their colleagues who didn't deal with it. Workers from both these groups had similar ways to overcome stress. Non-constructive ways to overcome stress were detected in 63 (21.0 %) workers in the group who treated people with COVID-19; there were 79 (21.1 %) such workers among those who didn't have any contacts with COVID-19 patients ($\chi^2 = 0.745$, $p = 0.388$).

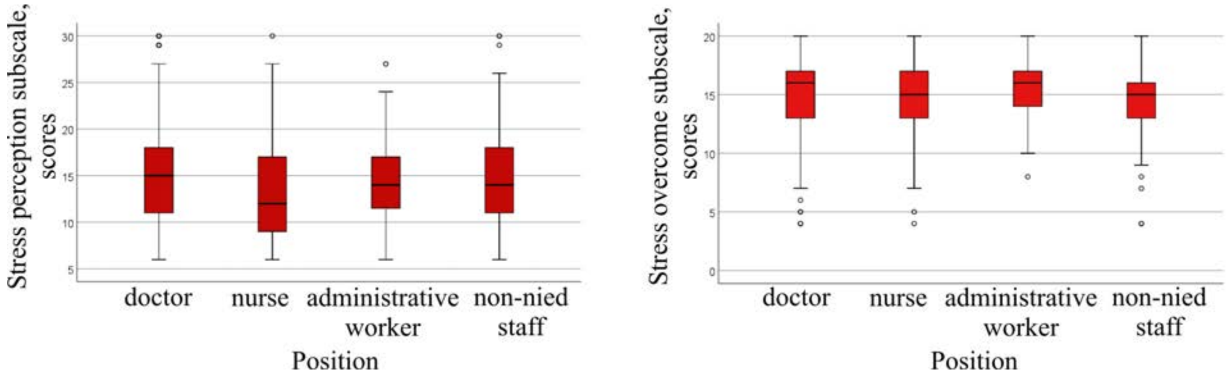

Figure 1. Poll results obtained for different occupational groups as per two sub-scales in PSS-10

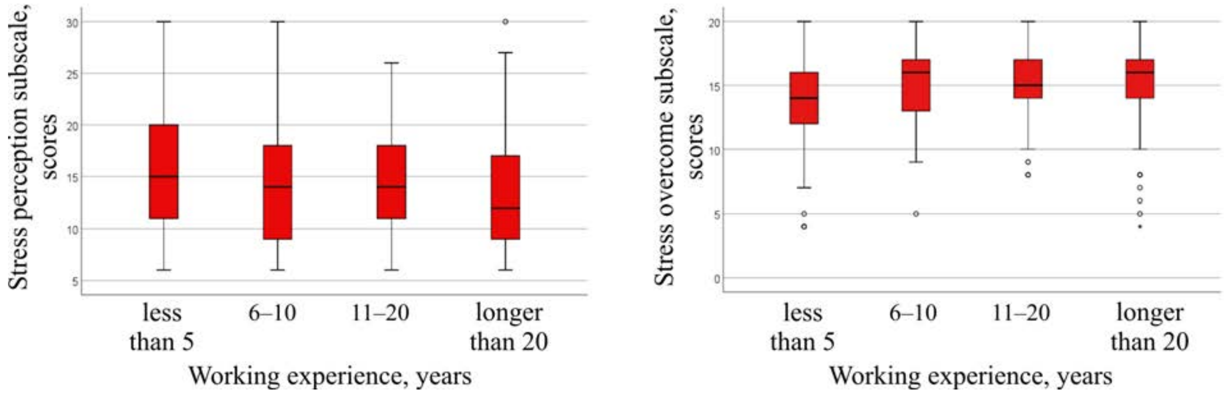

Figure 2. Poll results obtained for workers with different working experience as per two sub-scales in PSS-10

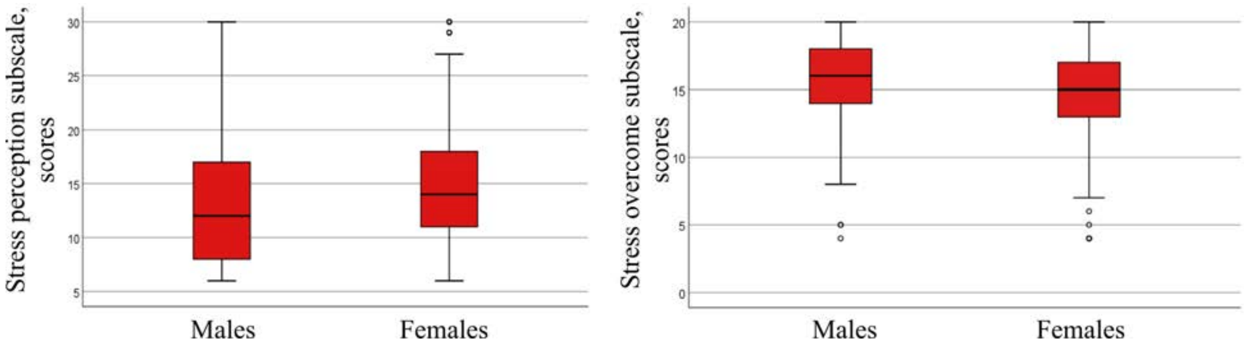

Figure 3. Poll results obtained for workers of different sex as per two sub-scales in PSS-10

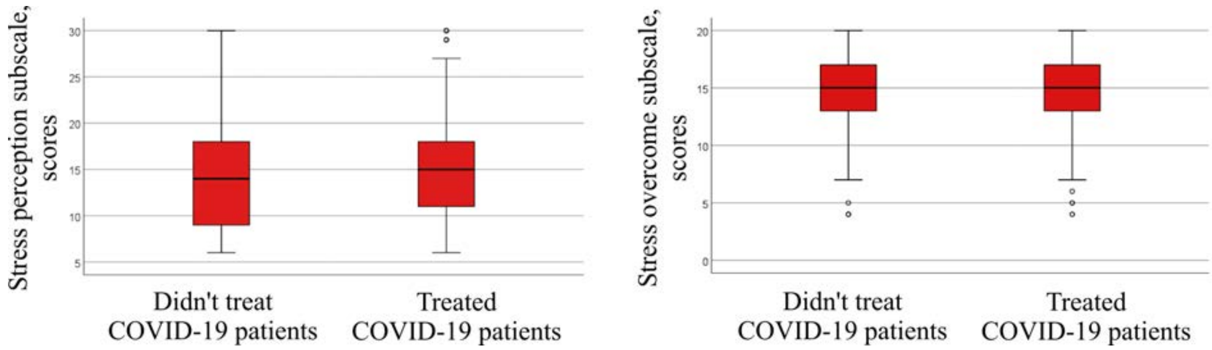

Figure 4. Poll results obtained for workers with different functional responsibilities per two sub-scales in PSS-10

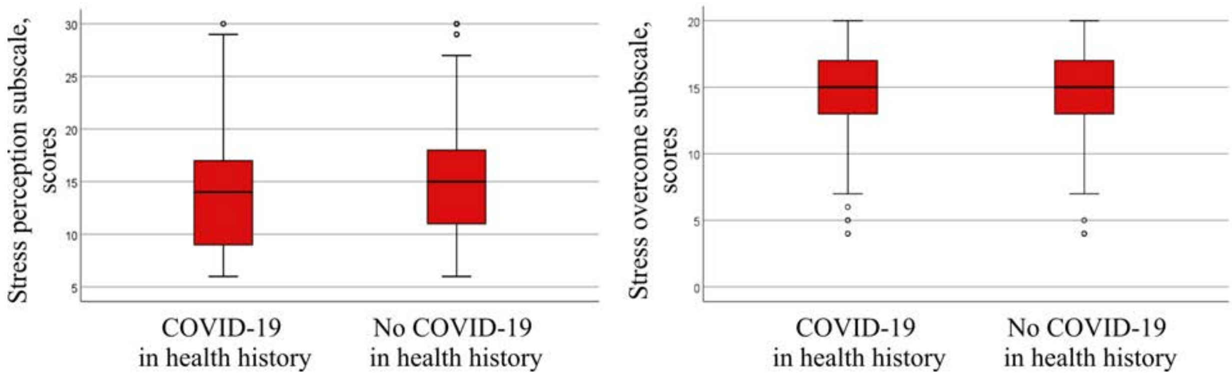

Figure 5. Poll results obtained for workers with different health history regarding COVID-19 per two sub-scales in PSS-10

COVID-19 in health history also didn't have any significant influence on how workers employed by medical organizations overcame stress. 88 (23.6 %) people among those who had had the disease spent too much effort on overcoming stress and there were 50 (20.4 %) such people among those who hadn't had the infections before (χ^2 = 0.926, p = 0.336).

Therefore, assessment of subjective stress perception and reacting to it among workers employed by medical organizations allowed us to determine a risk group as per inadequate strategies for perceiving and overcoming stress factors and, consequently, prone to more rapidly developing emotional burnout. This group included workers with their working experience being shorter than 5 years. It was them who needed expert psychological aid the most in difficult situations that involved grave physical and psychoemotional conditions at workplaces including the period during the new coronavirus infection pandemic. And medical workers who treat patients with COVID-19 as well as those who have already had the disease are also exposed to greater risks since they tend to pursue more apparent non-constructive ways to perceive stress though preserving certain resources to overcome it.

There were several leading factors that could destabilize psychoemotional state of workers employed by medical organizations, their stress perception and reacting to it. Thus, participants mentioned personal issues that were not related to work in 24.8 % cases; uncertainty, impossibility to have any plans for the future and to be sure they could be realized, 24.4 % cases; apparent time deficiency, 22.9 % cases; a fear to get infected with the coronavirus infection and a fear that relatives or close friends could get infected with it, 14.6 % cases; hard physical and psychological working conditions during the pandemic, 13.3 % cases.

In the existing situation it is advisory to provide workers employed by medical organizations with relevant remedial activities including psychological aid and developing their skills in psychological self-regulation in emergency situations. There have been several studies accomplished in the sphere. For example, there was a research work that described experience in organizing a psychological training for nurses and paramedics to get them ready to work with COVID-19 patients. The training was aimed at developing workers' communicative competence, creating skills of emotional self-regulation under stress, preventing emotional burnout and raising resistance to stress in extreme working conditions. 120 medical workers took part in the training. The program efficiency was assessed as per feedback provided by the participants. They were able to name and detect their "fears", determine their private motives and values, compare them with motives and values of other group participants, plan how to find a solution in a difficult work situation, get an insight into reasons for anxious reacting to various factors, and make use of certain recommendations on decreasing emotional strain and returning to a calm productive state of mind. The training participants stated that in future they wished to be provided with psychological aid in any form, both group and individual. The authors noted that it was obligatory to include a component related to psychological training into educational programs in higher and secondary medical educational establishments, skills development courses and training programs provided for personnel directly at their workplaces in medical organizations. This psychological training has become truly vital in the existing situation when rendering medical aid to population involves a lot of stress, multi-tasking, and uncertainty [40].

However, we should note that medical workers are not always ready to accept expert psychological aid and support. As it was noted in the study [39], medical workers were often too self-confident, thought themselves to be quite self-sufficient and preferred not to appeal for any psychological aid. All this may have negative consequences under constantly growing workloads and the necessity to solve tasks that are beyond their clinical knowledge and competences when medical workers have to fight new, previously unknown diseases they have never met before. The authors of another research work [41] highlight that when medical workers fail to communicate properly with their colleagues, it can lead to absenteeism and/or mistakes made when dealing with common occupational tasks as it has already been described in organizational psychology and psychology of health as consequences of occupational stress and occurring job burnout [42].

There was another work [43] where it was shown that apparent emotional burnout associated with developing additions might create certain obstacles for medical workers in appealing for psychological aid. These obstacles could include the following: medical workers denying they had the problem, that is, an addiction and loss of working capacity; a fear of probable stigmatization; concomitant mental disorders, a fear to acknowledge an addiction and the necessity to get treatment (regarding family relations, work, and financial well-being); lack of knowledge on the subject.

Chen Q. with colleagues [38] described in their study that medical personnel were rather unwilling to take part in any individual or group psychological trainings at the first stage in the pandemic. Some medical workers who were noticed by psychologists were so agitated and irritated that it influenced their behavioral patterns. But still they refused to get any rest and demonstrated even greater involvement into work. Those workers denied having any psychological problems and refused from any psychological support. When asked to give basic reasons for refusing from such aid, medical workers stated that they didn't have any psychological issues apart from concerns that not enough PPE would be available to them, a fear to become a source of the infection for relatives and close friends; they also mentioned they needed rest due to substantial physical loads but they didn't need any psychological aid.

The present research which was performed during the "second wave" of the pandemic revealed that 434 respondents (68.0 % of those who took part in the poll) were ready to appeal for expert psychological aid. This might indirectly imply that their psychoemotional state was already strained. Obviously, workers employed by medical organizations who took part in our research were well aware that they were unable to react to stress factors constructively on their own, understood that the situation was grave, wide-scale, and likely to linger for a long time and it was necessary to accept new living conditions in this "new reality". Our respondents already felt they needed psychological aid and were ready to accept it willingly.

Given that, it seems well-grounded that if we want to prevent developing complicated psychoemotional disorders, depressions and anxieties, and emotional burnout among workers employed by medical organizations, we should provide them with psychological aid already after the first meeting with a destabilizing factor. Bearing in mind that there are risks of similar epidemic situations in the future, it is necessary to implement a new component into medical organizations functioning, namely psychological aid and support aimed at preserving workers' health and working capacities. This can be done by creating specialized departments or services within medical organizations.

This suggestion correlates with statements given in several published works [44–46] where it was shown that a set of activities including efficient communications, access to adequate protection equipment, regular rest and rational work and leisure regimes, as well as organizational and psychological support could not only improve workers' psychoemotional state but also prevent mental diseases among them in short- and long-term prospects.

Conclusion. Therefore, the research results allowed us to establish that workers with their working experience being less than 5 years were a risk group with the highest overstrain when reacting to long-term stress factors both in everyday life and at a workplace during the COVID-19 pandemic. It is this group that requires psychological aid the most; this aid should include cognitive and behavioral therapy, training with its focus on how to use specific reacting algorithms (coping strategies) in order to develop constructive behavioral patterns aimed at overcoming destabilizing stress situations. Besides, workers who treat patients with COVID-19 and workers who have had the disease themselves are also exposed to high psychological risks. Such workers often tend to perceive stress in a non-constructive way, although, as it has been detected in our research, they still have sufficient resources for operative resistance to stress. This requires developing programs aimed at psychological prevention and rehabilitations for people with Long-COVID.

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Review

ANALYSIS OF OCCUPATIONAL RISK FACTORS CAUSING DISEASES OF THE CIRCULATORY SYSTEM IN MEDICAL WORKERS: LITERATURE REVIEW

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The review focuses on analysis of domestic and foreign literature sources concentrating on influence exerted by occupational factors and factors related to labor process on prevalence of diseases of the circulatory system (CSD) among medical workers. At present, specific features typical for occupational activities performed by medical workers are proven to be among major causes of high CSD prevalence among them. Experts have established most common occupational factors and labor-related factors that are able to induce and stimulate development of cardiovascular pathology. Labor intensity associated with neuro-emotional loads, high responsibility, round-the-clock working regime and night shifts (hazard category 3.2–3.3) is established to have a leading role among adverse labor-related factors for medical workers. Other significant contributions are made by adverse chemicals and biological agents, noise and ultrasound, laser exposure and ionizing radiation. Some authors showed that CSD prevalence was considerably higher among medical workers than among people employed in other industries. The highest CSD prevalence was detected among medical workers with the most adverse working conditions (hazard category 3.2–3.3). A high degree of occupational conditionality for CSD is typical for surgeons, therapists, and phthisiatricians. Emergency doctors run the highest risk of CSD (RR = 3.1; EF = 67.7 %). Assessment cardiovascular risks according to the SCORE system revealed that approximately 15 % medical workers older than 40 ran moderate cardiovascular risks; medical workers older than 50, high (20.0–22.0 %) or extremely high (10.0–12.5 %) total risks of death due to CSD.

Key words: *occupational and work-related risks; diseases of the circulatory system; medical workers.*

Diseases of the circulatory system (CSDs) hold the leading place as per prevalence and severity of complications in the structure of overall morbidity and are among major causes of disability and untimely deaths of employable population [1, 2]. The most common reasons for the epidemic of cardiovascular pathology are factors related to life style such as smoking, alcohol intake, irrational and unhealthy diets, hypercholesterolemia, hypertriglyceridemia, overweight, and hypodynamia [3, 4]. Social and hygienic studies indicate that CSDs are registered in 37–41 % people and at present there is unprecedented growth in CSDs among population. In Bashkortostan CSDs prevalence grew from 31,372.3 cases in 2013

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to 32,253.4 cases in 2017 per 100 thousand adults. They usually take the 3rd–5th place in the structure of overall morbidity (9.8–14.5 %) and the 1st–3rd place in the mortality structure (49.9 %) [5–7].

Public healthcare is an activity where workers are exposed to a set of adverse occupational factors including labor hardness and intensity, biological, chemical, and physical factors; they all make for a risk of occupational and work-related diseases, CSDs included. Working conditions and labor process that are typical for various categories and occupational groups in public healthcare are undoubtedly very significant when it comes down to health protection. A lot of medical workers are exposed to hazardous factors, notably, intense nervous and emotional strain, uncomfortable microclimate, adverse chemicals, biological agents, noise, ultrasound, laser exposure, ionizing radiation, and insufficient lighting at a workplace [8–11]. Medical workers are often simultaneously exposed to several adverse occupational factors, from 4 to 7, at their workplaces [12–16]. Occupational activities performed by medical workers involve substantial intellectual loads, elevated requirements to capacity of operative and long-term memory as well as attention; some specialists (doctors and paramedics in emergency aid teams, surgeons) often have to work under extreme conditions in case of an emergency and it requires developing a set of preventive activities aimed at preserving their health and maintaining necessary occupational skills [2, 17–23][1]. CSDs prevalence among medical workers is different in various occupational groups (from 39.6 to 55.8 cases per 100 patients); however, they occupy the first rank place in the overall morbidity (25.0–27.6 %) for doctors of practically all specialties and the second or third rank place for nurses and paramedics [24]. Bearing in mind that medical workers are exposed to a lot of variable adverse occupational factors at their workplaces and CSDs prevalence is high among them, a lot of studies have concentrated on assessment of working conditions with a focus being on risk factors of cardiovascular diseases and substantiating suggestions on how to prevent them [7–9, 11–16, 25–31]. Examination of working conditions and workers' health is accomplished according to valid regulatory documents. An evidence base for occupational risk assessment is results obtained in research works concentrating on hygienic assessment of working conditions and occupational activities as adverse factors that can cause damage to health of medical workers with various specialties employed at various healthcare organizations [1, 2, 17–27, 32–41][1, 2].

Hypodynamia, long-term static loads, local overstrain of some muscles, exposure to physical, chemical, and biological factors, psychoemotional stress, work in shifts and at night are a priori occupational risk factors that determine labor hardness and intensity. Another substantial health risk factor is decreasing labor motivation that has been detected recently [42, 43].

Labor intensity is the most substantial adverse occupational factor for all groups of medical workers; it occurs due to nervous and emotional loads, time deficiency, high responsibility for ultimate results (of treatment), and unpredictability of outcomes in urgent and emergency situations. Round-the-clock work and night shifts result in desynchronosis and chronic lack of sleep that contribute significantly to risks of cardiovascular diseases, make for developing hypertension, obesity, excessive consumption of caffeine, smoking, developing diabetes mellitus, and authentic increase in concentrations of hydrocortisone, adrenalin, and glucose in blood. It is well known that intense working regime induces stress in 31.1 % cases among surgeons and 23.2 % cases among therapists. As a result, 48.5 % of medical workers who have to work in shifts suffer from various diseases of the

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circulatory system. Practically all doctors (92.2 %) and 75.0–81.8 % nurses and paramedics complain about high nervous and emotional strain they have to face at their workplaces [14, 15, 20, 21, 23, 29, 44, 45].

Working conditions assessed as per labor intensity are classified as belonging to 3.1 hazard category (hazardous, the first degree) for therapeutic doctors and nurses and 3.2–3.3 hazard category (hazardous, the 2nd or 3rd degree) for surgeons and emergency aid teams [28–31].

Russian researchers showed in some previous works that signs of emotional burnout syndrome with various intensities were detected in 40–80 % doctors in the country [44, 45]. Permanent chronic psychoemotional stress and physical fatigue lead to occurring occupational burnout syndrome (OBS); 45.7 % surgeons, 39.7 % workers of emergency aid teams and 19.21 % therapists are already at the exhaustion stage in it [10]. Age of medical workers who already suffer from OBS is 45–50 years. Psychoemotional factors that influence OBS development also include job satisfaction, interpersonal and occupational relations at work and at home, salary, quality of life, and somatic wellbeing. Psychosocial state of a doctor or a nurse is vital for safety and quality of their occupational activities. It was established that average "total occupational stress" was by more than 7 times higher for a doctor with any specialty than, for example, for a worker employed at an oil processing enterprise. Major signs that indicate occurring OBS are physical fatigue (36.6–42.4 % of doctors, 54.6–61.7 % of nurses and paramedics), elevated blood pressure, low spirits, and asthenia. Morbidity is equal to 11,142.7 ‰ among people with already formed OBS and is by 1.8 times higher than among medical workers who do not suffer from it yet (617.2 ‰) with CSDs accounting for 21.8 % in it. A peak in CSDs occurrence is detected among workers aged 30–49 and with their working experience varying from 10 to 20 years; specific weight of CSDs reaches 37.0–50.8 % among such workers. Correlation analysis revealed a strong direct functional correlation ($r = 0.87$, $p < 0.01$) between morbidity levels and stages in OBS development [5, 10, 23, 38, 41–45].

Medical workers' labor is hard due to necessity to lift and move patients, forced working postures, and long-term static loads that result in physical fatigue, circulatory disorders, elevated blood pressure, and occurring asthenia [7, 8, 15, 16, 21, 25, 37]. Physical fatigue is mentioned by 36.6–42.4 % of doctors and 54.6–61.7 % of nurses and paramedics. Regular physical overloads are among factors that cause developing arterial hypertension. Short-term physical overload can induce atherogenic dyslipidemia and activate coagulation factors; it is also a factor that makes for developing Da-Costa's syndrome which involves breathlessness and heart disorders (elevated blood pressure and heart rate and chest pains). Long-term static load that occurs when a worker has to work standing makes for developing chronic venous insufficiency in the lower extremities.

Working conditions were assessed per labor hardness for various occupational groups of medical workers (lifting and moving heavy weights, working in a forced posture, and static loads); the assessment revealed that working conditions belonged to different categories, starting from category 2, permissible working conditions (therapeutic medical workers), to hazard category 3.2, hazardous working conditions with the 2nd hazard degree (surgeons, doctors and paramedics in emergency aid teams).

Medical workers are also exposed to chemical, biological, and physical occupational factors. Exposure to chemicals basically occurs due to dealing with medications, anesthetics, aseptic drugs and disinfectants. Medical workers widely use analgesics, hormones, antibiotics, vitamins, nootropic drugs and cardioprotectors at their workplaces; concentrations of such drugs can reach maximum permissible levels at some workplaces. Chronic exposure to certain compounds leads to elevated heart rhythm and minute blood volume and, as a result, influences atherogenic restructuring of vessels and the myocardium producing effects that correspond to their properties [2, 14–16, 22, 27, 32, 33, 36, 37]. Working conditions assessed as per the chemical factor belonged to hazard category 3.1 for some occupational groups of medical workers (nurses, paramedics, anesthetists, resuscitators, and surgeons).

Nurses and doctors employed at anti-tuberculosis medical organizations, infectiologists, otolaryngologists, and doctors working at out-patient and in-patient clinics are constantly exposed to biological factors of bacterial, viral, and fungi nature at their workplaces [15, 17, 21, 23, 25, 26, 31, 36]. Surgeons and diagnosticians have direct contacts with biological materials (patients' tissues, blood, urine, sputum, etc.). Working conditions assessed as per the biological factor corresponded to hazard category 3.2–3.3.

Diagnosticians and physiotherapists (X-ray specialists, radiologists, specialists who perform US, MRI or CT) are exposed to electromagnetic fields with different frequencies. Chronic exposure to electromagnetic fields with high frequencies produces atherogenic and cardiotoxic effects and can result in developing syndromes that involve sinus bradycardia, arterial hypertension (AH), diencephalic crisis, and angiospastic reactions; all this disrupts coronary and cerebral circulation. Exposure to ultrasound results in developing peripheral vegetative-sensory disorders, makes for developing angiodystonic syndrome and autonomic sensory neuropathy [3, 9, 11, 27, 37].

Complex studies with focus on health of medical workers in various regions in the country and our own long-term research revealed that CSDs prevalence and their specific weight in the structure of overall morbidity were higher among medical workers than among workers employed in various industries. Profound medical examinations accomplished in various public healthcare organizations showed that on average 48.3 cases of cardiovascular diseases were detected per 100 examined doctors and 37.4 cases per 100 examined nurses and paramedics [18, 24]. Their specific weight varies from 32.8 to 48.8 % in overall morbidity [24]. These rates are substantially higher than among workers employed at various industrial enterprises as well as among population in general. For examples, from 18 to 20 cases of cardiovascular diseases were detected at periodical medical examinations per 100 examined workers in different city districts, municipal districts and urban settlements and this was 23.9 % in overall morbidity [22]. CSDs were diagnosed in 28 % of workers employed at oil processing and petrochemical enterprises; in 26.0 % of workers employed at chromium compounds production; and in 34.6 % of workers employed at a poultry farm [2, 22, 26, 36, 41].

We compared CSDs prevalence among doctors, nurses and paramedics with various specialties and among total employable population in Bashkortostan in 2018 [41], the latter rate taken as background level; the comparison revealed that this pathology was much more frequent among medical workers.

From 7.2 to 37.8 new cases of cardiovascular diseases occurred per 100 medical workers against the background rate (attributive risk).

At present the leading role in health disorders among workers belongs to diseases that do not have any specific etiology and are caused by multiple exposures to low levels of various adverse factors; this combined exposure is an independent risk factor in itself. In most cases they are poly-etiological somatic diseases such as hypertension, ischemic heart disease, ulcer, etc. These diseases are usually called work-related. A work-related disease is the most significant indicator showing that working conditions are unsatisfactory; a number of such diseases tends to grow as working experience under adverse or hazardous working conditions becomes longer and is also higher than among workers who are not exposed to such factors at their workplaces [1–3, 5, 12, 18, 20, 24][1]. Work relatedness of circulatory diseases in medical workers is caused by adverse occupational factors that can potentially induce and support developing cardiovascular pathology.

CSDs are to a great extent work-related among surgeons, therapists, and phthisiatricians as well as among doctors from emergency aid teams (RR = 2.3–3.1; EF = 56.5–67.7 %). Emergency aid doctors run the highest risks of developing CSDs (RR = 3.1; EF = 67.7 %). Diagnosticians working in in-patient hospitals run an average risk of work-related CSDs and work relatedness is also average (RR = 1.6–1.8; EF = 33.3–44.4 %).

Some researchers [18, 24] note that CSDs account for 48.3 % cases in morbidity among doctors and 37.4 % cases among nurses and paramedics. In this case attributive risk amounts to 30.3 cases per 100 people for doctors and to 19.4 cases for nurses and paramedics; relative risks reach 2.6 for doctors and 2.0 for nurses and paramedics. Accordingly, etiological fraction of occupational risk factors amounts to 50.0–61.0 % and it means that work relatedness is high. These summarized rates allow estimating occupational activities performed by medical workers as those with high risks of developing cardiovascular pathology.

Risks of cardiovascular diseases were assessed as per SCORE system among medical workers employed at an emergency aid station, workers dealing with hemodialysis, phthisiatricians, infectiologists, resuscitators, dentists, and therapists in in-patient hospitals. The assessment revealed that most workers younger than 40 were exposed to moderate risks of such diseases and only 12.0–15.0 % among them were exposed to high relative risks of cardiovascular diseases. Workers who were older than 50 were exposed to high (20.0–22.0 %) or very high (10.0–12.5 %) total risks of death due to CSDs [5, 8, 11, 22, 32, 37, 39].

Some studies revealed early, including pre-clinical ones, signs of cardiovascular disorders. Myocardial hypertrophy was detected in 18.0 % of examined workers through electrocardiography (ECG) and echocardiography (Echo CG). Duplex ultrasound of vessels and main arteries in the brain revealed atherosclerotic stenotic signs in 8.0 % and non-stenotic ones in 12.2 % of examined workers; changes in brachiocephalic artery, in 5.0 % [2, 4, 5, 7, 34]. Persistent elevated blood pressure was determined in 16.8 % of workers both at day and at night through daily monitoring over blood pressure. Heart rhythm disorders and conductivity disorders were detected in 13.6 % of examined workers through daily ECG monitoring. ST segment was depressed under physical loads in 1.0 % of examined workers.

Analytical review of Russian and foreign research works has revealed that at present working conditions and occupational activities performed by medical workers involve exposure to adverse occupational factors that can potentially induce and support developing cardiovascular disorders. A set of occupational factors (labor hardness and intensity, chemical, biological, and chemical factors) was established for various occupational groups of medical workers based on hygienic studies that involved assessment of working conditions. Working conditions for medical workers with certain occupations belonged to 3.1–3.3 hazard category (they were hazardous, the 1st–3rd hazard degrees). Labor intensity is the leading adverse factor practically for all occupations (3.2–3.3). The most hazardous working conditions existed at workplaces of surgeons and all workers in emergency aid teams (3.2–3.3). We showed that CSDs prevalence was by 2.0 times higher among medical workers than among population in general (48.8 % and 23.9 % accordingly) or among workers employed in other industries. It was also proven that the highest CSDs prevalence and their high (up to 67.7 %) work relatedness were detected for medical workers with the most hazardous working conditions at their workplaces (surgeons and workers employed at an emergency aid station) [7]. Work relatedness of developing CSDs was average for medical workers from other occupational groups. Having assessed occupational risks of cardiovascular disorders for medical workers, we determined several stages in CSDs occurrence: the initial one when working experience didn't exceed 5 years; a stage of strained adaptation; and a clinical stage in pathology development. These stages are to be taken into account when periodical medical examination are held since it helps perform early diagnostics and determine "risk groups" as regards developing CSDs and implementing prevention and rehabilitation programs.

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Review

AEROGENIC POLLUTANTS AS RISK FACTORS CAUSING DEVELOPMENT OF CARDIO-METABOLIC PATHOLOGY (REVIEW)

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Ambient air pollution causes approximately 3.3 million untimely deaths annually (2.1 deaths due to ischemic heart disease and 1.1 million deaths due to stroke). Mortality caused by ambient air pollution is higher than mortality due to such traditional risk factors as smoking, obesity, and elevated dextrose contents in blood. Relative risk of mortality amounts to 1.26 (95 % CI 1.08–1.47) in cities with the highest air pollution against those where air pollution is the lowest. Occupational exposure to various chemical air pollutants can cause more than 1 million untimely deaths all over the world but its contribution to prevalence of cardiovascular diseases has not been determined sufficiently. Aerogenic pollutants are quite variable in their chemical structure and include both particulate matter (PM for short) and gaseous matter. The American Heart Association and the European Society of Cardiology consider $PM_{2.5}$ to be a risk factor causing cardiovascular diseases. This analytical review presents data on effects produced by aerogenic pollutants on development of cardio-metabolic pathology and population mortality due to vascular and metabolic diseases (arterial hypertension, atherosclerosis and ischemic heart disease, heart rhythm disturbances, and type 2 diabetes mellitus). There are also data on mechanisms of pathogenetic influence exerted by aerogenic pollutants on development of such diseases including generation of anti-inflammatory and oxidative mediators and their release into blood flow; developing imbalance in the autonomic nervous system with prevailing activity of the sympathetic nervous system and disrupted heart rate variability; direct introduction of aerogenic pollutants from the lungs into blood flow with developing direct toxic effects. We have also analyzed literature data on protective effects produced by reduction in ambient air pollution on prevalence of cardiovascular pathology.

Key words: *aerogenic pollutants, airborne particulate matter, persistent organic pollutants, cardiovascular pathology.*

Cardiovascular pathology remains a leading cause of mortality among employable population all over the world since 17 million untimely deaths result from it annually; 3.3 million out of them are associated with ambient air pollution with technogenic chemicals [1, 2]. Effects produced by ambient air pollution occupy the 6th rank place among mortality factors being ahead of such traditional risk factors as smoking (2.48 million), obesity (2.85 million), and elevated glucose contents in blood (2.84 million) [3]. Only arterial hypertension (AH) is more significant as a risk factor of cardiovascular mortality than ambient air pollution [2]. According to E. Braunwald, relative risk of mortality amounts to 1.26 (95 % CI 1.08–1.47) in the most polluted cities against the least polluted ones [4]. Occupational exposure to various chemical air pollutants can cause more than 1 million untimely deaths all over the world but its contribution to cardiovascular mortality hasn't been well-determined yet [5].

Ambient air pollutants are quite heterogeneous in their chemical structure and include both particulate matter (PM for short) and

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gaseous matter (volatile organic compounds, ozone, nitrogen oxide, carbon monoxide, sulfur dioxide, etc.). PM in their turn can have various sizes and are usually divided into three basic groups: coarse particles (PM_{10}, diameter is from 2.5 to 10 μm), fine particles ($PM_{2.5}$, diameter is less than 2.5 μm), and ultrafine particles (diameter is less than 0.1 μm); besides, particulate matter are divided into primary and secondary ones. Primary particulate matter are emitted into the atmosphere directly from a polluting source (dust, metals, soot, salt particles, and plants spores) whereas secondary ones are created from aerosol pollutants through nucleation and gaseous fraction transforming into solid one [4]. Chemical structure of PM varies depending on a polluting source and can include complex organic molecules (formaldehyde, acrolein, benzene, xylene, butadiene, and polycyclic aromatic hydrocarbons), carbon, metals, sulfates, and nitrates [1, 4–7]. The American Heart Association and the European Society of Cardiology determine $PM_{2.5}$ as a risk factor that can cause cardiovascular diseases [8]. Several research works confirmed that exposure to $PM_{2.5}$ created elevated risks of cardiovascular mortality and non-fatal cardiovascular events [3, 9–11]. However, no chemical components or $PM_{2.5}$ sources have been detected to possess any unique toxic effects or peculiarities related to pathogenesis of cardiovascular disorders [3]. It was shown in some research works that frequency of cardiovascular mortality grew by 1 % per each 10 $\mu g/m^3$ of growing $PM_{2.5}$ concentration in ambient air under short-term exposure [9]. According to meta-analysis data obtained by G. Cesaroni with colleagues, long-term exposure to $PM_{2.5}$ per each 10 $\mu g/m^3$ of its contents in ambient air resulted in a 6 % growth in mortality due to all reasons (95 % CI 4–8 %) and to an 11 % growth in cardiovascular mortality (95 % CI 5–16 %) [12]. R. Chen with colleagues showed in their study that there was no "safe" bottom limit in a curve showing "dose – effect" dependence for influence exerted by air pollution with $PM_{2.5}$ on cardiovascular prevalence and mortality [13].

H. Mustafic with colleagues showed in their meta-analysis that short-term exposure to aerogenic pollutants ($PM_{2.5}$, nitrogen, carbon, and sulfur oxides) was associated with a 1–5 % growth in risks of myocardial infarction during the next day [14]. Sub-analysis of acute coronary events in eleven cohorts included into ESCAPE project (more than 100 thousand participants) revealed a statistically significant association between their development and exposure to $PM_{2.5}$ even in concentration that was lower than permitted in the European Union (risk went up by 12 % per each 10 $\mu g/m^3$ of growing PM_{10} concentration and by 13 % per each 5 $\mu g/m^3$ of growing $PM_{2.5}$ concentration) [12]. 6.2 million strokes were analyzed in 28 countries and this allowed establishing rather small (approximately 1 %) but statistically significant increase in frequency of strokes and mortality due to them per each 10 $\mu g/m^3$ of growing $PM_{2.5}$ concentration [15]. At the same time, according to Woman's Health Initiative and ESCAPE surveys, a risk of stroke grew by 17.5 and 19 % in the USA and Europe accordingly per each 5 $\mu g/m^3$ of growing $PM_{2.5}$ concentration in ambient air [16, 17]. According to P. Zhang and others, combined exposure to PM_{10} and nitrogen oxide during 12 years was associated with elevated mortality due to cerebrovascular diseases in China and Korea [18, 19]. Results obtained in The Women's Health Initiative study revealed that long-term aerogenic exposure to $PM_{2.5}$ resulted in a 35 % growth in risks of stroke [17]. Short-term increase in concentrations of gaseous pollutants and $PM_{2.5}$ in ambient air was associated with a growing risk of admission to hospital due to heart failure and related mortality. Each 10 $\mu g/m^3$ of growing $PM_{2.5}$ concentration led to 1–1.5 % growth in a number of admissions to hospitals due to heart failure [4, 20]. A national cohort study performed in England revealed high frequency of heart failure cases associated with long-term exposure to elevated PM and nitrogen oxide concentrations in ambient air [17–22]; attributive risks of mortality due to progressing heart failure associated with exposure to aerogenic pollutants could reach 30 % [4, 23].

Pathogenetic mechanisms of cardiovascular pathology associated with exposure to aerogenic pollutants. Multiple studies that have been performed over the last two decades have revealed basic pathogenetic mechanisms of cardiovascular pathology development under exposure to aerogenic pollutants. When aerogenic pollutants penetrate the airways, they start interacting with the mucosa in the upper and lower airways. Coarse and fine particles ($PM_{2.5}$ and PM_{10}) are distributed in the airways in a different way; and since they have different chemical structure, they produce different biologic effects [24]. A primary affecting factor here is PM and other chemicals depositing in airways tissues; it activates three basic mechanisms [25]:

– pro-inflammatory and oxidant mediators are generated and released into blood flow;

– imbalance develops in the autonomic nervous system with prevailing activity of the sympathetic nervous system and disrupted heart rate variability (HRV);

– pollutants penetrate blood flow directly from the lung tissue and this produces direct toxic effects.

Generation of pro-inflammatory and oxidative mediators. Introduction of PM and other chemical components, especially those with redox potential, induces a cascade of oxidative stress reactions and inflammation in lung tissues [9, 22]. Free radicals can both occur in the lung tissue directly due to impacts exerted by some substances, metals, for example, and due to activation of the immune system cells as a result of contacts with PM. Stimulation of redox mechanism with free radicals formation (superoxide and hydroxyl) results in elevated activity of polymorphonuclear leukocytes and production of pro-inflammatory cytokines (interleukin 1β, interleukin-6, interleukin-8, tumor necrosis factor alpha) and chemokines to achieve sequestration of PM that penetrated the lung tissues. It should be noted that the smaller is a diameter of particles that have penetrated the lung tissues, the more apparent oxidative stress is induced by them. Several cohort studies revealed there was a relation between exposure to PM (both in occupational groups and population in general) with elevated contents of protein, lipid, and DNA oxidation products in blood and urine. People with already elevated contents of oxidative stress and inflammation products are more susceptible to effects produced by aerogenic pollutants [23, 26, 27]. Besides, PM contacts with the airways mucosa lead to damage to the surfactant system and induce mechanisms of inborn immunity thus creating a focus of chronic low level non-infectious inflammation in the lung tissues. A key hypothesis regarding this mechanism is that the process is deadaptation in its essence and occurring pro-inflammatory and oxidative reactions are not limited to the lung tissues but also result in excessive release of inflammation mediators in peripheral blood flow; thus, a systemic inflammatory reaction develops together with vascular oxidative stress and inflammation as well as endothelial dysfunction [4]. As redox and pro-inflammatory processes develop and generalize, blood cells (polymorphonuclear leukocytes, T-lymphocytes, macrophages, and thrombocytes) become activated; the same goes for a whole cascade of mediators that affect the cardiovascular system including adipocytokines (resistin and adiponectin) and acute-phase proteins (C-reactive protein, fibrinogen, and coagulation factors). These mediators and proteins are activated from adipocytes and hepatocytes accordingly. The aforementioned mechanism induces several basic chronic pathologic processes including atherosclerosis, endothelial dysfunction, cardiac hypertrophy, vasoconstriction, and pro-coagulant changes, and metabolic disorders [28]. However, this mechanism can potentially cause acute exacerbations such as disrupted stability of atherosclerotic plaque with developing acute ischemic syndromes [25].

Developing imbalance in the autonomic nervous system. Several nerve receptors (nociceptive and adrenergic ones) in the lung tissue are activated by PM and other chemicals that penetrate the airways due to breathing; this creates pathological autonomic reflex arcs. This mechanism induces both dysfunction of the central nervous system (activated vegetative centers) and peripheral disorders that become apparent through sympathetic impacts prevailing over parasympathetic ones (changes in heart rate, blood pressure, lower heart rate variability, and disrupted cardiac repolarization) [29]. Activation of the autonomic nervous system and synthesis of vasoactive mediators stimulate so called "neurogenic inflammation" with activated T-lymphocytes, adhesion molecules, pro-inflammatory cytokines, and free radicals [23]. These data indicate there is a close connection between the first and the second mechanism of pathologic influence by aerogenic pollutants and they produce complex effects on the cardiovascular system. Acute reactions induced by this mechanism include predominantly heart rhythm disturbances; chronic ones are arterial hypertension (AH), cardiac and artery hypertrophy, and metabolic disorders [25].

Introduction of pollutants from the lung tissue into blood flow. A few studies have revealed that fine particulate matter as well as soluble chemicals can penetrate blood flow and produce direct adverse effects on vessel walls and blood cells (thrombocytes in particular) and disrupt vasomotor regulation. However, since there are scarce scientific data on the matter, an insight into this mechanism is still considered to be rather vague and contradictory [25, 30].

In scientific literature, the aforementioned mechanisms predominantly explain most typical pathological processes in the cardiovascular system associated with exposure to aerogenic pollutants (AH, atherogenesis, heart rhythm disturbances, resistance to insulin, metabolic syndrome, and type 2 diabetes mellitus). Next we are going to pay closer attention to statistical, pathophysiological and clinical aspects regarding these disorders in relation with exposure to aerogenic pollutants.

Most common diseases, syndromes, and pathological processes that develop under exposure to aerogenic pollutants. ***Arterial hypertension.*** A lot of studies concentrate on examining correlation between AH and exposure to aerogenic pollutants. According to Global Burden of Disease Study, elevated blood pressure causes approximately 10.4 million deaths and 208.1 million disability-adjusted life years (DALY) worldwide [2]. An increase by 20 mm Hg in systolic blood pressure (SBP) or by 10 mm Hg in diastolic blood pressure (DBP) in people aged 40–69 is associated with more than 2-time growth in a risk of death due to cardiovascular events [31]. Even a slight decrease in blood pressure leads to significantly improved forecasts; a decrease by 2 mm Hg in SBP results in 5 % drop in mortality due to stroke; 4 % drop, due to ischemic heart diseases (IHD); 3 % drop in overall mortality [32]. Keeping in mind statistical data on cardiovascular prevalence and mortality, we can assume that even slight influence on AH risk factors can significantly improve forecasts for an overall population. A substantial database has been accumulated by now on impacts exerted by ambient air pollution on AH development or induction [8, 10, 11, 33–36]. Research works concentrated on describing influence by aerogenic pollutants on blood pressure, development of persistent AH, and a rise in appealability for emergency aid. According to E. Braunwald, blood pressure grows by 1–4 mm Hg per each 10 $\mu g/m^3$ of growing $PM_{2.5}$ concentration in ambient air under short-term exposure. Blood pressure can grow by 8–9 mm Hg during 2–5 days after exposure to elevated $PM_{2.5}$ concentrations [4, 35]. R. Liang with colleagues performed meta-analysis of 25 studies to show that blood pressure increased by 1.4 / 0.9 mm Hg per each 10 $\mu g/m^3$ of growing $PM_{2.5}$ concentration in ambient air [37]. P. Giorgini and colleagues examined 2,078 patients with AH and revealed that average $PM_{2.5}$ concentration in ambient air equal to 12.6 ± 8.2 $\mu g/m^3$ during several previous days was associated with statistically significant rise in blood pressure, by 2.1–3.5 /

1.7–1.8 mm Hg per each standard deviation towards growth in $PM_{2.5}$ concentration. This effect was detected in spite of all research participants constantly being treated with up-to-date hypotensive therapy and ambient air quality was quite optimal if taken in remote prospects [38]. R.D. Brook and others assessed impacts exerted by ambient air pollution on blood pressure of 65 people living in Beijing where $PM_{2.5}$ concentration varied within 9.0–552 μg/m^3. Exposure to high $PM_{2.5}$ concentrations during 1–7 previous days resulted in growth in SBP varying from 2 (95 % CI 0.3–3.7) to 2.7 (95 % CI 0.6–4.8) mm Hg per each standard deviation in $PM_{2.5}$ concentration (67.2 μg/m^3) [39]. Long-term exposure (during the whole previous year) resulted in more apparent hypertensive effects, growth by 7.3 / 9.5 mm Hg [36]. It was established in several research works that "acute" exposure to PM with a wide range of diameters ($PM_{0.1\text{-}10}$) and concentrations in ambient air led to rapid rise in blood pressure from 2 to 10 mm Hg and it remained high for several hours [35]. Long-term exposure to $PM_{2.5}$ (during several years) is associated with persistent AH occurrence. An increase in $PM_{2.5}$ concentration in ambient air by 10 μg/m^3 was associated with 13 % of AH prevalence (HR 1.13 (95 % CI 1.05–1.22)) among a cohort made up of 35,303 adult people living on a relatively ecologically clean territory in Canada [40]. Increased appealability for emergency aid due to exacerbated AH was detected during periods when there was growth in ambient air pollution both in countries with high pollution (China) and with lower one (Canada) [41]. Long-term exposure to $PM_{2.5}$ was proven to be associated with an increase in AH-related mortality [42].

Endothelial dysfunction and vasoconstriction. Several studies revealed that exposure to aerogenic pollutants resulted in vasoconstriction and endothelial dysfunction [25, 29]. In particular, S.D. Adar with colleagues established in Multi-Ethnic Study of Atherosclerosis (MESA) performed on a cohort made up of 4,607 patients that exposure to $PM_{2.5}$ influenced reduction of retinal artery lumen. This effects were also observed under both short-term (during a day) and long-term (2 years, on average) exposure [43]. A similar effect was revealed in a study accomplished in Belgium (84 patients) that concentrated on influence exerted by PM_{10} on retinal artery lumen under short-term exposure [44].

Endothelial dysfunction induced by affecting factors (aerogenic pollutants in particular) is among the most significant mechanisms of cardiovascular pathology. A slight increase in $PM_{2.5}$ concentration in ambient air results in authentic decrease in flow-dependent vasodilatation as it was shown in large cohort studies performed in the USA [45, 46]. An increase in average annual $PM_{2.5}$ concentration in ambient air by 3 μg/m^3 can be compared to effects produced on endothelial function by smoking (a decrease by 0.3 %) or additional 5 years of age [46].

Heart rhythm disturbances. According to literature data, exposure to aerogenic pollutants correlates with electrical instability of the cardiac muscle, changes in heart rate, and lower heart rate variability (HRV) [47–50]. High levels of systemic inflammation and oxidative stress markers were established to predispose to more apparent heart rhythm disturbances under exposure to aerogenic pollutants [49]. However, ventricular arrhythmia and atrial fibrillation induced by exposure to pollutants in most cases were detected in people who already suffered from heart diseases [51]. Moreover, studies that involved controlled inhalation exposure to pollutants didn't reveal any developing arrhythmia in healthy participants under acute exposure [52].

Changes in HRV were among first biological effects detected under exposure to aerogenic pollutants [25]. Meta-analysis of 29 epidemiologic studies performed on 18,667 patients revealed that an increase in $PM_{2.5}$ concentration in ambient air by 10 μg/m^3 led to statistically significant decrease in both time and frequency HRV parameters and imbalance in the autonomic nervous system towards prevailing sympathetic activity [53]. A decrease in HRV is a well-known factor that creates risks of cardiovascular death. Several studies revealed disrupted repolarization in ECG under exposure to PM. These data indicate there are certain changes in ion channels of cardiomyocytes and this can induce heart rhythm disturbances in predisposed people, right up to fatal ventricular arrhythmia [54, 55]. Neurogenic effects produced by exposure to aerogenic pollutants on developing imbalance in the autonomic nervous system were confirmed in a study accomplished by C.M. Barbosa in Brazil. When sugar cane was being burnt, PM concentrations grew in ambient air and this resulted in elevated blood pressure in healthy workers due to growing activity of peripheral sympathetic nerves established with microneurography [56].

Atherosclerosis. Long-term exposure to aerogenic pollutants makes for atherosclerosis development [25]. Several research works have concentrated on this effect by pollutants over the last two decades. According to E.H. Wilker long-term exposure to fine-disperse PM in high concentrations is associated with growing carotid intima-media thickness (CIMT), by 1.1 % annually per each 0.26 μg/m^3 of growing PM concentration in ambient air [57]. The most significant results were obtained in MESA survey. A series of ultrasound examinations were performed on 5,362 people living in 6 cities in the USA where ambient air pollution was high; they revealed that CIMT grew by 5 μm (95 % CI 2.6–7.4) annually per each 2.5 μg/m^3 of growing $PM_{2.5}$ concentration. At the same time, a fall in aerogenic exposure to $PM_{2.5}$ by 1 μg/m^3 resulted in negative CIMT progression (–2.8 μm annually (95 % CI from –1.6 to –3.9)) [58]. First data on influence exerted by ambient air pollution on atherosclerosis progression were obtained by N. Kunzli in a study performed among people in Los Angeles in 2005. Overall, 798 people were examined; they were older than 40 and didn't have either cardiovascular pathology or diabetes in their case history. It was established that carotid intima-media thickness grew by 5.9 % (95 % CI 1.0–10.9) per each 10 μg/m^3 of growing $PM_{2.5}$ concentration in ambient air (within 5.2–26.9 μg/m^3 range) [59]. M. Bauer with colleagues revealed in their study accomplished in 2010 in Germany that a growth in $PM_{2.5}$ concentration in ambient air by 4.2 μg/m^3, and PM_{10} by 6.7 μg/m^3, was associated with an increase in CIMT by 4.3 % (95 % CI 1.9–6.7 %) and 1.7 % (-0.7–4.1 %) accordingly [60]. According to C. Tonne and others, CIMT grows by 5 % (95 % CI 1.9–8.3 %) per each 5.2 μg/m^3 of growing PM_{10} concentration [2].

Insulin resistance, type 2 diabetes mellitus, metabolic syndrome. Over the last two decades a lot of data have been accumulated on impacts exerted by aerogenic pollutants on developing diseases and conditions related to insulin resistance (metabolic syndrome, type 2 diabetes mellitus (DM2), and non-alcoholic fatty liver disease) [61, 62]. These effects produced by aerogenic pollutants have been detected both in regions where ambient air pollution is relatively low and in those where it is considerably high [63, 64]. Insulin resistance is a key pathogenetic mechanism responsible for these disorders. As it was shown by R.D. Brook, when 25 healthy adults were exposed to elevated $PM_{2.5}$ concentrations during 5 days (south-eastern Michigan), it led to a decrease in sensitivity to insulin according to data by Homeostasis Model Assessment of Insulin Resistance Values (HOMA-IR) [65]. The research established that heart rate variability disorders correlated with growing insulin resistance. E.H. Wilker revealed growing insulin resistance and deteriorating control over DM2 in a study conducted in Germany [57]. Long-term exposure to $PM_{2.5}$ leads to elevated risks of manifest DM2 occurrence simultaneously with growing risks of AH development [61]. H. Chen with colleagues examined 62,012 people living in Canada in their research and showed that DM2 risk grew by 11 % per each 10 μg/m^3 of long-term growing $PM_{2.5}$ concentration in ambient air [63]. F. Liang and others observed 88,397 people in China with 6,439 new DN2 cases detected among them; the authors revealed that exposure to $PM_{2.5}$ increased DM2 risks by 15.7 % (95 % CI 6.42–25.70) per each 10 μg/m^3 [66]. A study by Lao X.Q. also established an increase in DM2 risks under long-term exposure to $PM_{2.5}$. As opposed to the first quartile of $PM_{2.5}$ concentration in ambient air, HR amounted to 1.28 (95 % CI 1.18–1.39), 1.27 (95 % CI 1.17–1.38), and 1.16 (95 % CI 1.07–1.26) for the second, third, and forth quartiles accordingly [67]. Meta-analysis by I.C. Eze and a review by X. Rao confirmed that DM2 risks grew by 8–13 % per each 10 μg/m^3 of growing $PM_{2.5}$ concentration in ambient air [68, 69]. Oxidative stress and chronic metaflammation play a leading role in pathogenesis of metabolic disorders and DM2 associated with exposure to aerogenic pollutants due to activation of pro-inflammatory cytokines and inborn immunity cells in visceral fat depots [61]. This mechanism is quite similar to pathogenesis associated with diabetogenic effects produced by some foods where inflammation plays a leading role in DM2 pathogenesis [70]. Exposure to aerogenic pollutants is associated with elevated levels of tumor necrosis factor, interleukin-6, resistin, and leptin in blood. There is also a growth in concentrations of prothrombotic adipokines (plasminogen activator inhibitor-1) and circulating adhesion molecules (ICAM-1, E-selectin). The latter make for leukocytes adhesion to endothelium of post-capillary venules [71]. Imbalance in the autonomic nervous system towards increasing activity of the parasympathetic section also makes a significant contribution to developing insulin resistance. Some lung receptors such as transient receptor potential ankyrin 1 (TRPA1) can be stimulated by aerogenic pollutants and the sympathetic section in the autonomic nervous system through central mechanisms [72]. Endothelial dysfunction often precedes insulin resistance and is associated with disrupted peripheral glucose utilization [73]. Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs) determine a pathogenetic mechanism responsible for a relation between exposure to aerogenic pollutants and obesity / DM2 [74, 75]. Redox reaction products (palmitoyl-arachidonoyl phosphocholine, hyaluronic acid fragments) activate TLR4 and also make for release of chemokines ligand (CCL-2) that activates monocytes [76]. Overall, there are 4 basic mechanisms of immune activation that lead to developing insulin resistance / DM2:

– direct inflammatory / oxidative stress that stimulates alveolar macrophages to synthesize interleukin-1, tumor necrosis factor alpha, interleukin-6, and chemokines (CCL-2 and CCL-5) which determine cellular response in the bone marrow and spleen [77];

– macrophages capturing inhaled pollutants and presenting them to T-lymphocytes in secondary lymphoid organs [78];

– some pollutants (organic compounds, metals) directly penetrating the blood flow with developing vascular inflammation and insulin resistance [79];

– central inflammation mechanisms being involved through reflex arcs connecting receptors in the lung tissue with the brain [73].

Cardio-metabolic effects produced by persistent organic pollutants. Cardio-metabolic effects produced by persistent organic pollutants (POPs) have been described in scientific literature in much lesser volumes than effects by PM. Such compounds are represented by a lot of toxicants such as polychlorinated biphenyls, dioxins, aromatic compounds, and halogen-substituted aromatic hydrocarbons. Biologic effects produced by such compounds on the cardiovascular system are predominantly examined in cross-sectional population and prospect studies that provide an opportunity to trace remote effects produced by low doses of organic toxicants [34]. As a rule, pathogenetic mechanisms of effects by POPs regarding metabolic disorders have few specific features and are just typical pathological processes. Thus, dioxins and polychlorinated biphenyls affect aryl hydrocarbon receptor (AHR). When this receptor is activated, this leads to growing activity of cytochrome P450 CYP1A1 and formation of reactive oxygen species together with developing low level inflammation [80]. Simultaneously apoptosis is disrupted and changes occur in the cellular lifecycle, there is also lipid oxidation and accelerated atherosclerotic processes in vascular walls [81]. Some substances influence peroxisome proliferator-activated receptors (PPAR) that disrupt adipocytes differentiation, lipid metabolism, reduce sensitivity to insulin and hence increase risks of DM2 development [82].

There are data in scientific literature on effects produced by POPs on risk factors causing cardiovascular diseases (AH, obesity, and DM2) and ultimate events (myocardial infarction, stroke, or diseases of peripheral arteries). There was an incident in Yucheng that involved mass exposure to polychlorinated biphenyls and polychlorinated dibenzofurans; as a result, a risk of AH development grew by more than 3 times over the next 24 years among women with chloracne manifestations in comparison with patients without this pathology [83]. A.V. Sergeev performed a study among people living on a territory polluted with POPs and revealed that AH risks was by 19 % higher for them (95 % CI 9–31 %) in comparison with the reference group [84]. NHANES cross-sectional study revealed that relative AH risk amounted to 1.8 (95 % CI 1.2–2.7) in the highest quartile as per environmental pollution with polychlorinated biphenyls [85]. It was established in the same study performed with 524 people participating in it that concentrations of dioxin and polychlorinated dibenzofurans in blood correlated with risks of developing AH in women, relative risks being equal to 5–6 for the highest quartile against the lowest one [86]. A cross-sectional study that involved 758 participants (Anniston, the USA) who lived on a territory polluted with polychlorinated biphenyls revealed that relative risk of developing AH amounted to 4.1 (95 % CI 1.3–14) for the upper tertile in comparison with the lower one [34].

Effects produced by POPs are associated with developing metabolic syndrome (MS). At present there are only results of cross sectional studies that focused on influence by POPs on MS occurrence. A national study was performed in Japan and as a result it was established that contents of dioxins and polychlorinated biphenyls in blood of more than 1,300 people correlated with developing MS (*OR* 3.2–4.8 when the upper and the lower quartiles were compared). Elevated POPs concentration in blood was associated with greater frequency of all components in metabolic syndrome [87]. NHANES survey revealed that pesticides concentration in plasma correlated authentically with developing MS (*OR* 5.3, 95 % CI 2.5–11, when the upper and the lower quartiles were compared). Besides, elevated pesticides contents in blood (the upper quartile against the lower one) were associated with *OR* = 2.4 for the waist circumference; 7.1, for triglycerides; 2.3, for low density lipoproteins; 5.6, for glucose; 1.8, for AH [88]. S.K. Park with colleagues (Korea) compared 50 patients with MS with a reference group and revealed a correlation between MS and concentrations of pesticides, beta-hexachlorocyclohexane and heptachlor epoxide in blood plasma (*OR* 4.4–6.0 for the upper and lower quartiles) [89]. Insulin resistance under exposure to POPs was examined as a key pathogenetic mechanism of developing MS in NHANES survey in 749 patients without DM2. 19 various POPs were examined; the most apparent association with HOMA-IR index showing insulin resistance was revealed for pesticides (*OR* = 3.8 for the upper quartile) and this dependence was maximum among people with large waist circumference [90]. PIVUS survey focused on examining an association between POPs and fat mass using DXA. Low-chlorinated polychlorinated biphenyls turned out to correlate positively with fat mass whereas high-chlorinated ones had an inverse correlation with the parameter [91]. This difference in influence exerted by POPs chlorination can be due to pharmacokinetic properties and the fact that low-chlorinated compounds have a shorter semiejection period. A peak in using such POPs was in 70ties last century. M.S. Wolff with colleagues noted that a correlation between POPs and overweight was always negative under short-term exposure to toxicants due to their depositing in fat tissue. However, it became positive after 2 or 3 semiejection periods in case there was no further POPs introduction [92]. NHANES survey revealed a direct correlation between dioxin concentrations in blood and body mass index (BMI) both in men and women [93]. A population study (13,000 participants) accomplished in Japan allowed establishing positive dependence between concentration of polychlorinated biphenyls in blood and BMI [87]. CARDIA survey yielded similar results during 25 years of observation [94]. Several studies revealed elevated DM2 risks under long-term exposure to POPs. O. Vasiliu with colleagues established in their study (more than 1,300 participants, Michigan) that odds ratio for developing DM2 amounted to 2.0–3.0 for women and 1.7 for men depending on concentration of polybrominated biphenyls in blood (the upper quartile compared with the lower one) [95]. It was established in CARDIA survey that elevated concentrations of trans-nona-chlodane pesticide and some polychlorinated biphenyls in blood were predictors of developing DM2. The authors noted that the effect occurred even if a rise in concentration of trans-nona-chlodane in blood was relatively low (*OR* = 5.3 for the second quartile against the first one) [94].

Long-term exposure to POPs can lead to developing atherosclerotic processes. PIVUS cross-sectional study established that polychlorinated biphenyls influenced formation of atherosclerotic plaques even after statistical adjustment per 10 well-known risk factors, lipids included. A similar effect was revealed for phthalate metabolites [96]. A study by IARC that involved 21,863 workers revealed that long-term exposure to dioxins at a workplace was associated with developing IHD (*RR* 1.6, 95 % CI 1.2–2.2). Relative risk of stroke amounted to 1.5 (95 % CI 0.8–2.8) in the same cohort [97]. A.V. Sergeev and I. Shcherbatykh examined a population living on a territory polluted with POPs (New York) and revealed that relative risks of myocardial infarction grew by 20 % (95 % CI 3–39 %); stroke, by 10 % (95 % CI 1.0–1.2) [84, 98]. NHANES survey established that relative risk of myocardial infarction under exposure to bisphenol A amounted to 1.2 (95 % CI 1.1–1.4) per one standard deviation in bisphenol A concentration in urine [99].

Effects produced by prevention activities aimed at reducing influence by ambient air pollution on the cardiovascular system. Randomized studies showed there was a direct protective effect produced by a decrease in pollutants concentrations in ambient air. Use of filtration devices and face masks that are able to filter PM results in decreasing blood pressure, microvascular function improvement, and lower levels of inflammatory biomarkers in adults exposed to $PM_{2.5}$ [100–102]. Results obtained by C.A. Pope with colleagues revealed that in 1970–2000 average life expectancy in the USA grew by 0.61 year per each 10 $\mu g/m^3$ of declining $PM_{2.5}$ concentration in ambient air (demographic, socioeconomic, and behavioral factors taken into account) [103]. According to M. Morishita, declining $PM_{2.5}$ concentration in ambient air in 1970–1990ties resulted in overall mortality going down by 27 %, and cardiovascular mortality, by 31 %, per each 10 $\mu g/m^3$ [104].

Activities aimed at reducing ambient air pollution may be implemented over decades; however, even a short-term decrease in pollutants concentration in ambient air (as it was shown during the Olympics in Beijing) leads to a rapid fall in levels of inflammation markers, oxidative stress, and thrombosis [105]. According to data provided by the US Environmental Protection Agency, activities aimed at ambient air purification prevented more than 160,000 deaths and 130,00 myocardial infarctions in 2010. It is pointed out that activities aimed at reducing concentrations of pollutants are likely to have more apparent effects in countries where quality of ambient air is rather poor [23].

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