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To organizers and participants of the X All-Russian theoretical and practical Internet-conference with international participation «HEALTH RISK ANALYSIS – 2020»

Dear colleagues!

On behalf of the Federal Service for Surveillance over Consumer Rights Protection and Human Well-being let me greet organizers, participants and guests of the X All-Russian conference «HEALTH RISK ANALYSIS – 2000»!

The Federal Service pays great attention to such strategic activities as developing theory, methodology, and practices of assessing and managing environmental, occupational, social, and other health risks as well as improving social and hygienic monitoring techniques aimed at assessing consequences of exposure to chemical, biological, physical and other factors and their influence on health in order to provide reduction and prevention of sanitary-epidemiologic threats. Participation in reaching and implementing strategic goals mentioned in the RF President Message to the Federal Assembly is a top priority.

At present national and federal projects are being implemented quite intensely in the country; the projects are aimed at providing drastic scientific-technological and socioeconomic development of Russia, increasing living standards in the country including population growth, decrease in mortality, creating conditions and possibilities for self-actualization and realizing talents of each particular person. All this requires a lot of efforts made by the Service's institutions and bodies to improve a risk-oriented model of control and surveillance activities in order to provide sanitary-epidemiologic welfare of the population as a basic condition for fulfilling citizens' right to get their health protected and to live in a favorable environment.

Rospotrebnadzor's basic efforts that are being made within «Public health improvement» Federal project, a part of «Demography» National project, are focusing on creating motivation for citizens to pursue a healthy lifestyle including healthy and safe nutrition as it helps increase life quality of the present generation as well as the next ones. A system for monitoring over actual nutrition rations is being created; it allows assessing nutrition consumed by various population groups, first of all, schoolchildren, and detecting correlation between health and nutrition structure and food products quality. Regional and municipal authorities are developing programs aimed at improving population's health; instrumental provision of testing laboratory centers is being modernized and the modernization has entered its final stage.

A system for social and hygienic monitoring is being improved within activities included into «Pure air» and «Pure water» Federal projects; it involves more profound assessment of air and water quality and comprehensive analysis of impacts exerted on health by environmental factors.

The unified information and analytic system (UIAS) of the Federal Service for Surveillance over Consumer Rights Protection and Human Well-being is being actively developed at the moment. The most significant results obtained via Rospotrebnadzor activities will be collected and stored in a unified database based on up-to-date IT; also there will be a unified system for collecting and keeping reports and operation analysis of occurring situations at all levels in the management hierarchy.

In 2020 Rospotrebnadzor is going to further develop and strengthen the cooperation with international scientific organizations as well as governmental bodies in foreign countries that are responsible for providing sanitary-epidemiological welfare of people living there.

Exchanging practical experience, learning new scientific developments and best available practices will undoubtedly provide more efficient work in the field and closer cooperation between experts working in different spheres.

It's good to see that the conference also includes a contest for young scientists and experts working within Rospotrebnadzor's system. When highly qualified experts communicate with their younger counterparts who are making their first steps in the sphere, it helps the latter to get more profound insight into working techniques and their specificity and to see what scientific and personal growth they can ultimately achieve.

The conference is taking place in a very complicated epidemiologic situation that exists now in the Russian Federation and is caused by a new highly contagious coronavirus infection. Rospotrebnadzor, its local bodies and dependent organizations are performing all urgent activities in these extreme circumstances being at the forefront of this struggle against the coronavirus infection spread in order to prevent health risks and protect health of the country citizens.

I'm sure that all the outlined topics will be discussed comprehensively and there will be constructive exchange of opinions between scientists and practical experts.

I wish the conference to be truly successful and the organizers, participants and guests to have fruitful work and productive discussions.

The Head of the Federal Service for Surveillance
over Consumer Rights Protection and Human Well-being
The Chief SanitaryInspector of The Russian Federation  A.Yu. Popova

PREVENTIVE HEALTHCARE: TOPICAL ISSUES OF HEALTH RISK ANALYSIS

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Research article

UNDERSTANDING THE PERCEPTION AND HIERARCHY OF RISKS: AN ENVIRONMENTAL MEDICO-SCIENTIFIC PERSPECTIVE WITH COVID-19 IN MIND

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The purpose of this article is to examine risk perception among some specific stakeholders, including international intergovernmental bodies, private western-based corporates, and among European public opinion surveys. We also address concerns of the Russian Federation and the impact of China's Belt and Road Initiative. Perception of risks is key to policy decision-making and probably more important than risk assessment. We offer a medico-scientific perspective based on factual evidence drawn mostly from official websites and publications. Our first goal is to understand if sufficient attention is given to human health, disease prevention and control relative to economic and financial considerations. Our second goal is to promote a translational and interprofessional approach to global risk prioritization by cooperation between the medico-scientific community and the financial-economic world. To this end, we examine the benefits for the practice of economic risk assessment of engaging biomedical expertise focused on global environmental health. Maintenance, expansion and sustainability of the human enterprise require health and wellness.

***Key words**: Environmental health, decision-making, World Bank Group, Organisation for Economic Co-operation and Development, World Economic Forum, World Health Organization, World Trade Organization, Asian Infrastructure Investment Bank, Belt and Road Initiative.*

Global Environmental Health identifies many risks to which humans are exposed. Among the major environmental threats that endanger the ever-expanding human population are: pandemics, climate change, pollution, malnutrition, war, poverty, water scarcity, and reduced biodiversity. The hierarchy of existential threats, their importance, urgency, and probability of occurrence, as well as their causes, are debated. However, a consensus exists in the medico-scientific community about the nature of the major threats to human and planetary health. Strangely, the expertise and commitment of hygienists and environmental scientists concerned with planetary health are often bypassed in political and economic decision-making. How and why this occurs are discussed here.

This cogitation started in 2005 following a visit (JR) to The Center for Health and the

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Global Environment, at Harvard Medical School, Boston USA. Since this visit, several disasters, shocks, viral epidemics and even a global pandemic have occurred. The COVID-19 pandemic demonstrates that global public health must occupy a preeminent role in risk assessment and decision-making. Public health is not something just to be called into action when disease strikes or disaster occurs; it has constant, ongoing pretensions and responsibilities that are directed to the *prevention* as well as the *control* of diseases. In the case of communicable disease prevention, the public health community has for decades warned of the risk of emerging viruses for which humans would have no defense, and the growing risk of rapid disease spread through the expansion of air travel and trade that greatly increase international people-to-people interactions. In 2017 in Xi'an, one (P.S.) of us called for heavy investment in public health to accompany China's gargantuan plans – the Belt and Road Initiative – for increased trade among 70+ countries. We suggest that both the control and prevention of disease should be guided by the Precautionary Principle, as applied to Global Environmental Health. *«While maintaining their objectivity and focus on understanding the world, environmental scientists should be aware of the policy uses of their work and of their social responsibility to do science that protects human health and the environment. The precautionary principle highlights this tight, challenging linkage between science and policy»* [1, 2].

Decision-makers, especially those in governmental organizations, are influenced not only by prevailing conditions but also by parties seeking to influence their decisions, including experts, lobbyists, activists and numerous stakeholders [3]. Public opinion, voiced through the media, communications and social networks, can also be influential. An analysis of the roles of all these influences in the decision-making process would need a sociological and political rather than the purely scientific approach taken here. Our interest lies in understanding the perception of risk and its hierarchy of leading stakeholders and bodies. We hypothesize that *perception of risk* is the key to decision-making and thus the outcome thereof. We have selected some bodies that operate at an international level, some Western corporate sectors, and two (European) public opinion surveys. We also examine Russian concerns and China's Belt and Road Initiative. Information is drawn mostly from official websites and publications.

Data and methods. We selected organizations, bodies and companies that operate internationally and have a variety of risk perceptions, analyses and management. Each entity was required to have an official publicly available website. Other selection criteria included: global reach, generally accepted expertise, and overall positive reputation. Selected institutions included: the World Bank Group (WBG) and International Finance Corporation (IFC), the Asian Infrastructure Investment Bank (AIIB), the Organisation for Economic Co-operation and Development (OEDC), the World Economic Forum (WEF), the World Trade Organization (WTO) and the World Health Organization (WHO). Private companies in the business of insurance, reinsurance and credit-rating assessment were also selected based on their prominence and global reach. Public opinions of risks were drawn from French and European sources. The data for the Federation of Russia concerns for Environmental health and Medicine, as well as hygiene, come from the experience of one of us (N.Z.). Due to the lack of an official web site, we chose to address the impacts of the Belt and Road Initiative via unofficial publicly available data.

International institutions.

Organisation for Economic Co-operation and Development (OECD). Created in 1948 as the Organisation for European Economic Cooperation, the body became the OEDC in September 1961. The OECD is an

intergovernmental economic organization based on an international convention, with nowadays 36 member countries. Its purpose is to deal with economic issues and world trade. Thus, its web site states: *«Our goal is to shape policies that foster prosperity, equality, opportunity and well-being for al»* [4]. In 1999, the OECD started to *«analyse the policy implications of emerging and systemic risks»* [5]. In the 10 years that followed, the world faced major threats, terrorist attacks, natural disasters (e.g., hurricanes, tsunami, volcanic eruptions), epidemics related to common germs (e.g., dengue fever, cholera), SARS-CoV in 2002–2024, the first declared pandemic due to the H1N1 virus in 2009, and the financial crisis in 2008. All these *«extremely disruptive events»* which *«destabilize critical systems of supply, producing economic spillovers that reach far beyond their geographical point of origin»* led to the concept of *global shocks*. The 2011 OECD report gives a precise definition of a global shock: *«a rapid onset event with severely disruptive consequences covering at least two continents»* [5]. This shock has specific characteristics: *«future global shocks may arise from previously unknown hazards for which there are no data and no model for likelihood and impacts (...), exhibit the potential for wide-ranging, destructive consequences that transcend national boundaries»*, and will challenge our world *«due to* its *speed of onset»*. Obviously, a global shock differs from slow-onset and/or chronic risks *«which provide time for society to adjust, react, and mitigate risk before, during and after onset»*.

The OECD has recognized five future global shocks: pandemics, financial crises, cyber risks, geomagnetic storms and social unrests. A detailed study of their impact on several complex key systems has been undertaken. A complete disorganization of several interdependent systems is predicted, for example: production, delivery and transportation, and supplies of energy, goods, drugs and food. The OECD analysis reveals that different shocks can cause comparable societal disorganization. *«The growing interconnectedness in the global economy could create the conditions and vectors for rapid and widespread disruptions»*. Massive urbanization and concentration of populations and assets, as well as the herd behavior and «groupthink» of corporations and regulators will drive and amplify the negative consequences of future global shocks [5].

World Bank Group and International Finance Corporation (WBG). Conceived in 1944 at the Bretton Woods United Nations Monetary and Financial Conference to regulate the international monetary and financial order after the conclusion of Second World War, the missions of the World Bank Group (WBG) have evolved in hand with ongoing global economic and financial challenges. Today, the WBG has several commitments, most notably provision of funding for the promotion of sustainable development. Its sister organization, the International Finance Corporation (IFC), was established in 1956 as the private-sector arm of the WBG, focusing on the role of the private sector in addressing poverty and development in low-income countries. In 2007, the IFC issued guidelines for Environmental, Health, and Safety (EHS) to achieve performance in line with Good International Industry Practices. These guidelines emphasize all known environmental and health hazards and risks. The first step for effective management is clearly stated thus: *«Identifying EHS project hazards and associated risks as early as possible in the facility development or project cycle»*. Sustainable banking also deals with these issues, with a constant public health interest; this is the case for air quality: *«Projects with significant sources of air emissions, and potential for significant impacts to ambient air quality, should prevent or minimize impacts»* [6].

Asian Infrastructure and Investment Bank (AIIB). The Asian Infrastructure In-

vestment Bank (AIIB) headquartered in Beijing is a new (2016) multilateral development bank of 102 members with a stated mission to improve social and economic outcomes in Asia and beyond. In May 2020, the AIIB announced a «water sector strategy» based on the recognition that *«water availability and management are crucial for economic growth, food security, public health and trade»* [7]. The document recognizes that population growth, rapid urbanization, and industrial and economic growth make Asia's water challenges more urgent than ever. *«Water is indispensable for agriculture and fisheries, industry, energy production, navigation and the provision of critical environmental services»*. Climate change, environmental degradation, poor sanitation and the water needs of agriculture are addressed. Plans for AIIB investment invoke its Environment and Social Framework to address social and human health risks relating to the quality and quantity of available water, equality of access to and affordability of water, as well as environmental factors including biodiversity and aquatic ecosystems. In sum, this significant document recognizes the interdependency of human and environmental health and economic growth and development.

World Trade Organization (WTO). Created 60 years ago under its original moniker, the General Agreement on Tariffs and Trade (GATT), the World Trade Organization (WTO) with 164 members *«provides a forum for negotiating agreements aimed at reducing obstacles to international trade and ensuring a level playing field for all, thus contributing to economic growth and development»*. The WTO has joined with the WHO *«to bring attention to the need for policy coherence between trade and health matters at global, regional and domestic levels»* [8]. Further, the Standards and Trade Development Facilities a joint initiative of the WTO, WBG, WHO, Food and Agriculture Organization (FAO) and the World Organization for Animal Health that *«aims to assist low-income countries establish and implement sanitary and phytosanitary standards (food safety and plant health) to ensure health protection and facilitate trade expansion»*. Health services is one of the least-committed sectors, such that fewer than 50 WTO members have undertaken commitments in one of the four health services subsectors; most of the commitments concern hospital services. *«Health and social services have attracted very limited attention in the services negotiations, which began in January 2000»* [9].

World Health Organization (WHO). The World Health Organization (WHO), which results from a constitution coming into force on 7 April 1948, is an avatar of the United Nations created in 1945. WHO's mission is *«to promote health, keep the world safe and serve the vulnerable, with measurable impact for people at country level»*. The organization adheres to the principle that *«Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity»* and it envisions *«a world in which all peoples attain the highest possible level of health»*. On January 13, 2020, the WHO issued a report titled: *«Urgent health challenges for the next decade»* [10]. The hierarchized list starts with *«health in the climate debate, health in conflict and crisis»*, places in the fifth and sixth position respectively *«infectious diseases»* and *«preparing for epidemics»*, and ends with *«earning public trust»*. Already for 2019, the WHO had issued an alarming report *«Ten threats to global health in 2019»* which placed air pollution and its links with climate change as the greatest environmental risk to human health [11]. National initiatives to promote environmental research and regulation began 50 years ago in the USA and 20 years later in Europe. Nowadays ambient air pollution remains a priority issue for many countries all over the world, Russia included. As per the WHO report Health

2020 European policy framework, the European region has the greatest load of non-communicable diseases in the world. Seventy-five per cent of deaths are caused by cardiovascular and oncologic diseases [12]. To successfully decrease the burden of non-communicable diseases, it is necessary to combine different approaches that take into account leading principles of environmental hygiene.

Western-based private bodies and institutions.

World Economic Forum (WEF). The European Management Forum was created in 1971 by Klaus Martin Schwab, Professor of Economics at the University of Geneva, as a not-for-profit foundation. Renamed in 1987 as the World Economic Forum (WEF) – better known as the Davos forum – the WEF is an international Organization for Public-Private Cooperation [13]. Its web site states: *«The Forum engages the foremost political, business, cultural and other leaders of society to shape global, regional and industry agendas»*. Prominent invited contributors have included Mrs. Gro H. Brundtland, three-term Prime Minister of Norway and the Club of Rome.

In 2020, the WEF issued several reports and notes, which seek to address the major risks faced by the world, including the COVID-19 pandemic. On the WEF website, the reports' introduction states: *«The global economy is facing an increased risk of stagnation, climate change is striking harder and more rapidly than expected»* [14]. Top five risks include biodiversity, which *«underpins global nutrition and food security»* and is *«critically important to human health, economies and livelihoods* is *declining globally, faster than at any other time in human history»* [15]. Additionally, Sheikh Hasina, prime minister of Bangladesh writes: *«poverty and inequality within and among societies will increase rapidly as a result of COVID-19»* [16].

WEF's Global Risk Report 2020 notes the *«slowing of health progress»*, the *«pressures on health systems»* and the *«ubiquitous risks of a weak health system»*. It points to the fact that *«no country is fully prepared to handle an epidemic or pandemic. Meanwhile, our collective vulnerability to the societal and economic impacts of infectious disease crises appears to be increasing»*. Highlighting an obvious neglected truth: *«Good health is the foundation for societal well-being and a dynamic and prosperous economy»* [17].

Insurance and reinsurance companies. Insurance companies are private organisations that deal with all kind of risks, with notable operations in human life, health and property casualty. The insurance company policyholder allows the insured entity to transfer risk to the company in exchange for periodic premium payments. Corporate reinsurers provide financial protection for insurance companies by handling very large risks. The reinsurance company writes business in direct collaboration with primary insurers and via brokers, such that reinsurance risk is spread across various participants. Since reinsurance companies handle various risks across the world, their business model allows diversification of risk and, therefore, its reduction [18]. Rating means prevision and anticipation, whatever the nature of the risks, whether emergent, chronic or long-term in nature.

Based on their 2018 net premiums, Swiss Re and Munich Re are the largest reinsurance companies worldwide. In 1978, Munich Re launched a series of publications dedicated to complex risks from natural hazards: The World Map of Natural Hazards [19]. More recently, Munich Re stated: *«Climate change…one of humanity's greatest challenges»* is *«predominantly the result of human activity, is real and has a major influence on weather-related natural disasters»*. In their 2017 report, Munich Re also underlines: «*the enormous economic challenges that people, companies and public institutions face in tackling the consequences of disasters»* concluding *«The threat to people*

and the need for increased resilience was highly evident in 2017» [20].

Acting in the same field, Swiss Re has similar interests and notes the same facts, sharing the same approach: *«Sustainable business is good business»* and *«Protecting the environment coupled with respect for human rights help underpin our social and regulatory license to operate»* [21]. In one of its many publications, Swiss Re proposes to address 15 emerging risks with their time frame and score of possible business impacts [22]. Among the short-term environmental factors are *«vaccination»*, which is judged to have a medium potential impact risk and *«pervasive and toxic – chemicals in our bodies»*, which is rated as low. *«Climate change and life & health»* is scored as a high potential impact risk in the next years (over 3 years).

Allianz, a global leader in the insurance and asset management business, provides property and casualty insurance. The first Allianz Risk Barometer was published in 2012. In 2020, its goal was *«Identifying the major business risks for 2020»* based on *«The most important corporate perils for the next 12 months and beyond, based on the insight of more than 2,700 risk management experts from 102 countries and territories»*. Risk ranking for the 5 major risks include: First cyber incidents followed by business interruption, changes in legislation and regulation, natural catastrophes (e.g. storm, flood, earthquake), and market developments. Climate change/increasing volatility of weather is assigned position № 7 and health issues (e.g. pandemic outbreak) appears in position № 17! [23].

Credit rating agencies (CRAs). A credit rating reflects the financial strength of companies and governmental entities, especially their ability to meet principal and interest payments on their debts. Three major companies assign credit ratings across the world: Standard & Poor's (S&P), Moody's, and Fitch Group. All provide retail and institutional investors with financial information and corresponding insights. These clues facilitate their ability to examine and understand the risks and opportunities associated with various investment environments. The interest of these agencies in non-financial issues has grown recently. For example, S&P states: *«For more than a decade, S&P Global Ratings has factored environmental, social and governance (ESG) risks into its ratings»* [24]. When considering the Fitch Group's rating methodology, applicable in particular to transportation infrastructure and power generation and transmission, criteria related to «events risks» appear under the denomination «macro risks» [25]. The report states: *«the potential event risks (...) may adversely affect the issuer's ability to repay the debt. Event risks arising from natural hazards (floods, earthquakes, hurricanes, tornadoes) as well as human error or mechanical malfunctions are identified and the presence of adequate mitigation such as reserves and insurance coverage (...). In some instances, events will be determined to be «uninsurable», meaning insurance of the related risk is unavailable, unavailable in sufficient amounts, or completely uneconomic (...). In some cases, risk mitigation will not be sufficient and the rating may be capped below an investment-grade threshold depending on vulnerability to the uninsured risk»*. According to the Fitch Rating Credit Outlook 2020, the most important risks for the coming year were only economic (fiscal policy and global trade) and political (for central banks) [26].

Public opinion surveys. The use of surveys to measure public opinion is an important factor for policy decision-makers. In France, the *Institut de Radioprotection et de Sûreté Nucléaire* (IRSN) has, since 1973, surveyed French citizenry perception of nuclear energy [27]. This mission was later extended to the psychological and sociological aspects of all kinds of risks. A barometer of public opinion on risks and security, which was started in 1988, allows the evolution of

opinions and attitudes towards risk issues to be tracked in real time. Among themes that have been examined are the perception of various hazardous situations in terms of personal risk, risk for the society, need for security, trust in authorities for public protection from risks, as well as prevailing social and environmental preoccupations. Public concern for environmental health risks has been constantly ranked low: only an average of 8–10 % of interviewed people declared a preoccupying interest in the subject! The major perceived issues have been dominated by socio-economic problems (e.g., unemployment, exclusion and poverty, lack of security) [28]. The quality of medical care has not been an issue.

Since 1973, European institutions have commissioned regular public opinion surveys to evaluate the views of the citizenry of member states [29, 30].

In 2007, the European Parliament launched its own specific Eurobarometer series. As for France, a change in favor of environmental and environmental health issues has been confirmed. The concern in 2010–2015 was constantly low, ranking 4 to 6 %, with important differences among countries [31, 32]. In 2018, environmental and climate concerns grew to 10 %. These concerns peaked in the Scandinavian area (peaking at 37 % in Sweden) and in Malta [33]. When questioned about the priorities for the European Union, the unified European opinion has cited *«protecting the environment»* (34 %) and *«fighting global warming»* (26 %) [32]. The last poll in October 2019 confirmed the trend: for the first-time, environmental concerns ranked first with a 32 % score! [33].

Russian concerns. Although the Russian Federation (RF) is not an official member of the Organisation for Economic Co-operation and Development, Russia participates notably in OCDE bodies, subcommissions and expert activities [34]. Russia shares OCDE goals and most of its positions and, since 2007, has actively participated and sometimes directly initiated many subject processes. Russia adheres to the World Bank Group's guiding principles in the sphere of health and environmental protection. The issue is urgent not only in terms of environmental improvement but also preservation of human capital possessed by Russia. Thus, the WBG, using The Changing Wealth of Nations (2018) database, gives a characteristic of aggregated wealth that belongs to Russia and highlights that human capital accounts for fully 46 %. The figure is relatively high for a country that is mostly a source of raw materials but it is substantially lower than that of high-income countries (70 %) [35].

There is a notably growth of awareness for environmental health issues (population health losses, additional mortality and morbidity cases) in Russia. The reasons are numerous, notably related to a rather slow decrease of in the cost (up to 6 % of country GDP) of damage caused environmental pollution. Besides the evolution of ecological legislation (which needs a legal approach), the positions of some stakeholders are very informative. Some large Russian companies (Gazprom, Gazprom Neft, Transneft) insure such risks voluntarily but these practices are not widespread (cited per N. Galushkin, the President of the Russian national reinsurance company) [36].

The role of the All-Russian Insurers Society (ARIS) is increasing as the ARIS is promoting legal mechanisms in its 2019–2021 strategic plan. These should substantially raise ecological safety and reduce the number of ecologically dependent mortality and morbidity cases among the country population [37].

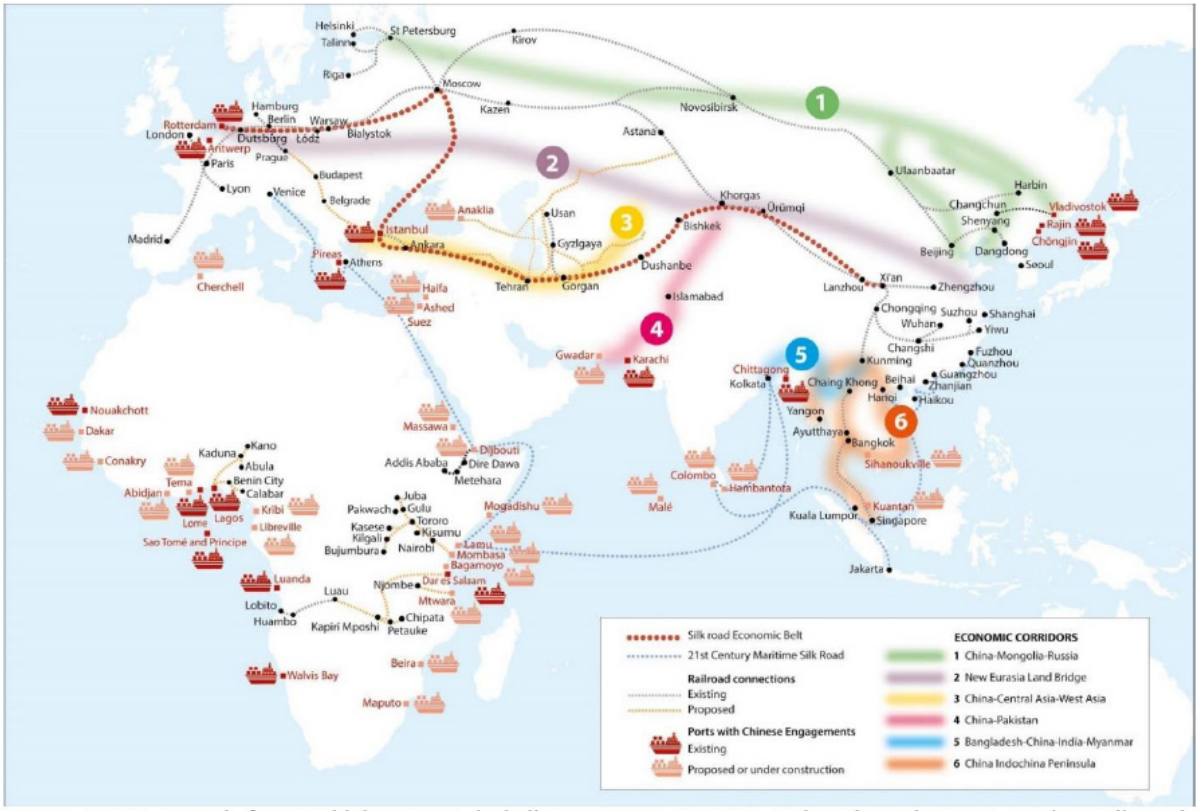
In Russia, great attention is paid to examining public opinion on issues related to environmental pollution. In 2019, the Expert analytical center at the HSE Ecology Institute performed a public opinion poll; it revealed that the majority of the RF population (94 %) is preoccupied with environmental issues, and only 1 % think there is no such

problem; 5 % state that the problem exists but is rather insignificant. According to opinions expressed by Russian respondents, their health is to the maximum extent influenced by polluted air and drinking water [38].

The latest poll performed by the Russian Public Opinion Research Center (RPORC) revealed that 23 % Russians believed ecological situation had improved; 31 % stated otherwise. At present, there are significant discrepancies in results obtained via public opinion polls on environmental issues performed by RPORC, «Public Opinion» fund, and Levada-center; this might result from questions being formulated in different ways, varying research techniques, and different respondents' samplings [39].

The Belt and Road Initiative (BRI). China's Belt and Road Initiative (BRI) is one of the most ambitious infrastructure projects ever conceived, originally covering more than 70 countries in Asia, Europe, Africa, Latin America and Oceania, including 65 % of the world's population and 40 % of the global gross domestic product as of 2017. Today, the BRI involves 4.3 billion people in 138 partner nations (Fig.) [40, 41].

The BRI project is two-pronged: the overland Silk Road Economic Belt (six inland trade corridors) and the Maritime Silk Road that together connect China with much of the world [42]. The global development strategy was incorporated into the constitution of the People's Republic of China in 2017. The BRI objective is *«to construct a unified large market and make full use of both international and domestic markets, through cultural exchange and integration, to enhance mutual understanding and trust of member nations, ending up in an innovative pattern with capital inflows, talent pool, and technology database»* [43]. The initial focus has been infrastructure



Source: OECD research from multiple sources, including: HKTDC, MERICS, Belt and Road Center, Foreign Policy, The Diplomat, Silk Routes, State Council Information Office of the People's Republic of China, WWF Hong Kong (China).

Figure. China's Belt and Road Initiative in the Global Trade, Investment and Finance Landscape

investment, education, construction materials, railway and highway, automobile, real estate, power grid, and iron and steel [44]. China's colossal infrastructure investments may usher in a new era of trade and growth for economies in Asia, Africa, South America and beyond. According to the BRI initiative, Russia, being a transport and energy base, cooperates with China and other countries in Central Asia as well as with European and African countries.

In May 2018, a BRI-related agreement on trade and economic cooperation was signed between China and countries of the Eurasian Economic Union (EEU), which consists of Armenia, Belarus, Kazakhstan, Kyrgyzstan and Russia [45]. In October 2019, Russia and China agreed on more intense BRI cooperation [46].

The colossal BRI initiative is supported in research, engineering and academic exchange by the University Alliance of the Silk Road centered at Xi'an Jiaotong University, which in 2017 held a Global Health International Conference with the Chinese Preventive Medicine Association and the Chinese Society of Global Health. Among the topics discussed was the need for parallel investment in global public health because of the increased people-to-people exchange that would result from the massive increase in international trade planned for the BRI. Others have expanded on the need to strengthen BRI-related global health cooperation, disease control, data sharing for pandemic threats, and disease control and elimination [47]. However, BRI implications for health were absent from a high-level analysis of BRI views from Beijing, Moscow and Washington DC [48]. Obviously, COVID-19 pandemic will have its influence on priorities in cooperation with the BRI, with the major shift in attention focus to reducing population health risks.

Results and discussion. This review of some stakeholders' positions and concerns for environmental risks and Environmental Health issues offers several important insights on the perception and management of global risks, by selected economic actors, health and trade organizations, and by public opinion. While the subject matter of draws heavily from Europe, we seek to avoid a purely Western-centered approach.

Obviously, global, national and personal economic concerns are the leading issues for the economic and trade actors, as well as for European public opinion which is largely but not exclusively based on their background knowledge and short-term interests. However, European and Russian public opinion have begun to shift greater interest toward environmental concerns, a trend that seems likely to continue as a result of the COVID-19 pandemic.

The distinction between acute global shocks and chronic problems is the major point for the economic world, as underlined by the OECD. The fear is always the same, namely sudden dangers that might compromise economic structure and business activity (which is the core of the Allianz barometer).This awareness of the possibility of economic and financial disasters arising from shutdowns and/or lockdowns has resulted in advice to anticipate, to prepare (OECD, IFC, CRAs) and to mitigate their predictable consequences. Use of financial leverage via credit ratings to mitigate (via insurance) and/or to refuse projects associated with high environmental risks (e.g. an extreme climatic change), reveals increasing awareness of financial risks associated with such «events» in the economic world (CRAs). Predictably, the differences and consequences of acute and chronic risks (long-term) should be questioned in risk assessments. WEF's last report perfectly anticipated the dramatic condition and unpreparedness of many nations that have had to fight the COVID-19 pandemic.

Lessons learned from the COVID-19 pandemic will probably underline the need to place public and environmental health issues high – perhaps number one – on the risk agenda. Predictably, such considerations will

also permeate thinking in regard to health and safety in international trade and people-to-people exchange, a core principle of the Belt and Road Initiative.

The long-term challenges posed by climate change, a preoccupation of many environmental activists, is also a concern addressed by some in the economic world. Private reinsurance companies as well as the WEF have ranked these issues number one. In a 2012 special report, the U.N. Intergovernmental Panel on Climate Change states in the summary for policymakers: *«Economic, including insured, disaster losses associated with weather, climate, and geophysical events are higher in developed countries. Fatality rates and economic losses expressed as a proportion of gross domestic product (GDP) are higher in developing countries (high confidence) (...). Increasing exposure of people and economic assets has been the major cause of long-term increases in economic losses from weather – and climate-related disasters (high confidence). Long-term trends in economic disaster losses adjusted for wealth and population increases have not been attributed to climate change, but a role for climate change has not been excluded (high agreement, medium evidence)»* [49]. With the present COVID-19 pandemic, which has also increased and pointed to global, national and ethnic population inequities, this observation can be extended to all manner of planetary threats.

WHO's hierarchy of concerns, albeit expressed prior to the present pandemic, seems to be based mainly on the mortality rate and attributable mortality of diseases related to air pollution, climate change and infectious and non-communicable diseases other than COVID-19. Presently, the mortality rate associated with diseases linked to or exacerbated by ambient air pollution is higher than the mortality rate associated with climate change. The WHO, which greatly impacts public health policies, has pointed to the importance of chronic diseases versus communicable diseases, the colossal impact of which is evidenced by the COVID-19 pandemic, may be dramatic not only on health and mortality but also on the global economy. This tremendous gap in the perceived risk of chronic versus acute viral and other health conditions should be questioned. Managing pandemics, chronic or acute, needs to embrace economic and political cooperation. Food safety, plant health and biodiversity are addressed by several cooperating agencies, but WTO planning for health, hospital and social services appears to have stalled.

If we adopt a holistic overview, we must note that stakeholders with global reach and impact have never considered Environmental Health as the key issue for worldwide development and economic security. Although most of the stakeholders are aware of some health-impacting environmental factors, including the prospect and now the reality of a pandemic, they have not considered the possibility and benefit of engaging with and learning from Environmental Health and Medicine. Given that taxpayers underwrite research advances in the form of vast numbers of projects relevant to planetary health, the world of biomedical and ecological science often seems far removed from the risk perceptions of government bodies, private enterprises specializing in risk assessment, and the public. Global cooperation across these sectors can bring a more realistic, science-based understanding of environmental risks for the human condition and its enterprise. Investments in health, as well as physical infrastructure, are critical components for BRI and other countries because the prevention and control of disease will lift all boats, including personal and population well-being, whether measured in health or economic terms.

This article was never designed to be an exhaustive review and therefore has several limitations. The selection of stakeholders is arbitrary and did not consider different types of governance. We have ignored several UN

dedicated agencies (e.g. the United Nations Environment Programme, UNEP, the Food and Agriculture Organization) as well as the European Union, the BRICS and SCO summits and the Association of Southeast Asian Nations (ASEAN). We have not addressed the role of numerous lobby groups, notably those from agricultural and industrial areas. The views expressed here are those of environmental scientists who function outside financial and economic sectors. Our goals were neither to examine legal and political issues nor to compare these aspects between countries. Our hope is that this approach will favor cooperative, multidisciplinary research and action that traverses biomedicine and economics.

Conclusions. The major concern of the environmental health community is maintenance human health and wellness with heavy dependence on the Precautionary Principle as defined above. Anticipation, prevention and preparedness are mandatory as growing risks and threats in increasingly urbanized countries with greatly centralized life support systems. The collective vulnerability of societies to social and economic consequences is also typical for conditions associated with exposure to environmental risk factors that create long-term and frequently low-level impacts.

Global risks can no longer be addressed with the usual «in-the-box» compartmentalized approach. Inter-professional and interdisciplinary cooperation are mandatory, as practiced in Environmental Health and Medicine. A long-term perspective is of great importance, with critical risk assessments applied to chronic health issues as well sudden, acute threats. Fifteen years ago, we were warned: *«Time is running out to prepare for the next pandemic. We must act now with decisiveness and purpose. Someday, after the next pandemic has come and gone, a commission… will be charged with determining how well government, business, and public health leaders prepared the world for the catastrophe when they had clear warnings. What will be the verdict?»* [50, 51]. Hopefully, lessons learned during the COVID-19 pandemic provoke salutary changes. Let's imagine a brighter future in which Environmental Health is a priority concern among stakeholders worldwide. Perhaps a positive trend can be seen in OECD's latest report where the body calls for global cooperation to develop and distribute a SARS-CoV-2 vaccine, strengthening of health care systems and public health and prevention strategies to contain viral spread [52].

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Short essay

STROKE AND AIR POLLUTION. A WORLDWIDE PUBLIC HEALTH PROBLEM

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After myocardial infarction, stroke is now associated with air pollution.

From local data and literature, we report the strength of the association between air pollution and stroke. We try to understand the biological mechanisms between exposure to air pollutants and stroke risk.

The association between air pollution and stroke is strong, confirmed and real. Air pollution and small particulate matter are the most toxic. Patients with classical neuro-vascular risk factors or a history of stroke or transient ischemic attack are at risk of stroke induced by air pollution.

Air pollution is a serious modifiable risk factor for stroke and a silent killer inducing stroke. This new neuro-vascular risk factor is useful for public health policies.

Key words: *ischaemic stroke, hemorrhagic stroke, stroke, air pollution, air pollutants.*

The relationships between air pollution and stroke are now well known and may be introduced in public health policy [1].

We propose to review the data from literature and personal data.

Air pollution. Air pollution is a complex association of air pollutants induced by different sources [2].

Air pollution is the product of small particulate matter (PM) and gaseous pollution with sulfur dioxide (SO_2), ozone (O_3), nitrogen dioxide (NO_2) and carbon monoxide (CO). $PM_{2.5}$ represent close to 70 % of PM measuring less than 10 μm (PM_{10}) [3].

Combustion of fossil products, as well as road traffic, industrial and home heating using coal, oil or wood, mainly produces PM and SO_2. Diesel engines produce high levels of nanoparticles, NO_2 and CO, while O_3 is produced by photochemical reactions [4].

Stroke and air pollution: clinical data. Results and discussion.

Thanks to cohort studies, ecological studies, meta-analyses, case-crossover studies and big data, we can summarize the following evidence-based data [5–15]:

– NO_2 and PM are associated to hospitalization from stroke induced by long-term exposure to air pollution [5, 6];

– Stroke risk is associated to the rise of PM2.5 levels [7];

– Residential proximity to major roadway is associated with a higher risk of ischemic stroke [5];

– The rise of $PM_{2.5}$ levels is associated with the rise of both ischemic and hemorrhage stroke mortality [9];

We have demonstrated the association between ischemic stroke and the number of vascular risk factors (hypertension, tobacco, hypercholesterolemia and diabetes) [13]; the role of SO_2, Co and NO_2 [12] is also demonstrated, as well as PM_{10} [11]; the place of air pollution in stroke onset is very important: 33.7 % in low- and middle-income countries, 30 % in high-income countries [15].

Mechanisms of action of air pollution:

Several mechanisms are well known:

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– translocation of nanoparticles able to cross the alveolar [16];

– capillary barriers towards the circulation [16];

– inflammation of endothelial cells [17];

– increase of endothelial cell permeability [18];

– autonomic dysfunction [1];

– atrial fibrillation [19];

– epigenetic mechanisms, acting on endothelial stem and progenitor cell functions and promoting DNA methylation [20].

Clinical impact.

Thanks to these data, we can identify people at risk (hypertension, diabetes, tobacco), children and elderly [1, 13].

Greater exposure to air pollution in patients having previous neuro-cardio-vascular risk factors is strongly associated with a greater risk of stroke and also myocardial infarction [1, 14].

Therefore, we provide tools to conduct a specific public health policy towards this new problem.

Conclusion. A new modifiable risk factor for stroke is present in the air, after analysis of epidemiological studies. New basic mechanisms suggest urgent effective strategy from public health policy.

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Research article

CONTEMPORARY CHALLENGES AND WAYS TO IMPROVE HEALTH RISK ASSESSMENT AND MANAGEMENT

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We analyzed basic trends in improving risk assessment and management in Russia taking into account international experience; these trends arise from needs occurring in contemporary hygienic science and necessity to provide stronger resistance against new threats to population health.

We substantiated specific tasks in development of health risk analysis mythology basing on preconditions for finding solutions to them in Russia; we also determined practical issues in its implementation that are the most vital and need solutions in the nearest future in order to eliminate adverse impacts on the environment and population health.

The primary results are creation of a long-term strategy for the development of health risk analysis principles that takes into account the latest scientific data and is aimed at solving the following methodological and practical tasks: implementation of a systemic approach in estimating carcinogenic / non-carcinogenic risks; development of a unified approach to accomplishing toxicological «dose – response» examinations and interpreting their results which will take into account background morbidity and background dose burdens and determine susceptible population groups and behavioral models; threshold levels obtained via determining «benchmark» concentrations taking spontaneous background into account in order to determine new RfD and RfC and revise existing ones; use of micro-environmental approach in exposure estimation; use of risk assessment methodology in BAT parameters implementation for providing control over health safety after new approaches aimed at reducing emissions have been implemented in environmental protection. The necessity to improve approaches to health risk assessment and management and tasks solved within the process have been taken into account when the Branch scientific research program for 2021–2025 was developed by Rospotrebnadzor.

Key words: *risk assessment, risk management, population health, environment, carcinogenic and non-carcinogenic effects, dose – response, micro-environment exposure, BAT.*

Nowadays health risk assessment and management are being given a lot of attention by experts from various spheres as their results underlie significant processes both in economically developed and developing countries. These processes are further development of regulatory and legal documents and methodical guidelines and substantiation of managerial decisions. Bearing in mind a wide range of possibilities for applying health risks assessments, validity of their results is being thoroughly analyzed by scientists, economists, politicians, and the society as a whole.

Scientific grounds for risk assessment have changed considerably over the last 15–20 years; they follow a common trend for things getting more complex in those spheres of

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knowledge with progress made in them being actively used in risk analysis methodology.

Risk assessment procedures are being implemented into practice at present; however, we can't see substantial progress in methodology development in many spheres.

Development of analytic research procedures allows scientists to concentrate on finding solutions to fundamental issues related to improvement of risk analysis methodology.

An issue that yet remains unresolved is methodical approaches to assessing combined and complex effects produced on a body by multiple chemicals; taking into account person's individual sensitivity; a probability to assess different factors (chemical, physical, and biological ones) that produce combined effects.

In Russia there is certain background for further development in some research spheres mentioned above. Practically from the very beginning of methodology implementation experts have been taking into account a hazard that influencing compounds would produce toxic effects on critical organs and systems and/or a carcinogenic hazard using the most conservative summation principle. Still there has been no detailed research on where adverse chemical impacts exerted by different substances would localize depending on their peculiar behavior in an influencing medium and in a body; nowadays it is becoming an obligatory condition for application of up-to-date risk assessment.

Combined assessment of different risks is based on searching for and applying similar potential effects on exposed population health. For example, radiation factor can produce effects similar to those produced by chemical carcinogens as well as by ambient air contamination in urban settlements (nitrogen and sulfur dioxides, carbon oxide, ozone, and particulate matter including fine-disperse fractions PM_{10} and $PM_{2,5}$) that are proven by epidemiologists to cause deaths and hospitalizations in a population in addition to background levels.

An algorithm for comparative assessment of radiation and chemical risks has been developed basing on long-term experience in studying similar consequences of exposure to radiation and chemical environmental factors [1, 2].

Another example of examining and taking into account combined effects produced on population by risk factors that are different in their nature is a study on exposure to high air temperature and ambient air contamination and its influence on population mortality with building an epidemiologic model exemplified with an emergency situation that occurred in Moscow city and the Moscow Area in summer 2010 [3].

But still there is a necessity to apply health risk assessment in a wider sense in order to find solutions to some complex tasks such as analysis of a substance or a product life cycle; scientific substantiation for economic cost estimate or advisability to replace one risk with another etc.

In order to improve health risk assessment procedures accepted by Rospotrebnadzor, concrete actions are going to be required. Let us stress that suggested measures are to provide more profound application of the latest scientific data in risk assessment and to make its results more useful for political decision-making. A necessity to modernize risk assessment requires a long-term strategy based on the existing methodology but at the same time it will be necessary to intensify coordination and information exchange between Rospotrebnadzor's institutions and bodies and to provide training and skills development for Rospotrebnadzor personnel. This new strategy should be based on executive authorities themselves being ready to implement risk assessment into decision-making and it should be both fixed in regulatory and legal documents and implemented into practice.

Today, risk assessment should become a procedure for assessing relative advantages of different risk management techniques and not be a goal in itself; it can be reached only provided that clear unambiguous risk management goals and tasks are set as they are the primary reason for health risks assessment to be performed at all.

A change in the existing views on risk assessment can raise its influence on decisions being made as the suggested measures envisage the leading role of the careful and correct planning aimed at making risk assessment truly vital in finding solutions to concrete problems when risk assessment results are to be applied for informing decision-makers on a range of solutions available to them taking into account economic and social benefits [4–6].

Since at present results of epidemiologic research and «dose/concentration – response» dependences determined on their basis are not sufficiently applied for comprehensive assessment of damage to health, it is extremely vital to make the process more active [7]. It is possible to obtain necessary data via implementing activities included into «Clean air» Federal program which is a part of «Ecology» National project[1].

A substantial contribution into health risk analysis improvement is made by finding a solution to a task on creating a unified approach to assessing «dose – response» dependence regarding carcinogenic and non-carcinogenic effects based on the latest scientific data. We should bear in mind that at present risk assessment entails different approaches to characterizing risks of carcinogenic and non-carcinogenic effects, and considerably less attention is paid to non-carcinogenic effects occurrence. Reference doses / concentrations (RfD/RfC) can't be considered a proper measure for quantitative risk assessment under different exposure levels; therefore, their application in comparative risk assessment and in economic costs and benefits analysis is considerably limited. Carcinogenic risk assessment usually doesn't take into account any differences between different people regarding an extent to which they are predisposed to oncologic diseases excluding probable difference existing at early stages of life.

Scientific considerations and risk management requirements predetermine a trend for unifying approaches to carcinogens and non-carcinogens when it comes to assessing «dose – response» dependences under low doses [8–11]. It is recommended to develop a unified approach to modeling «dose – response» assessment that should be based on systemic taking into account several vital parameters such as background morbidity and background dose burdens; differences in behavioral patterns; probable existence of susceptible population groups. Failure to take them into account can result in differences in individual «dose – response» profiles. World scientific society suggests a new concept of RfD/RfC values defining them as a risk-specific dose showing a share of population that is above and below a determined acceptable risk level with a certain degree of authenticity.

In the nearest future it is especially vital to perform toxicological studies aimed at determining threshold levels for substantiating RfD/RfC basing on «benchmark» concentrations taking into account spontaneous background and not only thresholds calculated with conventional procedures involving NOAEL/LOAEL determination [12].

Implementation of approaches into health risk assessment that take into account microenvironment influence will allow more profound assessment of population exposure and obtaining more valid results. A micro-environment in risk assessment methodology is a specific space in the environment where a person contacts some adverse substances. A microenvironment should be a homogenous space as regards contamination at a specific moment of time and should be characterized with contaminants concentrations with sufficiently low uncertainty. A typical micro-environment is an apartment, an office, a classroom, a workshop, a street, a vehicle etc. When assessing risks taking into account micro-environments, overall dose burden is calculated as a sum of doses

[1] «Ecology» National project profile / approved by the Presidium of the RF Presidential Council on strategic development and national projects, meeting report No. 16 dated December 24, 2018. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_316096/ (21.03.2020) (in Russian).

received in each micro-environment allowing for time spent in each of them [13].

Micro-environment approach was first tested in risk assessment in 90-ties last century in the USA under the EPA supervision. At present this approach is a powerful tool for exposure assessment due to, among other things, use of databases maintained by state structures. Its application is included into health risk assessment regulations as it can be seen from description of software tools recommended by the EPA to be applied for taking micro-environment exposure into account: «… to assess health risks and impacts on the environment caused by exposure to «criterion» air contaminants (including photochemical oxidizers such as ozone) and toxic air contaminants» [13].

In Russia application of micro-environments in health risk assessment was described in 2002; however, later it was rather rarely used due to difficulties in obtaining necessary initial data, first of all, concentrations that produced effects on health and periods of time spent in each micro-environment [1]. An example of micro-environment approached being applied in exposure and risk assessment is a study on establishing a contribution made by a living environment into total carcinogenic risk taking into account contamination with carcinogens occurring in ambient air, air inside apartments, and public transport, and amount of time people spent in each micro-environment [14].

Programs recommended by the EPA to assess exposure taking micro-environments into account involve use of data on population provided by the EPA itself and the US Census Bureau.

To determine exposure value, one requires a great initial data array; considerable part of these data can be obtained either via specific research (questioning) or within a national census due to additional questionnaires applied in the process. For example, in the USA hapem4 model can be applied to determine exposure duration for an individual; the model involves using activity patterns data and commuting patterns data [15].

An activity pattern is a consequence of discrete events (corresponds to time periods spent in different micro-environments) that describe a person's daily routines over a given day and his or her lifestyle. The pattern is characterized with different periods of times spent in each micro-environment mentioned in it. Hapem4 model uses data on different activities obtained from EPA complex database on human activities (CHAD) containing more than 22,000 person-day activity patterns [16].

A commuting pattern contains information on trips from home to work and back and it is important in situations when contaminants concentrations in micro-environments at work differ from those existing at homes. The task is solved via using a specialized database belonging to the US Census Bureau where there is a population number living in a given section that is assigned to each recorded section; that is, population that travels from a home section to a work one is clearly identified.

A similar micro-environment approach is implemented in TRIM.Expo (APEX) model for exposure assessment [13].

At present the RF Government is modernizing approaches to state regulation in environment protection sphere taking into account abundant international experience (EU countries and the USA)[2, 3].

A set of activities aimed at improving the state environmental policy has been developed; special attention here is paid to introduc-

[2] EU – Russia. The Cooperation program (Ecological standards harmonization II (ESHII)). The concluding technical report. Activity section 1 – Analyzing gaps in legislation; 1.4 – National strategy for ecological standards harmonization in Russia and Action plan for 2010–2025. *Strategy–2020*. Available at: http://2020strategy.ru/data/2011/07/26/1214727421/3.pdf (09.04.2020).

[3] Directive 2001/81/EC of The European Parliament and of the Council of 23 October 2001 on National Emission Ceilings for Certain Atmospheric Pollutants. *Eurolex*. Available at: https://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2001L0081:20090420:EN:PDF (26.03.2020).

ing unified principles for emissions standardization basing on implementation of the best available technologies (BAT)[4].

When implemented, the said standardization is assumed to make for a transition to more environmentally friendly and economically beneficial procedures for technical regulation and standardization of environmental contamination[5] [17, 18]. Given that, one should ensure that technologies already included or are planned to be included into BAT reference books[6, 7] are thoroughly analyzed before such inclusion takes place and probable negative impacts they may have on population health are to be assessed. That is, it is necessary to introduce certain procedures on assessing efficiency of BAT application for different industrial brunches taking into account residual health risks as well as target quality parameters of the environment (ambient air, water, and soil). BAT application, in its turn, will facilitate finding solutions to certain practical issues:

− introducing simpler procedures for accounting of priority contamination sources and contaminants;

− providing comparability of requirements for similar stationary sources;

− updating the state system for ecologic control;

− giving free access to data on BAT environmental efficiency.

When reforming a state system for environmental quality management, it is vital to remember that fixing standards for contaminants emissions into ambient air, even given all BAT parameters, doesn't ensure ambient air quality near emissions sources to correspond to levels that are safe for population health. In other words, fixing standards for contaminants emissions basing on BAT is not an alternative for conformity with hygienic standards for contaminants concentrations in ambient air and can't provide completely safe impacts on the environment and health in all cases [15, 16]. A necessity to take this factor into account can also be found in international documents, for example, EU Directive or alterations to clauses in the US Clean Air Act [16, 19].

Therefore, when BAT parameters are implemented, it is necessary to obligatorily apply risk assessment methodology as it is only on its basis that one can determine whether there are no threats for population health (residual health risk levels) on a given territory after new procedures for emissions regulations have been implemented [19, 20].

Overall, a transition to technological regulation involving use of BAT parameters requires giving certain attention to such factors as legal aspects, economic advisability, health protection provided for specific population groups, roles played by all the counterparts participating in the process, costs and benefits analysis, and activities aimed at control and provision of decisions implementing [15, 16].

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[4] On developing, fixing, and reviewing standards of the environment quality for chemical and physical parameters of the environment, as well as on approving on regulatory documents in environmental protection sphere that fix technological parameters for the best available technologies (together with «Provisions on developing, fixing, and reviewing standards of the environment quality for chemical and physical parameters of the environment»): The RF Government Order issued on February 13, 2019 N 149. *Konsultant Plus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_318449/ (23.03.2020) (in Russian).

[5] On Approval of The rules for technological standards development: the Order by the RF Ministry of Natural Resources and the Environment issued on February 14, 2019 № 89. *KODEKS: an electronic fund of legal and regulatory documents*. Available at: http://docs.cntd.ru/document/542643374 (08.04.2020) (in Russian).

[6] On making alterations into The rules for determining a technology as the best available one as well as development, actualization and publication of reference and technical guides on the best available technologies: The RF Government Order issued on March 09, 2019 No. 250. *Konsultant Plus*. Available at: http://www.consultant.ru/cons/cgi/online.cgi?req=doc&base=LAW&n=319873&fld=134&dst=100001,0&rnd=0.13379705097259964#07000201105021768 (25.03.2020) (in Russian).

[7] On Approval of stage-by-stage schedule for actualization of reference and technical guides on the best available technologies: The RF Government Order issued on April 30, 2019 No. 866-r. *Konsultant Plus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_324048/ (11.04.2020) (in Russian).

Implementation of such an approach will allow confirming efficiency of best available technologies introduced at productions; use of such technologies makes for preventing or reducing negative impacts on health and the environment down to acceptable levels.

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Research article

ESSENTIAL ELEMENTS AND STANDARDS FOR THEIR CONTENTS IN DRINKING WATER

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Certain essential and conditionally essential natural elements (selenium, chromium, iodine, molybdenum, cobalt, vanadium, fluorine, lithium, silicon, boron, and bromine) are standardized in terms of their contents in drinking water as per sanitary-toxicological parameters of adverse health effects.

Our research goal was to determine a contribution made by drinking water into supplying a human body with essential natural elements as well as to substantiate the necessity to update standards regarding these substances.

We applied calculation models for dose equivalents of essential elements MPC (maximum permissible concentration), MPC calculations for these substances basing on a necessary 20 % contribution made by drinking water into reference doses, and calculation of non-carcinogenic health risks due to essential elements occurrence in specific drinking water sources with these elements being distributed into different groups as per similar effects produced on certain organs and systems in a body.

We took existing drinking water sources containing 6 essential elements with similar effects as an example and applied a procedure for assessing non-carcinogenic health risks.

Acting nickel and selenium MPC do not supply a body with an optimal daily intake whereas their determined MPC are not only harmless but also conform to the minimum necessary intake dose. At the same time neither acting lithium MPC nor its calculated one taking into account risk assessment based on internationally accepted reference doses doesn't provide the minimum necessary daily intake into a human body. When boron and vanadium are contained in drinking water in a concentration close to their MPC, then their 20 % contribution into the reference dose is exceeded (71.4 % and 164.7 % accordingly). Introduction of these essential elements with food can become a factor that determines non-carcinogenic risk level.

Key words: *essential elements, MPC in drinking water, non-carcinogenic risks, reference doses, minimum necessary daily doses, nickel, selenium, lithium, boron, vanadium.*

The valid Sanitary-Epidemiologic Rules[1] contain standards for concentrations of substances that are essential and conditionally essential such as selenium, chromium, iodine, molybdenum, cobalt, vanadium, fluorine, lithium, silicon, boron, and bromine. Their maximum permissible concentrations in drinking water ($MPC_{d.w.}$) are fixed as per sanitary-toxicological parameters related to adverse health effects. In some cases their occurrence in drinking water is determined by natural quality of a water source [1, 2]. And it is quite possible that water contains several elements in different concentrations. According to

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available literature data[2, 3, 4] underground water sources contain boron in concentrations reaching 0.46 mg/L; bromine concentrations in them vary within 0.029–0.9 mg/L; vanadium, from 0.0013 to 0.074 mg/L; calcium, from 20 to 430 mg/L; cobalt, from 0.0004 to 0.0074 mg/L; silicon, from 3.7 to 24.2 mg/L; lithium, 0.019–0.071 mg/L; molybdenum, 0.001–0.021 mg/L; nickel, 0.0043–0.021 mg/L; selenium, 0.001–0.052 mg/L; fluorine, 0.4–4.8 mg/L; chromium, 0.0016–0.1 mg/L [3–9]. Therefore, we can state that essential elements contents in potential and already exploited sources for communal and drinking water supply vary from levels being much lower than MPC to values that are more than 4 times higher than the hygienic standards, for example, for fluorine, bromine, and selenium.

Our research goal was to determine what role the drinking factor played in supplying a human body with essential elements of natural origin.

Data and methods. We used the following data in our research:

– basic information on contents of essential elements in water sources in the RF with their concentrations being standardized in drinking water as per sanitary-toxicological parameters related to adverse health effects;

– standards for essential elements contents in drinking water and food products;

– reference doses for essential elements at chronic oral introduction.

The following research techniques were applied: we calculated dose equivalents of $MPC_{d.w.}$ for essential elements standardized as per sanitary-toxicological parameters related to adverse health effects; $MPC_{d.w.}$ taking into account a 20 % contribution made by the drinking factor into a reference dose for essential elements at chronic oral introduction; non-carcinogenic health risks caused by essential elements occurring in specific drinking water sources and differentiated as per similar effects produced on functional state of specific organs and systems.

Results and discussion. Given that essential elements perform certain functions related to regulating activity of metabolic systems and cellular genome apparatus, and a human body reacts to their occurrence not only in a dose that is toxic but also in case there is deficiency of such elements, it seems advisable to update standards fixed for them [2, 6, 10–13].

Several works have dwelled on an issue related to minimum essential quantities of elements that made drinking water physiologically adequate as it can be seen in the WHO report; their results have found their practical implementation in a regulatory document that fixes quality standards for bottled drinking water[5] [14–17]. For example, these works substantiate minimum essential calcium and magnesium concentrations. At the same time, minimal water hardness (determined mostly by these two elements concentrations) is not fixed in the existing regulatory documents[6], and the only standard for it concerns solely the upper permissible level[7]. As for publications on other

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essential elements being in shortage, they don't provide sufficient grounds for regulating their minimal essential concentrations in drinking water [18–21].

Theoretical and practical issues related to providing people with essential elements in necessary quantities are mostly dealt with by experts in nutrition hygiene[8]; they tend to neglect the drinking factor completely in spite of the WHO recommendations to create standards for chemicals contents in drinking water taking into account their introduction with food products[9, 10] [15, 22–24]. Moreover, the WHO Guidelines on drinking water quality, the 4th edition[11], recommend estimating a contribution made by the drinking factor into a reference dose at oral exposure to be equal to 20 %. Most experts believe the previously fixed 10 % contribution is too conservative and obviously insufficient.

Data on probable pathologic states occurring in a human body and caused not only by excess quantities of essential elements standardized in dirking water as per sanitary-toxicological parameters related to adverse health effects but also by their deficiency (Table 1) indicate it is vital to take such elements into account when predicting probable health risks.

Our choice on essential elements to be considered in the present work is limited to those standardized in drinking water only as per sanitary-toxicological parameters related to adverse health effects; it is due to such elements as copper, zinc, and iron being regulated as per organoleptic parameters related to adverse health effects and belonging to the 3rd and 4th hazard category; according to the conventional health risk assessment methodology, these elements are not included into any summation in case of their combined occurrence in drinking water.

The present work involved the following procedures:

– elements concentrations (mg/L) were recalculated into unified measurements with minimal essential daily introduction (mg/kg/day); the following constants were used in calculations: an adult's body weight is 60 kg, consumed water volume is 2 liters (Table 3)[11];

– doses equivalent to essential elements MPC in drinking water were compared with minimal essential and reference ones (Table 3);

– apart from determining a contribution made by MPC dose equivalents into a reference dose, we determined doses with their contribution into a reference one being equal to 20 %. Minimal essential doses that were first recalculated into concentrations were compared with existing and calculated MPC (Table 3);

– doses equivalent to existing $MPC_{d.w.}$ were compared with doses that corresponded to introduction with food (Table 4);

– calculated MPC that secured a 20 % contribution made by the drinking factor into a reference dose, were compared with concentrations that secured 100 % of minimal essential introduction as per a given essential element (Table 5);

– hazard indexes were calculated for existing $MPC_{d.w.}$ taken for processing data on elements and their concentrations detected in a scenario source;

– an existing underground water source was taken as an example for calculating non-carcinogenic risks (as per hazard index) taking into account several essential elements occurring in water that were standardized as per sanitary-toxicological parameters related to

[8] MG 2.3.1.2432-08. The standards for physiological needs in energy and nutrients for different population groups in the Russian Federation. *KODEKS: an electronic fund for legal and regulatory documents*. Available at: http://docs.cntd.ru/document/1200076084 (06.04.2020) (in Russian).

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adverse health effects and differentiated as per similar effects produced on the kidneys. Calculations were performed as per a conventional domestic procedure supplemented with determining a contribution made by detected elements into minimal essential levels that provided proper functioning of a human body. Hazard index was compared with a calculated sum of detected elements concentrations to their MPC ratios[11].

Table 1

Pathologies caused by deficiency and excess of essential and conditionally essential elements standardized in drinking water as per sanitary-toxicological parameters related to adverse health effects

Element	Changes in a human body in case of:	
	deficient doses	excessive doses
Lithium	Bipolar disorders. Growing probability of pancreatic diabetes, cardiovascular disorders, and hypertension occurrence	Neurologic and mental disorders, the thyroid gland functioning inhibition, renal failure
Chromium	Improper tolerance to dextrose, risks of reproductive disorders in men	Damage to liver, kidneys, and gastrointestinal tract functioning
Selenium	Improper protein formation by the liver, immune status failure, pancreatic dysfunction. The symptoms get only worse in case of fluorine, calcium, and iodine deficiency	Damage to the liver, spleen, and skin
Cobalt	Blood making organs dysfunction, liver dysfunction, heart rate dysfunction, damage to bone tissue. The symptoms get only worse in case of fluorine deficiency	Damage to the endocrine, blood-making, and cardiovascular system
Molybdenum	Tachycardia, night blindness	Damage to the kidneys, blood-making and musculoskeletal systems
Silicon	Arthrosis. The symptoms get only worse in case of calcium deficiency	Damage to the kidneys and musculoskeletal system
Fluorine	Caries, periodontal disease. The symptoms get only worse in case of calcium deficiency	Damage to the musculoskeletal system
Iodine	Hypothyroidism, fetus pathologies in the 1st trimester. The symptoms get only worse in case of selenium, cobalt, and calcium deficiency	Hyperthyrosis
Boron	Sex hormones imbalance, susceptibility to pancreatic diabetes, osteoporosis development	Damage to the liver, kidneys, nervous system, and reproductive function
Bromine	Anemia, elevated risks of miscarriage	Damage to the endocrine system, blood-making system, and kidneys
Vanadium	A drop in sugar contents in blood	Damage to the kidneys, liver, and blood-making organs
Nickel	Dermatitis	Damage to the liver, cardiovascular and blood-making systems, gastrointestinal tract
Calcium	Osteoporosis, improper blood coagulability. The symptoms get only worse in case of selenium, silicon, iodine, and fluorine deficiency	Alkalosis, hypercalcinemia

Note: the table is made up basing on data taken from the works [1, 11–13, 16, 18–21, 25–31].

Table 2

Parameters and criteria that characterize health risks caused by essential elements contents in water taken from a «scenario» drinking water source

Elements	Concentration in water, mg/l	Dose equivalent of a concentration, mg/kg/day*	MPC in water, mg/l	C/MPC	Minimal essential daily introduction, mg/kg/day	% of minimal essential daily introduction
Lithium	0.06	0.003	0.03	2	0.0014	214
Boron	0.04	0.002	0.5	0.08	0.0028	71.4
Vanadium **	0.017	0.00085	0.1	0.1	0.00014	164.7
Chromium	0.019	0.000006	0.05	0.38	0.0007	8
Nickel	0.001	0.00003	0.02	0.05	0.0014	46.7
Selenium	0.0039	0.0002	0.01	0.13	0.00042	47.6
Molybdenum	0.005	0.00014	0.07	0.07	0.0007	20

Σ C/MPC = 2.71

Note:

* the value is calculated basing on exposure factors that are conventional for substantiating MPC in water according to MG 2.1.5.720-98 (60 kg body weight, 2 L daily water consumption)[12];

** means the substance belongs to the 3rd hazard category and their concentrations ratio to MPC is not included into the calculation.

Table 3

Properties of essential elements standardized in drinking water as per sanitary-toxicological parameters related to adverse health effects

Elements	MPC, mg/L in water	Minimal essential dose, mg/kg/day [1]	RfD, mg/kg/day [2]	$MPC_{d.w.}$ dose equivalent mg/kg/day
Boron	0.5	0.0024	0.2	0.016
Bromine	0.2	0.0059	1.0	0.0066
Vanadium	0.1	0.00012	0.007	0.0032
Iodine	0.12	0.00059/0.002[3]	0.017	0.004
Cobalt	0.1	0.0004	0.02	0.0032
Lithium	0.03	0.0012	0.02	0.00098
Molybdenum	0.07	0.00059/0.008[3]	0.02	0.0023
Nickel	0.02	0.00112	0.02	0.00066
Selenium	0.01	0.00035/0.002[3]	0.005	0.00032
Fluorine	1.0	0.0178/0.021	0.06	0.032
Chromium	0.05	0.00059/0.0025	0.005	0.0016

Note:

[1]are average data taken from the works[8] [11, 13, 24];

[2]are data taken from Guide 2.1.10.1920-04[13];

[3]means a value is recalculated into doses per 1 kg body weight.

[12] MG 2.1.5.720-98. Substantiation of hygienic standards for chemicals contents in water taken from water objects aimed for communal and drinking water supply: Methodical guidelines. Approved by the RF Chief Sanitary Inspector on October 15, 1998. Sanitary rules and standards and State standards. Reference database. Available at: https://www.snip-info.ru/index.html (06.04.2020) (in Russian).

[13] Guide 2.1.10.1920-04 Guide on assessing population health risks under exposure to chemical that pollute the environment. *KODEKS: an electronic fund for legal and regulatory documents*. Available at: http://docs.cntd.ru/document/1200037399 (06.04.2020) (in Russian).

Table 4

Comparing contributions made by dose equivalents of $MPC_{d.w.}$ and doses consumed with food into reference doses

Elements	$MPC_{d.w.}$ dose equivalent mg/kg/day	Dose consumed with food, mg/kg/day [3]	Reference dose, mg/kg/day	$MPC_{d.w.}$ dose equivalent contribution into RfD, %	Food introduction contribution into RfD, %
Boron	0.016	0.0018	0.2	8	0.9
Vanadium	0.0032	0.0006	0.007	45.7	8.5
Cobalt	0.0032	0.004	0.02	16.5	20
Lithium	0.00098	0.003	0.02	5.0	15
Iodine	0.004	0.003	0.017	23.5	17.9
Molybdenum	0.0023	0.0028	0.02	11.5	14.0
Selenium	0.00032	0.002	0.005	6.4	40
Fluorine	0.032	0.025	0.06	54	41.6
Chromium	0.0016	0.002	0.005	32	40

Table 5

Calculated concentrations that secure a 20 % contribution made by the drinking factor into reference doses and 100 % minimal essential introduction of an essential element

Elements	MPC, mg/L	Calculated MPC that secures 20 % contribution into RfD, mg/L	Calculated MPC that secures 100 % minimal essential dose, mg/L
Boron	0.57	1.4	0.072
Bromine	0.2	0.06	0.2
Vanadium	0.1	0.05	0.0037
Iodine	0.125	0.13	0.02
Cobalt	0.1	0.14	0.0083
Lithium	0.03	0.014	0.041
Molybdenum	0.07	0.14	0.02
Nickel	0.02	0.14	0.041
Selenium	0.01	0.034	0.011
Fluorine	1.0	0.42	0.62
Chromium	0.05	0.032	0.029

It was established that existing MPC of such essential elements as fluorine, chromium, cobalt, boron, vanadium, iodine, molybdenum, and bromine could provide a human body with minimal essential introduction.

In case boron and vanadium are contained in water in concentrations equal to their MPC, their contributions into a reference dose will be higher than 20 % (71.4 % and 164.7 % accordingly). Introduction of these essential elements with food products can be a factor that might determine non-carcinogenic risks.

Calculated $MPC_{d.w}$ for nickel and selenium are more optimal as compared with their existing ones as they not only secure safety but also provide minimal essential introduction of these essential elements.

Both existing and calculated standards for lithium do not provide minimal essential introduction of the elements into a body.

There were calculations performed to assess non-carcinogenic health risks caused by use of the selected «scenario» water source; the results revealed the following (Table 6) [3].

Non-carcinogenic risks regarding renal pathology occurrence were assessed as acceptable and amounted to 0.8925 [31]. However, quality of water taken from the examined

Table 6

Parameters and criteria that characterize health risks caused by element structure of water taken from the «scenario» drinking water source

Elements	Concentration, mg/L	Dose equivalent for concentration, mg/kg/day	HQ	Minimal essential daily introduction, mg/kg/day	% to which detected concentration provides minimal essential daily introduction	C/MPC
Lithium	0.06	0.017	0.85	0.0014	80	2
Boron	0.04	0.001	0.005	0.0028	35.7	0.2
Vnadium [x]	0.017	0.0005	0.07	0.00014	350	0.085
Chromium [x]	0.00019	0.0006	0.001	0.0007	7.8	0.0038
Nickel [x]	0.001	0.003	0.0015	0.0014	2.14	0.05
Selenium	0.0039	0.0001	0.028	0.00042	25	0.13
Molybdenum	0.005	0.00014	0.007	0.0007	20	0.25
			HI=0.8925			Σ C/MPC = 2.74

Note:

[x] means a substance belongs to the 3rd hazard category and their concentrations ratio to MPC is not included into the calculation.

water source can't be seen as acceptable for health as per chromium and nickel concentrations as dose equivalents of these elements concentrations are significantly lower than deficient ones and amount to 0.0006 mg/kg/day for chromium and 0.003 mg/kg/day for nickel whereas a deficient dose for both elements amounts to 0.028 mg/kg/day.

This fact should be taken into account when social and hygienic monitoring is performed; great attention should be paid to pathologies caused by relevant elements being in shortage (reproductive function disorder in men and tolerance to dextrose in people with the drinking factor being predominant for them among other ones influencing prevalence of analogue disorders in a body).

Parallel calculations performed as per the conventional procedure for estimating total effects produced by substances standardized as per sanitary-toxicological parameters related to adverse health effects[8,9] indicate that an acceptable hygienic standard for all the substances that occur in the examined water source is violated as the total sum of all the detected concentrations to their MPC ratios amounts to 2.74.

It doesn't seem sufficient to look for a solution to an issue related to essential elements shortage primarily within nutrition hygiene frameworks as it belittles a role played by the drinking factor in providing a body with them. Nutrition hygiene practically neglects the fact that water is always used in food processing and cooking with consumed volumes varying from 1,000 to 4,000 liters per one ton of food products, and up to 23 % essential elements contained in food products are lost due to thermal treatment [22, 31]. Given that, the WHO recommendation to increase a contribution made by the drinking factor into reference doses from 10 % to 20 % is quite well-timed. A way to resolve the issue may be found in wider use of drinking water sources with water containing essential elements in quantities sufficient to cover any deficiency in their essential consumption [24–31].

Conclusions:

1. In case fluorine, chromium, cobalt, boron, vanadium, iodine, molybdenum, and bromine are contained in water taken from a drinking water source in concentrations being equal to their existing MPC in water, it pro-

vides their minimal essential introduction into a human body.

2. When assessing water sources that contain nickel and selenium, it is advisable to apply calculated MPC that provide their minimal essential introduction into a human body whereas existing MPC for these elements can't secure this effect.

3. When selecting a drinking water source, it seems advisable to give preference to those with natural contents of essential elements providing their minimal essential introduction into a human body that corresponds to its physiological needs.

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Research article

DEVELOPING METHODICAL APPROACHES TO SUBSTANTIATING AVERAGE ANNUAL MAXIMUM PERMISSIBLE CONCENTRATIONS OF HAZARDOUS SUBSTANCES IN AMBIENT AIR IN SETTLEMENTS AS PER ACCEPTABLE HEALTH RISK

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A methodological basis for providing chemical safety for population is obtained via fixing safe concentrations of hazardous substances, including those in ambient air, as it allows absence of unacceptable risks for people's life and health. In the Russian Federation average daily maximum permissible concentrations (MPC av.d.) are applied to prevent chronic effects on human health produced by hazardous substances that are present in ambient air. But in world practice it is conventional to apply average annual concentrations when assessing chronic exposure to hazardous substances as it allows applying existing acceptable health risks as assessment criteria. We propose an algorithm for substantiating average annual MPC of chemicals in ambient air as per health risks criteria; the algorithm is harmonized with international approaches and takes into accounts research results taken from previous research works that have been published in relevant scientific sources. The algorithm also involves accomplishing toxicological and/or epidemiologic examinations solely aimed at obtaining missing data. The proposed algorithm envisages selecting starting points for substantiating a hygienic standard and uncertainty factors. Proposed methodical approaches have a distinctive feature that is verification of obtained standards as per acceptable (permissible) carcinogenic risk criteria and assessment of safety under exposure equal to MPC av.an. during the whole life span. Development and implementation of average annual maximum permissible concentrations of hazardous substances in ambient air will promote harmonization of the domestic regulatory base with hygienic standards and norms accepted in world practice.

Key words: *ambient air, average annual MPC, health risk, permissible risk, uncertainty factors.*

Providing sanitary-epidemiologic well-being of the population is a basic condition for fulfilling citizens' constitutional rights to health protection and favorable environment[1, 2, 3]. Given that, it is important to eliminate ambient air contamination as a most significant ecological risk for human health; the necessity to do it is fixed within basic programs developed for achieving goals stated by the WHO agenda in the sustainable development sphere over a period up to 2030 [1, 2].

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Significance of the issue in the Russian Federation is also confirmed by the RF President Order issued on May 07, 2018 No. 204 «On national goals and strategic tasks in the Russian Federation development for a period up to 2024»[4], in particular, as implementation of «Clean air» Federal project which is a part of «Ecology» National project.

A methodological basis for providing chemical safety for the population is research on hygienic standardization that involves fixing such safe concentrations of hazardous substances including those occurring in ambient air that secure absence of unacceptable risks for people's life and health [3–6].

In the Russian Federation hygienic standards calculated as average daily ones (MPC average daily) are applied to prevent chronic effects produced on human health under exposure to chemicals contained in ambient air. These standards are fixed according to hygienic standardization principles basing on a document entitled «The temporary methodical guidelines for substantiating maximum permissible concentrations (MPC) of contaminants in ambient air in settlements»[5]; they are established as adverse chemicals concentrations in ambient air in settlements that should not exert direct or indirect impacts on people under unlimited long-term inhalation (years).

But still in world practice average daily values are used to prevent consequences caused by exposure to chemicals within 24 hours after an incident that can become apparent within a 2-week period, not longer. They are substantiated and accepted from this point of view by all experts and decision-makers in the sphere related to regulating health risks caused by ambient air contamination [7]. When chronic exposure to adverse substances is assessed, average annual concentrations are usually applied. According to data provided by the WHO, an interest in average annual parameters calculation is related to an opportunity to determine whether programs aimed at eliminating ambient air contamination are efficient and (or) to obtain criteria showing the environment deterioration caused by industrial development and increase in overall well-being[6].

In the European Union air quality standardization is performed via fixing quality standards based on certain limits or target values that are usually fixed at such levels that prevent or reduce hazardous impacts on human health and/or the environment; these levels should be reached anywhere where it is possible during a certain period of time[7]. Target values serve as a criterion for assessing to what extent proper quality of environmental objects has been achieved [8]. And ambient air quality standards can be considered analogues to Russian MPC as per their principles and ways to substantiate them. Standards are averaged according to their average annual values for most substances, and as for $PM_{2.5}$ particulate matter the averaging period is as long as 3 years [9].

The US Environmental Protection Agency determines and fixes National Ambient Air Quality Standards (NAAQS) according to The Clean Air Act. These standards provide public health protection, including that pro-

[4] On national goals and strategic tasks in the Russian Federation development for a period up to 2024: The RF President Order issued on May 07, 2018 No. 204. Available at: http://kremlin.ru/acts/bank/43027 (25.06.2020) (in Russian).

[5] The temporary methodical guidelines for substantiating maximum permissible concentrations (MPC) of contaminants in ambient air in settlements. Approved by the Deputy to the RF Chief Sanitary Inspector on July 15, 1988 No. 4681-88. Moscow, 1989, 110 p. (in Russian).

[6] WHO Air Quality Guidelines. *The World Health Organization*, 1980. Available at: https://apps.who.int/iris/bitstream/handle/10665/276929/9290202017-rus.pdf.pdf?sequence=5&isAllowed=y (25.06.2020).

[7] Directive 2008/50/EC of the European Parliament and of the Council of 21 May 2008 on ambient air quality and cleaner air for Europe. *EUR Lex*. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32008L0050 (08.07.2020).

vided for the most sensitive population groups, as well as public well-being protection including that provided for animals, agricultural plants, flora, and buildings [10]. Chronic effects are taken into account due to these standards with averaging periods equal to 1 year.

Apart from national ambient air quality standards fixed in foreign countries (Canada, the USA), and international organizations (the WHO, EU Commission, the Organization on economic cooperation and development, etc.), there are reference exposure doses differentiated depending on exposure duration and severity of probable changes in health of sensitive population groups [11].

The US Environmental Protection Agency (US EPA) fixes reference concentrations (RfC) that are used to assess risks including those occurring under chronic inhalation exposure to adverse chemicals. It is assumed that daily introduction of a chemical in a concentration equal to RfC during the whole life span that is established taking into account all the latest available scientific data probably does not result in unacceptable health risks for sensitive population groups[8] [12].

The Agency on Toxic Substances and Diseases Registration (ATSDR) also fixes reference values for chemicals concentrations in ambient air that are called minimum risk levels (MRL). They are such chemicals concentrations that will probably not result in unacceptable risks of unfavorable effects on health under everyday exposure [13]. A period of chronic exposure is usually 365 days or longer, that is, an averaging period is 1 year.

These parameters allow assessing exposure to chemicals accoridng to principles fixed in risk assessment mehtodology that is an up-to-date set of instruments necessary to assess and predict negative changes in health on individual and population levels as well as to establish basic hazard factors, to select priority measures aimed at preventing health disorders, and to create conditions necessary for preserving population health [14–17].

Despite the use of this methodology is fixed in the RF sanitary legislation, the regulatory base is not sufficient for its wide implementation into everyday practice. Among other things, there are no annual average hygienic standards, and acceptable risks for people's life or health are not fixed as criteria for estimating whether environmental factors are safe or not [14]. These aspects are extremely important as risk criteria inclusion into a system for hygienic standardization is a strategic issue since it allows preventing adverse effects occurrence under exposure to chemical contamination during the whole life span.

Therefore, foreign norms and standards of ambient air quality are oriented at using average annual period for averaging and it allows preventing chronic negative effects on health during the whole life span more efficiently. Given that, it is advisable to supplement a list of hygienic standards for ambient air quality with average annual MPC substantiated as per criteria of permissible (acceptable) health risks. It will allow achieving greater harmonization of the RF legislative base with its foreign analogues and applying average annual MPC as criteria for health risk assessment under chronic inhalation exposure.

Our research goal was to develop methodic approaches to fixing average annual MPC of adverse substances in ambient air as per health risk criteria.

Tasks.

1. To analyze domestic and foreign methodical approaches to developing norms and standards for ambient air quality.

[8] G 2.1.10.1920-04. Guide on assessing population health risks under exposure to chemicals that pollute the environment. Moscow, The Federal Center for State Sanitary and Epidemiologic Surveillance of the RF Public Healthcare Ministry, 2004, 143 p. (in Russian).

2. To develop a harmonyzed algorithm for fixing average annual MPC of adverse substances in ambient air as per criteria of permissible (acceptable) health risk.

3. To update methodical approaches to determining and selecting points of departure and establishing uncertainty factors for substantiating average annual hygienic standards.

4. To work out methodical approaches to verifying average annual MPC of adverse substances in ambient air using health risk criteria.

Data and methods. The research was accomplished basing on results obtained via analysis, synthesis, comparison, and generalization of approaches to fixing norms and standards for ambient air quality that exist in the RF regulatory and methodical documents as well as in foreign ones.

Domestic approaches to fixing MPC of adverse substances in ambient air were identified basing on «The temporary methodical guidelines for substantiating maximum permissible concentrations (MPC) of contaminants in ambient air in settlements No. 4681-88 issued on July 15, 1988» and principles stated within the hygienic standardization paradigm.

To analyze foreign methodical approaches to fixing standards for ambient air quality, we took regulatory documents issued by the World Health Organization (WHO), European Union (EU), US Environmental Protection Agency (US EPA), and US Agency on Toxic Substances and Diseases Registration (ATSDR). Given that there was a task in the research to establish approaches that allowed fixing hygienic standards with the use of permissible risk criteria, we also took into account the existing procedures for substantiating reference concentrations (RfC) in case of inhalation introduction.

Uncertainty factors for calculating average annual MPC were established according to the documents issued within the WHO International Program on Chemical Safety (IPCS) [18–20].

Average annual MPC of chemicals in ambient air were verified as per carcinogenic and non-carcinogenic risk criteria according to the Guide R 2.1.10.1920-04 «Guide on assessing health risks under exposure to chemicals that pollute the environment»[8]; verification via a procedure for health risk prediction with the use of evolution models was accomplished according to the Methodical guidelines «Quantitative assessment of non-carcinogenic risks under exposure to chemicals basing on evolution models creation»[9].

Results and discussion. Having analyzed domestic methodical approaches to development of hygienic standards for adverse chemicals contents in ambient air within an averaging period, we established that average daily maximum permissible concentrations ($MPC_{av.d.}$) were, as a rule, substantiated basing on maximum non-effective concentrations taking into account general toxic effects and specific ones obtained via a chronic toxicological experiment. A transfer from a threshold value to a calculated non-effective concentration was assumed to be performed with an assurance factor; this factor allowed taking into account a few uncertainties related to conditions and factors that could influence precision of threshold values substantiated in an experiment as well as extrapolation of data obtained for a limited number of experimental animals onto population[5].

MPC were experimentally substantiated during a long period of time and it was efficient when it came to standards for short-term and daily exposure periods; however, the process is labor- and time-consuming and rather expensive. A procedure for establish-

[9] Quantitative assessment of non-carcinogenic risks under exposure to chemicals basing on evolution models creation: Methodical guidelines. Moscow, Rospotrebnadzor's federal Center for Hygiene and Epidemiology Publ., 2012, 36 p. (in Russian).

ing reference concentrations (RfC) [21, 22] involves determining NOAEL/LOAEL for adverse effects in accordance with exposure levels established via toxicological experiments or epidemiologic studies. Therefore, RfC is a value based on $NOAEL_{[HEC]}$ for a critical effect using uncertainty factors (UFs) [23]. When it comes to the necessity to substantiate hygienic standards for adverse chemicals contents in ambient air as per health risk criteria, it is advisable to harmonize the existing approaches with those applied for establishing risk assessment parameters, including results obtained in previous research works [24, 25].

Overall, analysis of methodical approaches to establishing safety criteria within hygienic standardization and safety in health risk assessment revealed that they all were quite similar and involved using threshold, non-effective, or reference exposure levels with adjustment via use of assurance factors in hygienic standardization and uncertainty factors in health risk assessment.

Basing on the results obtained via analyzing domestic and foreign methodical approaches to fixing hygienic standards for chemicals contents in ambient air, we proposed an algorithm for substantiating average annual MPC of chemicals in ambient air as per health risk criteria (Figure 1); the algorithm included the following stages as its key elements:

1. Establishing points of departure;
2. Establishing uncertainty factors;
3. Substantiating and verifying MPC.

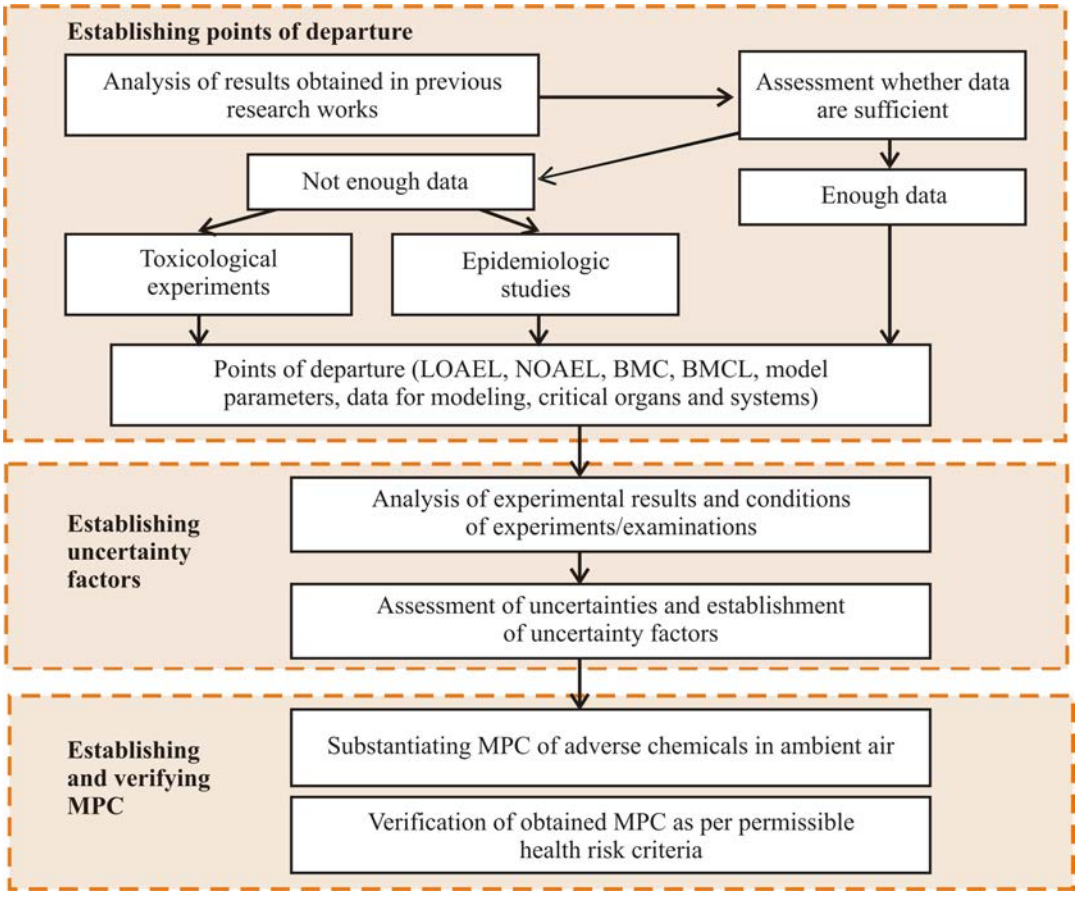

Figure 1. Algorithm for substantiating average annual MPC of chemicals in ambient air as per health risk criteria

The 1st stage in the algorithm involves establishing points of departure that are exposure levels proposed to be used as initial ones for substantiating average annual maximum permissible concentrations of adverse chemicals.

To establish points of departure (POD), it is necessary to analyze data obtained in previous research works and published in available literature in order to assess whether they are sufficient. Preference is to be given to data contained in domestic and foreign reviewed scientific editions and databases, for example, ATSDR Toxicological Profiles, IRIS (Integrated Risk Information System), HSDB (Hazardous Substances Data Bank), IPCS-INCHEM, National Toxicology Program, IARC databases, etc.

When data obtained in previous research works are being analyzed, it is necessary to perform qualitative assessment of selected relevant research works.

Essential data from each toxicological and epidemiologic research work that was selected as per results of qualitative assessment are generalized in a unified toxicity profile; this profile is to be quantitatively assessed. The assessment involves analyzing quantitative data in previously selected key research works in order to determine whether it is possible to select certain values that can be used as points of departure for substantiating MPC and model parameters for «exposure – effect (response)» dependence. All the above mentioned is necessary for establishing maximum exposure levels that secure absence of unacceptable health risks.

Analysis of quantitative data obtained via toxicological and epidemiological research can yield three types of initial data: points of departure that can be used for calculating MPC (NOAEL (non-effective level), LOAEL (threshold level), BMC/BMCL); models for relationship between changes in probability of gravity of a negative response and exposure level; as well as data that can be used for building up models.

It is advisable to use research results that allow quantitative assessment of impacts exerted by adverse chemicals on health as criteria showing whether there are sufficient data for establishing average annual MPC basing on them. They can be data on negative responses probability under different exposure levels; data on threshold, non-effective, or reference exposure levels for different types of responses.

Should the analysis of results obtained in previous research works reveal that available data are not sufficient, than, according to the proposed algorithm, there is a necessity to accomplish experimental toxicological and/or epidemiologic studies in order to establish the missing parameters. Such studies are accomplished according to conventional procedures; however, their results are interpreted in such a way so that they become applicable in risk assessment. Thus, results obtained via toxicological experiments allow detecting points of departure (NOAEL/LOAEL), determining critical organs and systems, and establishing parameters for models that characterize «exposure – effect (response)» dependence. Results obtained via epidemiologic studies allow calculating points of departure (BMC/BMCL), determining critical organs and systems, and establishing parameters for models that characterize «exposure – effect» dependence.

Therefore, the 1st stage in the algorithm involves selecting points of departure for substantiating average annual standards for adverse chemicals contents in ambient air. Should there be data on several points of departure then preference is to be given to those that in future will demand the least adjustment with uncertainty factors. In case there are points of departure that characterize different types of critical effects (responses), it is advisable to use a principle of a limiting hazard parameter, that is, the lowest exposure level is to be taken as a point of departure as it secures safety regarding all types of negative impacts exerted by toxicants.

After all the points of departure have been selected, the next stage in the algorithm for fixing average annual MPC of chemicals in ambient air as per health risk criteria involves establishing uncertainty factors values. To do that, it is necessary to analyze results and conditions of toxicological experiments and/or epidemiologic studies that allowed establishing these uncertainty factors. The analysis results in establishing their values (from 1 to 10). After all the points of departure and relevant uncertainty factors have been established, it is possible to calculate and verify average annual MPC values.

To establish average annual MPC of adverse chemicals in ambient air as per non-carcinogenic risk criteria, the following formula (1) is to be applied:

$$MPC_{av.an.}^{non-carc} = POD / \prod UF \qquad (1)$$

where $MPC_{av.an.}$ is an average annual maximum permissible concentration of an adverse chemical in ambient air; *POD* is a point-of-departure value (concentration), mg/m^3; *UF* is uncertainty factor value.

To establish average annual MPC of adverse chemicals in ambient air for chemicals that produce carcinogenic effects, the following formula (2) is to be applied as it allows calculating such a concentration of a chemical in ambient air that secures acceptable carcinogenic risk level which is equal to $1 \cdot 10^{-4}$ ($CR_{acc.}$):

$$MPC_{av.an.}^{carc} = \frac{(CR_{np})}{(UR)} \qquad (2)$$

where UR is a unit risk, (mg/m^3)$^{-1}$ (is calculated according to the Guide R 2.1.10.1920-04)[8].

Acceptable carcinogenic risk value $1 \cdot 10^{-4}$ is used as a safety criterion since it is this level that is used in most hygienic standards for ambient air quality that are valid in foreign countries or recommended by international organizations. Uncertainty factors for establishing MPC of adverse chemicals in ambient air are not applied when they are established as per carcinogenic health risk criterion as in this case such factors are taken into account when carcinogenic potential is determined.

A minimum concentrations consisting of $MPC_{av.an.}^{carc}$ and $MPC_{av.an.}^{non-carc}$ is recommended as average annual MPC.

The next stage involves verifying obtained average annual MPC as per health risk criteria. Risks of non-carcinogenic effects are assessed basing on hazard quotients (HQ) calculation where HQ ≤ 1 value means risk is acceptable.

It is also necessary to assess whether health risks occurring under exposure to chemicals in concentrations not higher than average annual MPC during the whole life span are acceptable. To do that, it is advisable to apply health risk prediction using evolution models. A criterion that indicates risk is acceptable under life-long exposure to MPC being considered is a value of reduced risk index at the moment which is equal to life expectancy. This value should not exceed 0.05 as it means that risks are negligible.

The proposed algorithm was tested in a practical situation for establishing average annual MPC of manganese and nickel which were harmonized with international standards [26, 27]. When those standards were being substantiated, all the published data on effects produced by these metals were analyzed; apart from that, reference exposure levels were determined basing on the results obtained in epidemiologic studies, and relevant uncertainty factors were substantiated as well. Obtained average annual MPC were verified as per carcinogenic risk criteria using evolution models.

Conclusions. Safety (absence of unacceptable risks for people's life and health) under chronic exposure to contaminants in ambient air can be provided via developing and

conforming to average annual hygienic standards substantiated as per acceptable health risk criteria.

The proposed algorithm for substantiating average annual MPC of chemicals in ambient air as per health risk criteria is to a great extent harmonized with world practice for establishing not only hygienic standards but also reference levels of inhalation exposure to chemicals.

When substantiating average annual hygienic standards for adverse chemicals contents in ambient air it is advisable to use results obtained in previous research works published in relevant scientific literature and accomplish toxicological and/or epidemiologic studies with the only goal being to obtain missing data.

A distinctive feature of the proposed methodical approaches is that obtained standards are verified as per carcinogenic risk criterion and safety is assessed under exposure equal to $MPC_{av.an.}$ with its duration equal to the whole life span.

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Research article

PRIORITY RISK FACTORS RELATED TO DRINKING WATER FROM CENTRALIZED WATER SUPPLY SYSTEM THAT CREATE NEGATIVE TRENDS IN POPULATION HEALTH

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Our research object was long-term dynamics of parameters describing drinking water from centralized water supply systems and additional cases of health disorders among population in Russia directly caused by low-quality drinking water.

Our research goal was to perform hygienic assessment of priority risk factors related to drinking water and potential health disorders that could be caused by them.

Our research technique was hygienic analysis of drinking water parameters as per data taken from the federal statistical form No. 18 entitled «Data on sanitary situation in a RF region» over 2000–2019, the federal information fund of social and hygienic monitoring over 2012–2019, and calculation of associated health disorders as per MG 5.1.0095–14.

Specific weight of centralized water supply sources that didn't conform to sanitary-epidemiologic requirements decreased by 4.7 % over 2000–2019 and amounted to 14.9 %. Over the last 20 years there has been a descending trend in specific weight of water samples taken from centralized water supply sources that don't conform to sanitary requirements as per sanitary-chemical parameters (by 2.7 %) and microbiological parameters (by 4.8 %). Over 2000–2019, specific weight of water distribution networks not conforming to sanitary-epidemiologic requirements decreased by 10.7 % and amounted to 15.9 % in 2019.

Over the last 20 years there has been an increase in quality of drinking water taken from centralized distribution networks. Specific weight of water samples from centralized distribution networks not conforming to sanitary requirements as per microbiological and sanitary-chemical parameters fell by 6.7 % and 7.9 % respectively.

In 2012–2019 in the RF hygienic parameters of drinking water quality were the most violated as per contents of bromine, silicon, chlorine, iron, sodium, lithium, magnesium, manganese, chloroform, boron, strontium, sulfides, and hydrogen sulphide.

Overall, in the RF in 2019 more than 1.66 million cases of digestive diseases, cardiovascular diseases, diseases of skin and subcutaneous tissue, and other health disorders were directly related to drinking water being contaminated with chemicals and microbiological agents; it was by 13.3 % lower than in 2012 regarding morbidity associated with drinking water quality. Priority risk factors were chlorine, chlorine organic compounds (COC), ammonia, iron, manganese, arsenic, nickel, copper, boron, magnesium, and other compounds.

Key words: *drinking water, hygienic standards, health risk, associated morbidity, «Pure water» federal project.*

Availability of qualitative and safe drinking water is a basic human right. Drinking water is most significant for human health and it determines life quality and overall health of any nation [1]. Experts from the World Health Organization (WHO) note that a lot of diseases can be prevented by safe water supply systems and strict adherence to hy-

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gienic requirements when it comes to drinking water supply. Only diarrhea diseases account for approximately 3.6 % of the global diseases burden and they annually result in 1.5 million death cases all over the world. Approximately 58 % out of them (842 thousand deaths per year including 361 thousand children younger than 5) are caused by safe water supply, hygiene, and sanitary not being available to people [2].

Water quality can also deteriorate due to infectious and parasitic agents, toxic chemicals, and other risk factors [3]. According to data provided by the WHO, in 2017 three out of each ten people all over the world were not provided with safe and easily available water supply at a place where they lived [4]. According to data provided by the UN, more than 2 billion people in the world do not have access to Clean drinking water, and more than 800 million people spend not less than 30 minutes every day on obtaining water or don't have any access to it at all [5].

Despite an increase in a share of RF population provided with safe drinking water in 2018 almost 10 % of the country population was not provided with qualitative drinking water from centralized water supply systems[1]. Given that, a vital task set by the state authorities is to increase quality of drinking water supplied to the population in the RF.

«Clean water» Federal project envisages finding solutions to issues related to raising drinking water quality via modernizing water supply and treatment systems with the use of the most advanced technologies [6]. The Federal Service for Surveillance over Consumer Rights Protection and Human Well-being as well as other participants in «Clean water» Federal project have to tackle ambitious tasks: in 6 years time the project implementation should result in more than 90 % of the RF population being provided with qualitative drinking water; the parameter should be equal to approximately 99 % in urban settlements.

Risk assessment and management procedures are the most efficient tool for providing persistent safety of drinking water supply systems as they cover all the stages in water supply starting from water intake and up to water consumption [7–32].

Our research goal was to reveal and hygienically assess priority risk factors related to dirking water and potential health disorders among the RF population caused by them.

Data and methods. We performed hygienic analysis of drinking water from centralized water supply systems as per data taken from the Federal Statistic Report Form No. 18 entitled «Data on sanitary situation in a RF region» issued in 2000–2019 and data provided by the Federal information fund of social and hygienic monitoring (FIF SHM) over 2012–2019[2].

Provision of the overall RF population as well as urban population specifically with qualitative drinking water was assessed according to the methodical guidelines MR 2.1.4.0143-19[3].

Statistic data on population morbidity in the RF in 2012–2019 were provided by the RF Public Healthcare Ministry and applied as a source of data on population health in the country[4].

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Table 1

The top 10 RF regions and the worst 10 ones as per a share (%) of population provided with qualitative drinking water from centralized drinking water supply systems in 2019

No.	RF region	A share (%) of population			No.	RF region	A share (%) of population		
		planned	actual	difference			planned	actual	difference
The top 10					The worst 10				
1	Saint Petersburg	–	100.0	–	76	Karachai-Cherkess	66.3	61.5	-4.8
2	Moscow City	–	99.6	–	77	Smolensk region	63.1	60.2	-2.9
3	Murmansk region	99.7	99.4	-0.3	78	The Jewish Autonomous Area	61.3	59.9	-1.4
4	Kamchatka	98.5	98.8	0.3	79	Yakutia	59.8	54.0	-5.8
5	Kemerovo region	98.3	98.3	0.0	80	The Nenets Autonomous Area	51.4	53.6	2.2
6	Sevastopol	97.6	97.5	-0.1	81	Vologda region	43.6	51.6	8.0
7	Kursk region	93,6	95,9	2,3	82	Buryatia	44,1	46,5	2,4
8	Stavropol region	98,5	95,3	-3,2	83	Transbaikalia region	51,1	45,2	-5,9
9	Magadan region	98,5	95,3	-3,2	84	Tyva Republic	24,5	24,7	0,2
10	Krasnodar region	94,5	94,5	0,0	85	Kalmyk Republic	72,6	7,4	-65,2

We assessed a number of health disorders related to drinking water quality and revealed priority risk factors that caused them for the Russian Federation as a whole and RF subjects in particular according to Appendix 2 to the methodical guidelines MR[5].

Results and discussion. We assessed whether target figures fixed in «Clean water» Federal project had been achieved; the assessment revealed that in 2019 an actual share of the RF population provided with qualitative drinking water from centralized drinking water supply systems amounted to 85.5 % and it was lower than the target figure for the year (87.5 %)[6].

Having analyzed data as per RF regions, we established that the target figure for 2019 fixed in «Clean water» Federal project hadn't been reached in 39 regions. The lowest values of the parameter were detected in Kalmyk Republic (7.4 %), Tyva Republic (24.7 %), Transbaikalia region (45.2 %), and Buryatia (46.5 %) (Table 1).

Other target declared within «Clean water» Federal project for 2019 (94.5 % of urban population in the RF should be provided with qualitative drinking water from centralized drinking water supply systems) wasn't reached either. The overall value in the country amounted to 93.2 % and it was by 1.3 % lower than declared in the project. In 2019 the highest shares of urban population provided with qualitative drinking water from centralized drinking water supply systems were detected in Saint-Petersburg (100 %), Kabardino-Balkaria (100 %), Kamchatka (99.9 %), Murmansk region (99.7 %), and Moscow city (99.6 %).

Analysis of data collected over 2000–2019 revealed that overall number of water sources used for centralized drinking water supply went down by more than 10.7 thousand (Figure 1). A share of underground water sources remained steady and was equal to approximately 98 % (Figure 2).

Over the last 20 years a specific share of water sources that did not conform to sanitary-epidemiologic requirements decreased by 5 %. In 2019 14.9 % water sources did not conform to sanitary requirements, 35.1 % of them being surface ones.

[5] MR 5.1.0095-14 Calculation of actual economic losses and losses prevented due to control and surveillance activities regarding losses caused by population mortality, morbidity, and disability caused by negative effects produced by environmental factors. Approved by A.Yu. Popova, the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Well-being, the RF Chief Sanitary Inspector on October 23, 2014. *KODEKS: an electronic fund for legal and reference documentation*. Available at: http://docs.cntd.ru/document/1200129398 (03.08. 2020) (in Russian).

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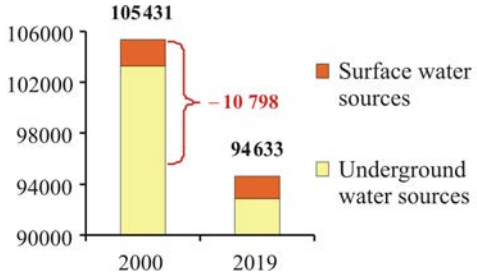

Figure 1. Quantity of surface and underground drinking water supply sources

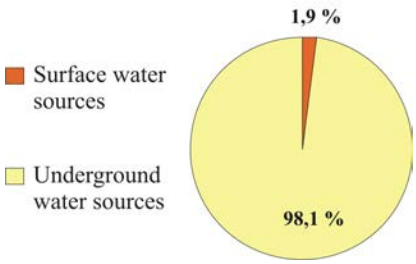

Figure 2. Shares of surface and underground drinking water supply sources, 2019 (%)

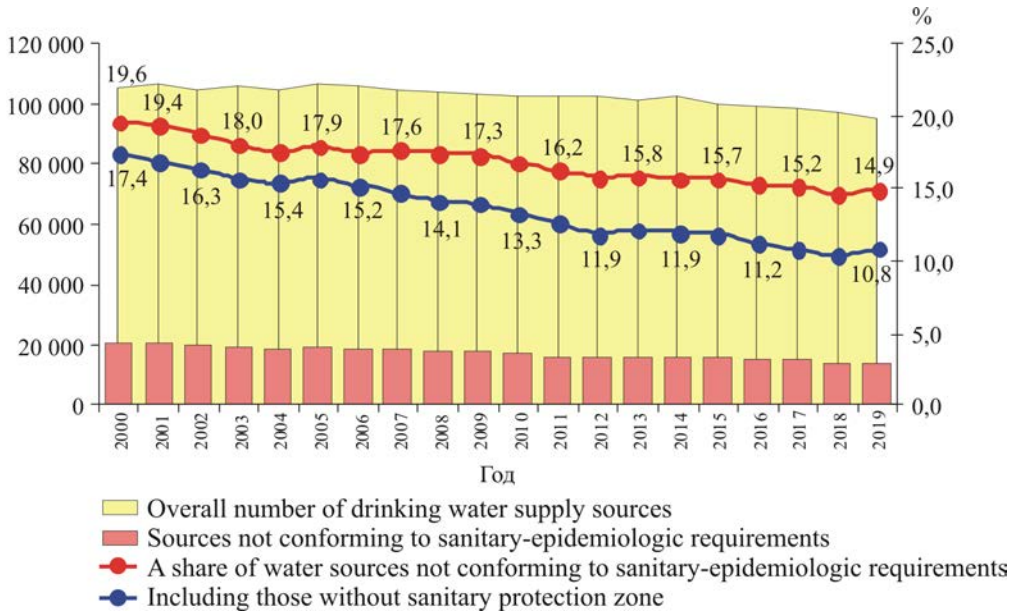

Figure 3. A specific weight of drinking water supply sources that do not conform to sanitary-epidemiologic requirements (%)

Absence of sanitary protection zones remains the priority reason for drinking water supply sources not conforming to sanitary-epidemiologic requirements. Despite a number of sources used for centralized drinking water supply that didn't have any sanitary protection zone went down by more than 44 % over the last 20 years (Figure 3), at present approximately 10.2 thousand water sources still don't have it. It is a significant risk factor that can produce negative effects on quality of drinking water taken from centralized water supply systems.

Better organization of sanitary protection zones around sources used for centralized drinking water supply and an increase in number of water sources conforming to sanitary requirements resulted in better quality of water taken from those sources.

Over 2000–2019 there was a 5 % decrease in a share of water samples taken from centralized drinking water supply systems that did not conform to hygienic standards as per microbiological parameters (the figure went down to 4.1 % un 2019). But still, quality of water measured as per sanitary-chemical parameters remains stable as approximately 25–28 % water samples taken over the last 20 years from both surface and underground water sources do not conform to hygienic standards.

Quality of drinking water supplied to consumers via centralized water supply systems is determined not only by quality of water sources but that of supply networks as well. Number of supply networks operated in the Russian Federation increased over the last 20 years and amounted to more than 63.5 thou-

sand in 2019. In 2019 more than 10.0 thousand supply networks (15.8 %) that supplied water from both surface and underground water sources did not conform to sanitary-epidemiologic requirements including more than 5.0 thousand (7.9 %) due to absence of necessary treatment facilities and more than 1.6 thousand (2.7 %) due to absence of disinfection equipment (Figure 4).

In 2000–2019 regional programs on building and reconstructing (modernizing) water supply networks including those developed within «Clean water» Federal project were implemented and it allowed reducing a share of water supply networks not conforming to sanitary-epidemiologic requirements by 10.7 %.

A growth in number of water supply networks that conformed to sanitary requirements allowed improving drinking water quality before it was supplied into distribution networks. Over the last 20 years a share of water samples taken from water supply networks that deviated from sanitary requirements decreased by 6.9 % for microbiological parameters and by 4.8 % for sanitary-chemical ones.

Improvements in quality of drinking water from supply networks influences quality of water in distribution networks. Analysis revealed that over the last 20 years a specific weight of water samples taken from distribution networks that didn't conform to sanitary requirements as per sanitary-chemical parameters decreased by 7.9 %, and as per microbiological ones, by 6.7 % (2.7 % in 2019) (Figure 5).

In 2019 a high share (more than 20 % drinking water samples with chemicals contents being higher than MPC) of drinking water samples taken from distribution networks that deviated from sanitary requirements as per sanitary-epidemiologic parameters was detected in 22 RF regions; and as per microbiological parameters, in 17 regions (more than 5 % drinking water samples with microbiological contents exceeding MPC). A share of samples taken from water distribution networks that deviated from sanitary requirements as per sanitary-chemical parameters was higher than average country level in 49 RF regions, and as per microbiological parameters, in 41 RF regions.

The lowest quality of drinking water as per microbiological parameters was detected in 2019 in Karachai-Cherkess Republic (24.6 % samples deviating from hygienic standards), Ingushetia (20.7 % samples), and Chechnya (14.0 % samples); as per sanitary-chemical parameters, in Kalmyk Republic (58.3 % with chemicals contents exceeding MPC), Karelia (43.1 %), Kostroma region (38.0 %), Chukotka (36.0 %), and Kurgan region (35.2 %).

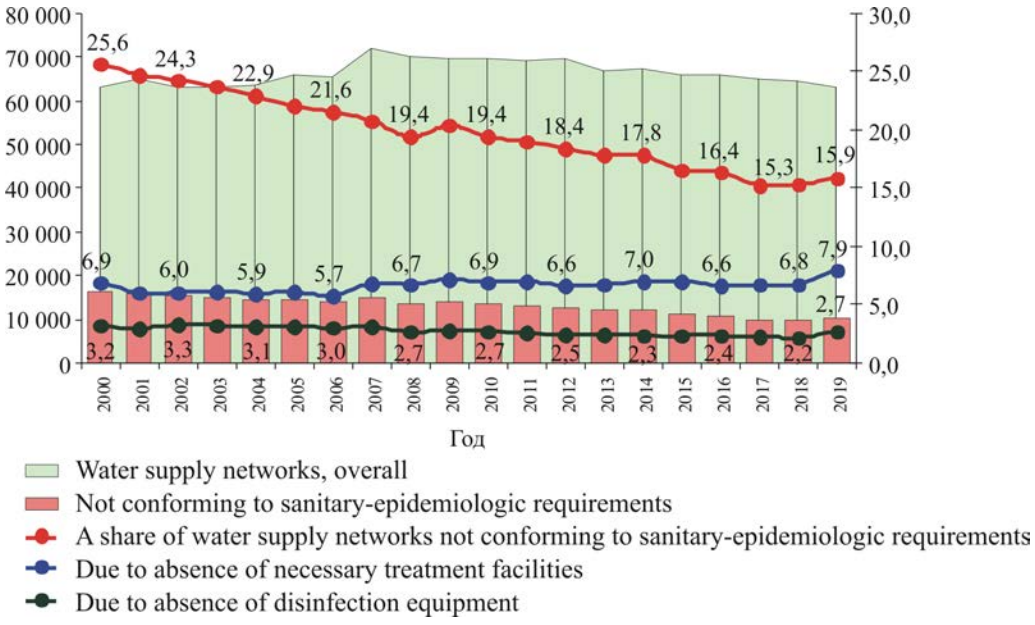

Figure 4. A specific weight of water supply networks no conforming to sanitary-epidemiologic requirements (%)

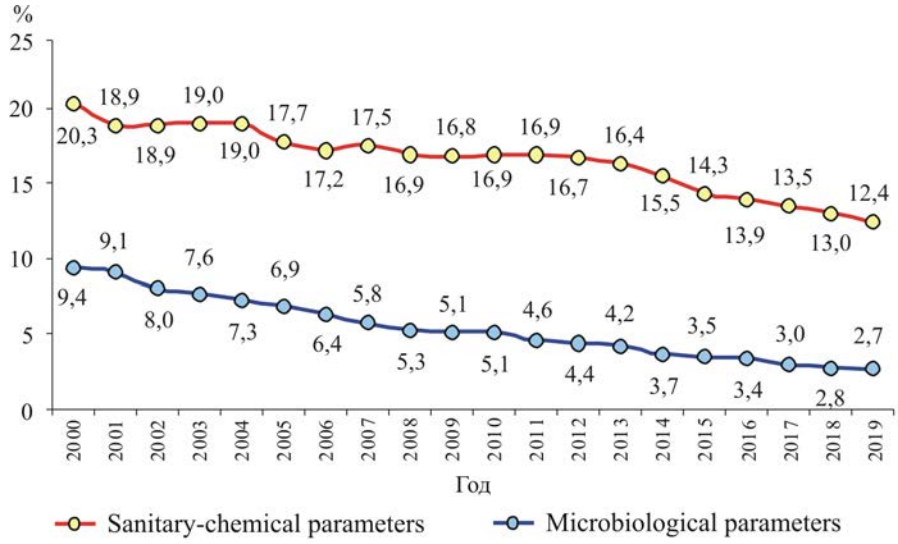

Figure 5. A specific weight of water samples from distribution networks not conforming to sanitary-epidemiologic requirements (%)

Table 2

Priority chemicals influencing quality of drinking water taken from centralized drinking water supply systems

Chemical	A share of samples with contents higher than MPC								Changes in the parameter over 2012–2019, %
	2012	2013	2014	2015	2016	2017	2018	2019	
Bromine	8.87	61.02	43.94	20.0	60.0	50.0	75.0	100.0	+91.1↑
Silicon (as per Si)	4.09	6.21	20.54	24.86	22.92	22.72	20.99	18.9	+14.8↑
Chlorine	39.05	32.99	0.02	0.62	0.37	3.28	13.48	14.66	–24.4↓
Iron (as per Fe)	21.25	16.53	15.13	14.26	12.31	11.21	13.14	13.47	–7.78↓
Sodium	21.39	12.76	13.86	14.95	11.88	11.61	12.04	12.81	–8.58↓
Lithium	35.89	28.35	38.1	17.75	14.91	21.07	17.46	11.69	–24.2↓
Magnesium	11.75	8.34	7.35	8.7	8.06	7.72	10.15	9.81	–1.94↓
Manganese	10.6	7.1	7.1	6.92	6.31	6.82	7.19	9.81	–0.79↓
Chloroform	18.72	9.1	11.31	9.22	7.89	8.96	11.26	9.34	–9.38↓
Boron	4.51	6.29	8.55	8.69	8.36	6.98	8.05	8.52	+4.01↑
Strontium	1.26	6.96	4.14	3.5	5.58	7.93	6.01	7.16	+5.9↑
Sulfides and hydrogen sulphide H_2S	6.63	5.21	2.84	1.41	1.49	3.79	5.49	6.7	+0.07↑

Contents of chemical contaminants in drinking water exerted their influence on drinking water quality as per sanitary-chemical parameters.

Having analyzed data collected by FIF SHM over 2012–2019, we determined the following priority chemicals in drinking water: bromine, silicon, chlorine, iron, sodium, lithium, magnesium, manganese, chloroform, boron, strontium, sulfides, and hydrogen sulphide. A specific weight of drinking water samples that contained these chemicals in concentrations higher than fixed by hygienic standards was constantly higher than 5 %.

There were certain positive trends detected in 2012–2019; for example, there was a decrease in a share of drinking water samples deviating from hygienic standards as per chlorine (by 24.4 %), iron (by 7.78 %), sodium (by 8.58 %), lithium (by 24.2 %), magnesium (by 1.94 %), manganese (by 0.79 %), and chloroform (by 9.34 %).

However, over the same period of time there was an increase in number of drinking

water samples that deviated from hygienic standards as per contents of bromine (by 91.1 %), silicon (by 14.8 %), boron (by 4.01 %), strontium (by 5.9 %), various sulfides and hydrogen sulphide (by 0.07 %).

When chemicals (chlorine and chlorinated organic compounds, ammonia, iron, manganese, arsenic, lead, nickel, copper, boron, magnesium, etc.) occur in drinking water in concentrations higher than MPC, it can cause additional cases of health disorders in the nervous, cardiovascular, endocrine, and urogenital systems as well as in digestive organs, skin and mucosa, blood system, and immune system, and it can also have certain effects on changes in body mass, development processes, and infectious diseases prevalence[7].

We analyzed data provided by FIF SHM and state medical statistic data on population health in the RF collected in 2012–2019; the analysis revealed that approximately 1.98–1.68 million disease cases in the country were caused by chemical and microbial contamination of drinking water from centralized drinking water supply systems.

Additional diseases cases among the overall country population that are directly caused by drinking water quality have its structure with the first rank place belonging to digestive organs diseases (37.0–37.8 %) followed by the diseases of urogenital system (26.0–27.4 %); skin and subcutaneous tissue diseases (12.7–13.7 %); diseases of the endocrine system, gastric and metabolic disorders (5.5–7.4 %); diseases of the musculoskeletal system and connective tissue (4.8 %–5.6 %); neoplasms (5.2–5.5 %). Other diseases account for 4.9 %–6.8 % of total additional cases.

Additional morbidity among the whole RF population with digestive organs diseases in 2012–2019 (423.6–522.1 cases per 100 thousand people, 12–14 % of primary morbidity among the RF population with nosologies from this group) was probabilistically influenced by quality of water taken form centralized water supply systems deviating from sanitary requirements as per sanitary-chemical parameters including contents of arsenic, nickel, copper, boron, fluoride, chlorine, chloroform, and tetrachloromethane, in 79–83 regions in the country (Figure 6). Drinking water contamination that occurred in those regions probabilistically caused from 5.11 up

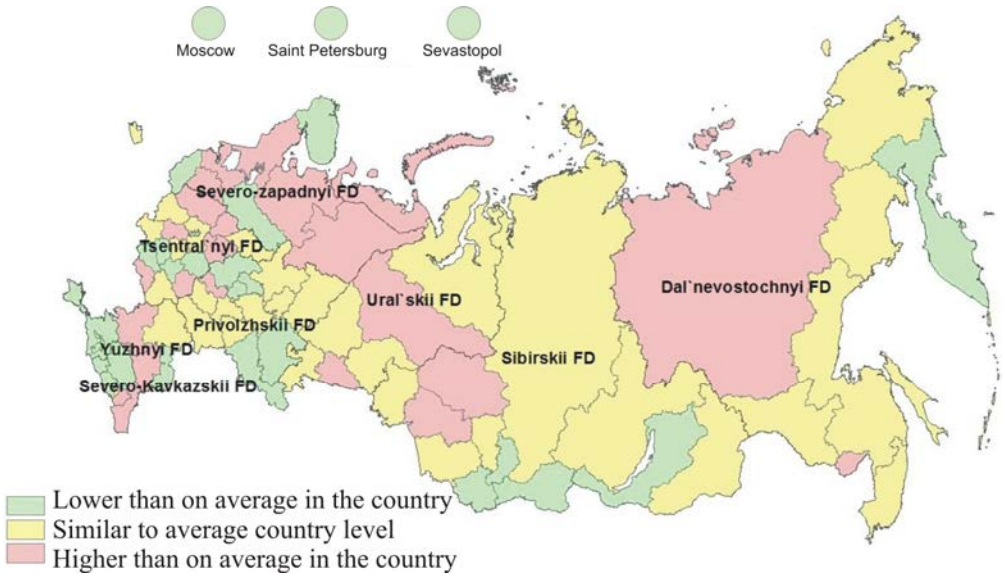

Figure 6. The RF regions distributed as per additional morbidity among the overall population with digestive organs diseases caused by poor quality of water taken from centralized water supply systems in 2019

[7] R 2.1.10.1920-04. Guide on assessing population health risks caused by exposure to chemicals that pollute the environment. Moscow, The Federal Center for State Sanitary-Epidemiologic Surveillance of the RF Public Healthcare Ministry Publ., 2004, 143 p. (in Russian).

to 2,450.5 additional cases of digestive organs diseases per 100 thousand people. In 2019 the greatest number of additional cases as per these nosologies was detected in Mordovia, Kalmyk Republic, and Dagestan, as well as in the Jewish Autonomous Area and Chechnya (from 1,276.38 to 2,233.67 cases per 100 thousand people).

Additional morbidity among the county population with urogenital system diseases (from 305.0 to 371.5 cases per 100 thousand people, 6.7–7.5 % from primary morbidity with these nosologies on average in the RF in 2012–2019) caused by quality of drinking water deviating from sanitary requirements as per sanitary-chemical parameters including contents of boron, cadmium, lead, mercury, chloroform, tetrachloromethane, barium, etc., probabilistically occurred practically in all regions in the country (79–83 regions, from 3.75 to 1,728.5 additional cases per 100 thousand people). In 2019 the parameter varied from 937.33 to 1,651.22 additional cases per 100 thousand people in priority regions (Mordovia, Kalmyk Republic, Dagestan, the Jewish Autonomous Area, and Chechnya).

Additional cases of skin and subcutaneous tissue diseases caused by a high share of water samples deviating from hygienic standards as per arsenic and iron contents occurred in 79–83 RF regions 1.76–1,113.5 cases per 100 thousand people in 2012–2019). Primary morbidity with these nosologies was higher than on average in the country (147.4–188.6 additional cases per 100 thousand people, 3.4–4.0 % of overall primary morbidity among population in 2012–2019) was detected in 22–39 RF regions (179.6–1,113.5 cases per 100 thousand people). In 2019 the parameter varied from 445.1 to 911.6 additional cases per 100 thousand people in priority regions (Komi, Mordovia, Kalmyk Republic, Dagestan, and the Jewish Autonomous Area).

In 2012–2019 additional morbidity among the RF population with endocrine system diseases, gastric and metabolic and disorders, directly caused by drinking water quality (deviation from hygienic standards as per contents of chloroform, arsenic, cadmium, lead, etc.) was registered in 79–83 RF regions (in 81 regions in 2019) and amounted to 74.0–94.8 cases per 100 thousand people on average in the country (5.6–8.9 % of primary morbidity with these nosologies among population). 16–32 RF regions were considered priority ones if taken in dynamics (86.5–952.2 cases per 100 thousand people): in 2018 there were 18 such territories including Komi Republic, Yakutia, Mordovia, Kalmyk Republic, Novosibirsk region, Tambov region, the Jewish Autonomous Area, etc. (from 130.3 to 857.8 additional diseases cases per 100 thousand people).

Additional cases of musculoskeletal system and connective tissue diseases among the overall TR population that were directly caused by poor quality of water taken from centralized water supply systems (as per strontium, fluorine contents, etc.) probabilistically amounted to 58.4–69.9 cases per 100 thousand people in 2012–2019 (2.0–2.4 % of all primary morbidity cases as per these nosologies). Additional morbidity with these nosologies caused by poor water quality was higher than on average in the country in 20–35 RF regions (74.8–436.1 cases per 100 thousand people). In 2019 there were 29 priority territories as per this parameter including Kalmyk Republic, Dagestan, Mordovia, the Nenets Autonomous Area, the Khanti-Mansi Autonomous Area etc. (101.6–305.3 additional morbidity cases per 100 thousand people).

Additional cases of neoplasms caused by drinking water quality deviating from sanitary requirements as per sanitary-chemical parameters (high contents of cadmium, arsenic, lead, tetrachloromethane, etc.) amounted to 61.3–74.3 cases per 100 thousand people on average in the country. Additional morbidity higher than on average in the country was detected in 22–36 RF regions (74.4–343.5 cases per 100 thousand people). In 2019 there were 22 priority regions as per this parameter including Mordovia, Kalmyk Republic, Chechnya, the Jewish Autonomous Area, Novgorod region, etc. (99.7–343.5 additional cases per 100 thousand people).

Additional cases of certain infectious and parasitic diseases caused by poor drinking water quality probabilistically amounted to 39.2–65.9 cases per 100 thousand people for overall RF population (1.5–2.1 % of all primary morbidity with these nosologies). The parameter was higher than on average in the country in 22–29 regions. In 2019 maximum levels (more than 280.0 additional cases per 100 thousand people) were detected in the Jewish Autonomous Area, Chechnya, Karelia, Yakutia, Tyva, Karachai-Cherkess, Kalmyk Republic, and Ingushetia.

Overall, additional morbidity among country population (from 4,720.5 to 5,705.2 additional cases per 100 thousand people in 2012–2019) directly caused by poor drinking water quality was detected in 82–83 RF regions in 2019. In 2019 the greatest number of additional cases (from 3,727.7 to 5,705.2 cases per 100 thousand people) was detected in Mordovia, Kalmyk Republic, Komi, Chechnya, and Dagestan.

The research results revealed that the highest contributions into additional morbidity cases caused by poor quality of drinking water taken from centralized water supply systems were made by deviations from hygienic standards regarding chemicals contents in drinking water, namely arsenic, chloroform, nickel, chlorine, copper, boron, fluorine, tetrachlorometahne, cadmium, lead, mercury, barium, iron, strontium, as well as microbiological contamination.

Conclusions. We analyzed how frequently obligatory sanitary requirements to quality of drinking water from centralized drinking water supply systems were violated and how these violations were distributed in the country. The analysis revealed that over 2000–2019 quality of drinking water taken from centralized water distribution networks improved as per both microbiological and sanitary-chemical parameters. Specific weight of drinking water samples not conforming to sanitary requirements as per sanitary-chemical parameters went down by 7.9 %; and by 6.7 % as per microbiological ones.

Hygienic assessment revealed that quality of drinking water taken from centralized water distribution networks not conforming to sanitary requirements as per sanitary-chemical and microbiological parameters could be considered a priority risk factor related to drinking water from centralized drinking water supply systems that created negative trends in a situation with population health in the Russian Federation.

Considerable concentrations of chemicals (arsenic, nickel, copper, manganese, iron, ammonia, chlorine, chloroform, boron, strontium, fluorine, etc.) and microbe agents in drinking water probabilistically cause more than 1.68 million additional morbidity cases among overall country population.

Basically adverse effects for population health occur in digestive organs, urogenital system, skin and mucosa, endocrine system, and musculoskeletal system; they also become apparent via a growth in number of neoplasms.

Priority risk factors that result in additional morbidity cases among population caused by poor quality of drinking water taken form centralized drinking water supply systems are violated hygienic standards regarding contents of arsenic, nickel, chlorine, copper, boron, fluorine, cadmium, lead, mercury, barium, iron, strontium, chlorinated organic compounds (chloroform, tetrachlorometahne, etc.) as well as microbial agents in drinking water.

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Research article

HYGIENIC ASSESSMENT OF AEROGENIC EXPOSURE TO PARTICULATE MATTER AND ITS IMPACTS ON MORBIDITY WITH RESPIRATORY DISEASES AMONG CHILDREN LIVING IN A ZONE INFLUENCED BY EMISSIONS FROM METALLURGIC PRODUCTION

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At present an outstanding task is to concentrate on chemical and fractional structure when examining and assessing influence exerted by particulate matter on morbidity among children. The main goal of any such research is to prevent negative effects produced on the respiratory organs.

Our research objects were ambient air in residential areas contaminated with particulate matter that were components in emissions from non-ferrous metallurgic enterprises (the test territory) and ambient air in residential areas free of such contamination; morbidity among children was also given our attention.

Our assessment of ambient air quality as per PM_{10} and $PM_{2.5}$ contents revealed they exceeded the standards recommended by the WHO and were by 1.4 times higher than recommended MPCa.d. Respirable fraction of particulate matter tends to have complicated chemical structure and contains metals that are specific for emissions from metallurgic enterprises such as nickel, copper, iron, aluminum, titanium, gallium, and neodymium. The latter can enhance negative effects produced by particulate matter on the respiratory organs. Epidemiologic assessment in a contaminated zone (the test territory) allowed establishing 1.8 times higher general and primary morbidity as per respiratory organs diseases than on the reference territory; it was even up to 14.8 times higher as per specific nosologies such as chronic disease of tonsils and adenoids, asthma, and status asthmaticus. We also established authentic dependence between probability of respiratory diseases and elevated concentrations of particulate matter in ambient air.

Results of the proven dependence allow predicting up to 500/1000 additional respiratory diseases cases per year on the test territory; all these additional morbidity cases among children are associated with aerogenic exposure to particulate matter.

Key words: *ambient air, particulate matter, PM_{10}, $PM_{2.5}$, respiratory organs, children, additional morbidity.*

Industrial complexes operating in non-ferrous metallurgy which are located in RF regions are, as a rule, large objects both in terms of production volumes and masses of contaminants emissions into ambient air [1]. Dust and gas mixtures discharged from metallurgic productions include commonly spread gaseous substances (sulfur, nitrogen, and car-

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bon oxides), specific compounds (iron, manganese, nickel, lead, aluminum, etc.), and particulate matter as well. Dust emissions make a substantial contribution into ambient air contamination in residential areas. Effects produced by particulate matter can result in negative consequences for health, first of all, respiratory diseases. Effects are especially hazardous for children since protective and adaptation capabilities of children's bodies are underdeveloped[1] [2].

The World Health Organization (WHO) ranks particulate matter including fine-disperse particles sized 2.5 and 10 μm among priority contaminants according to gravity of the effects they produce on population health [3]. According to WHO recommendations, average daily maximum permissible concentration for $PM_{2.5}$ in ambient air is 0.025 mg/m^3; for PM_{10}, 0.05 mg/m^3, and it is 1.4 and 1.2 times stricter than corresponding hygienic standards existing in the Russian Federation[2]. Chemical structure of particulate matter emitted by metallurgic enterprises depends on peculiarities of technological processes applied at them and includes various non-organic components, primarily metals [4–6]. Research works that dwell on assessing influence exerted by particulate matter on population health contain data on a wide range of negative effects, including those produced on respiratory organs and resulting in more frequent bronchitis cases and other symptoms in upper and lower respiratory tracts, exacerbated asthma attacks, more frequent pneumonias and greater mortality due to respiratory diseases [7]. The largest-scale epidemiologic research performed on 22 population cohorts in Europe confirmed dependence between total mortality and $PM_{2.5}$ concentrations in ambient air; mortality grew by 7 % per each 5 μg/m^3 [8].

As per data provided by the WHO, ambient air contamination with fine-disperse particulate matter produces apparent negative effects directly on respiratory tracts. Particles with aerodynamic diameter being less than 10 μm are proven to be able to penetrate via the bronchial tree and accumulate in lung tissues; PM with their diameter less than 2.5 μm are able to reach bronchioles and alveoli; PM with their diameter being less than 0.1 μm can even penetrate the blood flow [4, 6, 9, 10]. Experimental research works allowed establishing than effects produced by $PM_{2.5}$ on the respiratory tract mucosa resulted in a decrease in chalice cells number and epithelium thickness [11]. These changes lead to a reduction in phagocytes macrophages and epithelial cells that participate in protective functions performed by respiratory tracts and aimed at protection from negative effects produced by contaminants in ambient air [6].

Multiple Russian and foreign research works contain evidence that there is a direct correlation between a significant growth in respiratory diseases and additional cases of diseases in the respiratory organs and effects produced by particulate matter in ambient air [7, 12–14]. It is well-proven that when average daily PM_{10} concentration grows by 10 μm/m^3, there is a 2.4–3.4 % growth in application for medical aid or admission to hospitals among population due to diseases of the upper and lower respiratory tracts, and bronchitis cases number grows by 10–25 % [15, 16]. When PM_{10} concentration grows by 10 μm/m^3 during 2 months, frequency of bronchial asthma attacks among children increases by 4.2 % [16].

At present it is vital to examine and assess negative effects produced by particulate matter on morbidity among children taking into account their chemical and fraction structure as it allows working out efficient preventive activities aimed at reducing or eliminating negative consequences for respiratory organs.

Our research goal was to hygienically assess aerogenic exposure to particulate matter and effects produced on morbidity with

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respiratory deceases among children living in a zone exposed to emissions from metallurgic enterprises.

Data and methods. The research objects were ambient air samples taken in residential areas where ambient air was contaminated with particulate matter due to emissions from enterprises operating in non-ferrous metallurgy (the test territory) and in residential areas without such contamination (the reference territory) and databases with data on morbidity among children.

Fraction and chemical structure of particulate matter was examined via analyzing daily ambient air samples taken at a point located 2 km away from the boundary of a sanitary-protection zone around a metallurgic enterprise. Samples were taken over a period of time starting from 00.30 to 18.30 with PA-300M-2 air intake device (Russia) on AFA-VP-20-2 filters (Russia). Granulometric structure of particulate matter was examined via analyzing images obtained with S-3400N electronic scanning microscope (Hitachi, Japan) with Image J-FiJi software (Germany); chemical structure was examined via x-ray analysis performed with X Flash Detektor 4010 energy-dispersive spectrometer (Bruker, Germany).

Hygienic assessment of particulate matter contents including their $PM_{2.5}$ и PM_{10} fractions in ambient air samples was performed according to HS 2.1.6.3492-17 «Maximum permissible concentrations (MPC) of contaminants in ambient air in urban and rural settlements» by experts from the Collective Use Center at the Perm State Research Polytechnic University.

We comparatively assessed overall and primary morbidity with respiratory diseases among children (younger than 14) on the test and reference territories using data from the Federal Statistic Report Form No 12 «Data on number of diseases registered among patients living on a territory where medical services were rendered by a particular medical organization» over 2014–2018 and results obtained via analyzing data on actual application for medical aid provided by the Regional Fund for Obligatory Medical Insurance over 2017–2018. All the cases when exposed and non-exposed population applied for medical aid were bound to specific locations on maps of both residential areas. We performed spatial intersection with *ArcGIS 9.3* software to establish number of children exposed to chemical factors that were tropic to respiratory organs.

Data were statistically analyzed with Statistica 6.0 software package and specific software packages with *MS-Office* applications. Normalcy of measured variables distribution was tested with Kolmogorov-Smirnov test. To quantitatively characterize the examined parameters, we used mean value and error of mean since random variables of analyzed parameters conformed to normal distribution. Validity of discrepancies in morbidity among children population on the test territory and the reference one was performed with Student's t-test. Statistical significance was taken as $p \leq 0.05$ [17].

We revealed and assessed cause-and-effect relations between probability of respiratory diseases occurrence and particulate matter content in ambient air with help provided by experts from the Department for Mathematic Modeling of Systems and Processes at the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies; it was done via simple linear regression analysis.

We assessed whether a regression model was authentic and relevant using significance (p) and correlation coefficient (r). Statistical significance was tested according to conventional procedure for statistic hypothesis testing based on Student's t-test (t) calculation [18].

Results and discussion. Emissions from metallurgic enterprises contain more than 80 different chemicals. Particulate matter and metal oxides that occur in their structure account for approximately 20 % of the overall emission masses.

Having assessed fractional structure of particulate matter, we revealed that PM were emitted into ambient air on the test territory and particles with their diameter being 2.5–10.0 μm accounted for approximately 57.0 % of the overall particles number. Particles with diameter 0.1–2.5 μm accounted for 21.0 %; particles with diameter being smaller than 0.1 μm accounted for 22.0 % (Table 1).

Table 1

Fraction structure and average daily concentration of particles with different sizes; particles were deposited on filters when ambient air on residential areas was examined

Particles size range, μm	MPCav.d*, mg/m^3	MPCav.d.**, mg/m^3	Test territory		Reference territory	
			Particles share, %	Average daily particles concentration, mg/m^3	Particles share, %	Average daily particles concentration, mg/m^3
less 0,1	–	–	22.3	0.018	2.23	0.002
0,1–2,5 ($PM_{2,5}$)	0.035	0.025	20.8	0.034	79.88	0.024
2,5–10,0 (PM_{10})	0.06	0.05	56.9	0.057	17.87	0.014

Note:
* is average daily maximum permissible concentration of a substance as per Hygienic Standard 2.1.6.3492-17[3];
** is average daily maximum permissible concentration of a substance as per EU Directive.

It should be noted that a share of particles with their aerodynamic diameter being 2.5–10 μm and less than 0.1 μm was by 3.0–10.0 times higher in ambient air on the test territory than on the reference one.

We assessed PM_{10} and $PM_{2.5}$ contents in ambient air in residential areas on the test territory; the assessment revealed that average daily concentrations fixed in Russian hygienic standards were not violated. But still, the occurring concentrations were 1.2 and 1.4 times higher than average daily maximum permissible concentrations recommended by the WHO and also 1.4 and 4.0 times higher than the same parameters on the reference territory.

Chemical structure of fine-disperse particles with different sizes is rather complicated and includes approximately 15 metal and non-metal oxides. And most metals that occur in particles (iron, nickel, copper, titanium, gallium, and neodymium) are typical for emissions from metallurgic production (Table 2).

Ambient air samples taken on the test territory more frequently contain fine-disperse particles with commonly spread sodium oxides in their structure, their mass fraction varying from 1.5 to 7.1 %, and oxides that are specific for metallurgic production, such as copper, iron, nickel, and titanium oxides, their mass fraction varying from 0.16 to 6.5 %; titanium, gallium, and neodymium oxide are less frequent with their mass fraction varying from 0.6 to 11.9 % and they are completely absent in the structure of fine disperse particles contained in ambient air samples taken on the reference territory. Figures 1 and 2 give examples of spectrograms showing chemical structure of a specific fine-disperse particle and its electronic image.

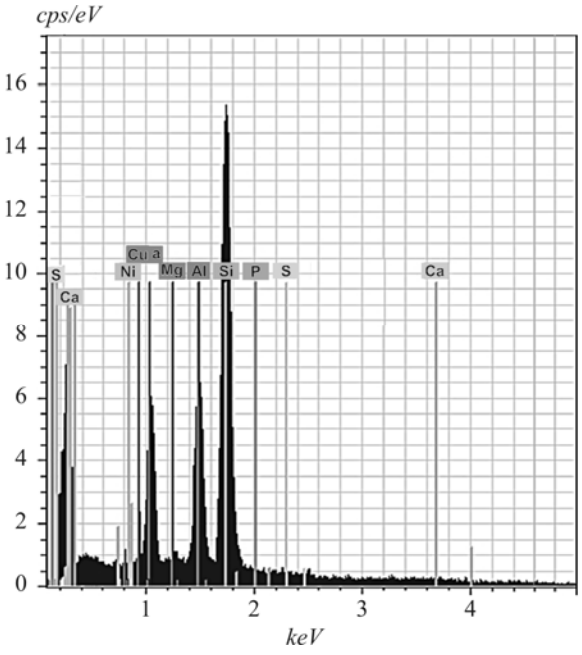

Figure 1. Chemical structure of a fine-disperse particle from an ambient air sample taken in residential area on the test territory
Note: cps/eV is a number of impulses a 1 second per electron-Volt, keV is kilo-electron-Volt

[3] HS 2.1.6.3492-17. Maximum permissible concentration (MPC) of contaminants in ambient air in urban and rural settlements: The Order by the RF Chief Sanitary Inspector issued on December 22, 2017 No. 165. *KODEKS: an electronic fund for legal and reference documentation.* Available at: http://docs.cntd.ru/document/556185926 (07.02.2020) (in Russian).

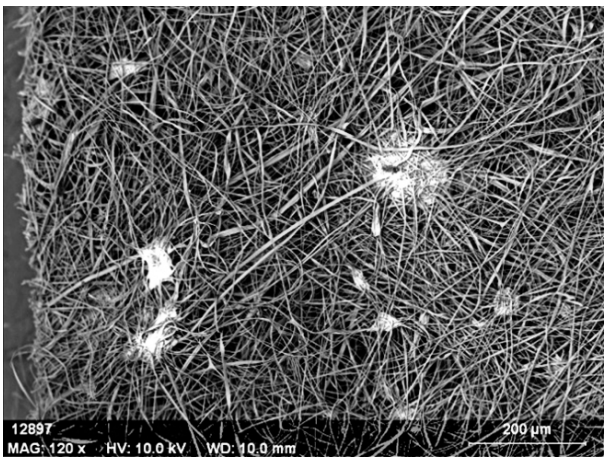

Figure 2. An image obtained with an electronic scanning microscope; it shows fine-disperse dust particles deposited on a filter during ambient air examination on the test territory (scale 120:1)

Morbidity among population was analyzed basing on data taken from state statistic reports issued in 2014–2018; the analysis revealed that respiratory diseases held the 1st rank place both in the primary and overall morbidity among children on the test territory and the reference one as well. Overall morbidity with respiratory diseases amounted to 1,342.03 cases per 1,000 children on the test territory and it was 1.8 times higher than the same parameter among children on the reference territory (760.95 cases per 1,000 thousand people, $p \leq 0.05$) (Table 3). Overall morbidity among children living on the test territory taken as per specific nosologies on average over 5 years was authentically higher than the same parameters among children living on the reference territory. As for specific nosologies, the figures were as follows: allergic rhinitis, 80.3 times higher; chronic diseases of the tonsils and adenoids, 14.8 times higher; asthma and status asthmaticus, 4.14 times higher ($p \leq 0.05$).

A rather alerting trend is a growth (up to 1.7 times) in primary morbidity with respiratory diseases among children living on the test territory (1,274.97 cases/1,000 children) against the same parameter on the reference territory (752.03 cases/1,000 children) (Table 4). Primary morbidity with chronic diseases of the tonsils and adenoids over 5 years was 5.4 times authentically higher among children on the test territory among the reference one ($p \leq 0.05$).

There were new cases of allergic rhinitis registered in children living on the testy territory in the analyzed period whereas there were no such cases among children living on the reference one. We didn't detect any authentic discrepancies as per other nosologies.

According to data on application for medical aid in 2017–2018, morbidity with respiratory diseases among children on average amounted to 1,426.46 cases/1,000 children and 788.99 cases/1,000 children on the test and reference territory accordingly, discrepancy was 1.8 times ($p = 0.0001$).

We assessed cause-and-effect relations within «ambient air quality – morbidity among children» system and it allowed us to reveal direct dependence between growing probability of respiratory diseases (as per data on application for medical health) and particulate matter concentrations ($a = 0.534$; $b = 1.787$; $r = 0.19$; $p = 0.001$). A contribution made by particulate matter into respiratory disorders amounted to approximately 20 %.

Table 2

Chemical structure of some disperse particles in ambient air samples taken in residential areas influenced by metallurgic production

Residential area	Particles size, µm	Chemical structure, mas. %									
		Na	Mg	Ca	Al	Cu	Fe	Ni	Ti	Ga	Nd
Test territory	66.89	7.11	4.87	9.58	6.51	–	0.63	–	–	–	–
	39.55	6.80	1.82	1.86	–	1.25	5.48	4.14	–	–	–
	1.12	1.50	7.49	6.59	1.46	3.54	0.16	5.0	3.68	0.64	4.10
	0.98	–	–	–	–	62.01	–	11.97	–	–	–
Reference territory	61.58	–	10.23	1.41	3.663	–	10.10	–	–	–	–
	19.43	–	6.29	0.86	11.50	43.14	–	–	–	–	–
	72.56	–	9.08	5.00	7.25	–	0.60	–	–	–	–

Table 3

Overall morbidity among children on the test territory and the reference one over 2014–2018, cases/per 1,000 children

Disease class / nosology (as per ICD-10)	Test territory		Reference territory		
	Average over 2014–2018, cases per 1,000 children	Growth rate, 2018 to 2014, % *	Average over 2014–2018, cases per 1,000 children	Growth rate, 2018 to 2014, % *	Validity of discrepancies as per mean value, p≤0.05
J00-J98 Diseases of the respiratory system	1,342.03±90.11	–3.30	760.95±20.14	–5.67	≤0.05
J30.1 Allergic rhinitis (pollinosis)	10.44±1.25	–8.72	0.13±0.02	0.00	≤0.05
J35-J36 Chronic diseases of tonsils and adenoids	49.84±8.52	45.62	3.36±0.05	–68.55	≤0.05
J44 Other chronic obstructive pulmonary disease	2.29±0.51	287.55	1.55±0.21	–64.09	0.29
J45-J46 Asthma, status asthmaticus	18.12±2.47	-33.77	4.37±0.85	81.43	≤0.05

Note: * means that if a parameter was equal to zero in 2014, growth rate was not calculated.

Table 4

Primary morbidity among children on the test and reference territory in 2014–2018, cases/per 1,000 children

Nosology (as per ICD-10)	Test territory		Reference territory		
	Average over 2014–2018, cases per 1,000 children	Growth rate, 2018 to 2014, % *	Average over 2014–2018, cases per 1,000 children	Growth rate, 2018 to 2014, % *	Validity of discrepancies as per mean value, p≤0,05
J00-J98 Diseases of the respiratory system	1,274.97	–1.21	752.03	–3.40	0.30
J30.1 Allergic rhinitis (pollinosis)	1.47	–40.97	–	–*	≤0.05
J35-J36 Chronic diseases of tonsils and adenoids	16.66	–24.98	3.07	–90.21	≤0.05
J44 Other chronic obstructive pulmonary disease	0.76	764.71	0.54	–100.00	0.34
J45-J46 Asthma, status asthmaticus	1.78	–21.72	1.28	116.35	0.14

Note: * means that if a parameter was equal to zero in 2014, growth rate was not calculated.

Our research results indicated that average daily concentrations of particulate matter were up to 5 times higher than maximum permissible ones fixed in hygienic standards recommended by the WHO; as for PM_{10} и $PM_{2,5}$, their contents were up to 1.4 times higher. And it should be noted that $PM_{2.5}$ and PM_{10} account for a big share (up to 57 %) of the overall particulate matter volumes in dust and gas emissions form metallurgic production. It is well in line with opinions on the issue expressed by the WHO experts and also confirms data obtained by Russian scientists in their research works [18–20]. And particles with their size exceeding 1 μm and containing specific metal oxides (nickel, copper, iron, titanium, gallium, and neodymium) can aggravate negative impacts exerted on the respiratory tract due to their toxicity.

As per data taken from state reports and application for medical aid registered for children living on the test territory, both overall and primary morbidity among them was 1.7–1.8 times higher than among children living on the reference territory if taken as per respiratory diseases in general; it could be from 4.0 to 14.8 times higher if taken as per specific nosologies (chronic diseases of tonsils and adenoids, asthma and status asthmaticus). The obtained results coincide with data taken from foreign and domestic research works on epidemiologic assessment of impacts exerted by particulate matter in ambient air on respiratory diseases prevalence among children [7, 21, 22].

We detected direct dependence between elevated morbidity with respiratory organs diseases among children under aerogenic exposure to particulate matter and it allows us to assume there could be up to 500 additional disease cases annually per 1,00 children caused by the increased levels of the examined contamination factor. Use of scientifically grounded results which we obtained allows revealing cause-and-effects relations between living on a specific territory and diseases occurrence; in its turn, it helps make efficient managerial decisions aimed at reducing negative consequences for respiratory organs in children who live under aerogenic exposure to chemicals [23].

Particulate matter including PM_{10} and $PM_{2,5}$, occur in ambient air on residential areas due to metallurgic enterprises located nearby; exposure to them results in apparent negative effects and it allows assuming there can be additional morbidity with respiratory diseases among children caused by particulate matter contents in ambient air as it has been confirmed by results obtained in this research work. Particulate matter contents in ambient air in industrial regions, including territories where metallurgic enterprises are located, can be efficiently reduced via updating the regulatory basis, in particular, fixing stricter standards for fine-disperse particulate matter contents in ambient air and developing technological and sanitary-hygienic activities aimed at reducing emissions from primary emission sources. It is necessary to implement targeted medical and preventive activities for children who permanently live under aerogenic exposure to particulate matter; these activities should be aimed at reducing respiratory diseases cases.

Conclusions.

1. Hygienic assessment of ambient air quality regarding particulate matter contents revealed that existing PM_{10} and $PM_{2.5}$ concentrations exceeded average daily maximum permissible ones as they were up to 1.2 and 1.4 times higher than MPCav.d. accordingly than hygienic standards recommended by the WHO.

2. Respirable particulate matter fraction has complex chemical structure and contains metals (nickel, copper, iron, titanium, gallium, and neodymium) that are specific for emissions discharged into ambient air by metallurgic enterprises; it can intensify negative effects produced by particulate matter on the respiratory organs.

3. Assessment of morbidity revealed higher primary and overall morbidity among children population on the test territory than among those living on the reference territory; it was up to 1.8 times higher if taken as per all respiratory diseases; it could be up to 14.8 times higher as per specific nosologies such as chronic diseases of tonsils and adenoids, and asthma and status asthmaticus against the same parameter among non-exposed children.

4. We proved there was dependence between probability of respiratory diseases and elevated particulate matter concentrations in ambient air; it allowed us to predict annually up to 500/1,000 additional cases of respiratory diseases among children caused by aerogenic exposure to particulate matter.

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Research article

ASSESSING EFFICIENCY OF PRE-AMMONIZATION AIMED AT REDUCING CARCINOGENIC RISKS CAUSED BY TRIHALOMETHANES IN DRINKING WATER

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In most Russian regions there is still a pressing issue related to providing population with high quality and safe drinking water. Up to now, chlorination has been the primary technique applied to disinfect drinking water as it is highly efficient, reliable, and relatively cheap. However, when chlorine is used to disinfect natural water that contains organic pollutants, it results in risks of by-products occurrence. These products are trihalomethanes, epigenetic carcinogenesis promoters that cause elevated carcinogenic risks under oral, inhalation, and subcutaneous exposure.

Our research goal was to hygienically assess efficiency of pre-ammonization applied in water treatment procedures in order to prevent occurrence of carcinogenic organic chlorine compounds during chlorination and to minimize carcinogenic risks. We determined trihalomethanes and residual chlorine contents in model samples of natural water taken from a surface water source after chlorination with different doses of chlorine. We examined 52 pair parallel samples that had undergone pre-ammonization with ammonia sulfate and control ones. Trihalomethanes concentrations were determined in model water samples with gas-liquid chromatography.

Basing on the results obtained via experiments on laboratory chlorination of river water, we determined quantitative characteristics and built regression models showing dependence between concentrations of organic chlorine compounds occurring due to chlorination (chloroform, dichlorobrommethane, dibromchloromethane) and chlorine doses and pre-ammonization parameters. It was established that pre-ammonization was the most efficient in terms of preventing trihalomethanes occurrence under such disinfection modes when contents of residual active chlorine didn't exceed recommended levels (0.8–1.2 mg/L). Basic ways to minimize carcinogenic risks caused by trihalomethanes are systemic control over their contents in drinking water during social and hygienic monitoring procedures; preliminary ammonization of water taken from surface water sources; prevention of unjustified hyper-chlorination; preliminary deep purification of initial water; disinfection with ultrasound radiation instead of preliminary chlorination; etc.

Key words: *drinking water, chlorination, trihalomethanes, chloroform, dichlorobrommethane, dibromchloromethane, malignant neoplasms, carcinogenic risk, health risk assessment, social and hygienic monitoring.*

An issue related to providing population with high quality and safe drinking water remains vital in most Russian regions [1, 2]. At present the most widely spread procedure for providing safety of water taken form centralized communal and drinking water supply systems is disinfection with chlorine or chlorine-containing reagents. Chlorination has certain benefits as it is efficient, reliable, has apparent after effects due to residual chlorine occurrence in distribution water supply networks, and is relatively cheap [3–5]. At the same time, when it comes to chlorinating water taken from surface water sources that contains natural and anthropogenic organic compounds, chlorination may result in occurrence of such by-products as trihalomethanes including chloroform (trichloromethane), dichloro-

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brommethane, dibromchloromethane, etc. Probability of trihalomethanes occurrence grows linearly in case there is an increase in periods of time during which water is kept in tanks and distribution networks; it also depends on water temperature, doses of chlorine-containing reagents applied at water treatment facilities, and residual chlorine contents [6–13]. Occurrence of chloroform and other trihalomethanes in drinking water results in elevated risks of both potential carcinogenic and non-carcinogenic risks as such substances have epigenetic properties of carcinogenesis promoters under combined oral, inhalation, and subcutaneous exposure. These risks become apparent via increase in pathologies occurring in the liver, kidneys, cardiac muscle, blood system, nervous system, and endocrine system [14–23]. All the above mentioned means it is necessary to implement such water treatment procedures that will prevent or minimize trihalomethanes occurrence in drinking water in centralized water supply systems; for example, water can be disinfected with ultrasound radiation, or pre-ammonization with subsequent chlorination can be applied, etc. [24].

Our research goal was to hygienically assess efficiency of pre-ammonization applied to prevent trihalomethanes occurrence during chlorination of water taken from surface water source for centralized communal and drinking water supply.

Data and methods. Our experiment research involved determining trihalomethanes and residual chlorine contents in model samples of natural water from the main water source for centralized and drinking water supply system in Taganrog (The Don river) after chlorination with different chlorine doses performed in a laboratory taking into account chlorine absorption capacity of water. Overall, we examined 52 pair parallel samples, experimental ones that underwent pre-ammonization with ammonia sulfate used as a reagent, and reference ones, that didn't undergo preliminary pre-ammonization. Trihalomethanes concentrations in model water samples were performed according to the State Standard (GOST) R 51392-99[1]. Results obtained via experiments were statistically processed both with conventional variations statistic procedures and non-linear regression models showing dependence between chloroform, dichlorobrommethane, and dibromchloromethane concentrations on total residual active chlorine contents. We applied our own software package that provided an opportunity to use procedures for statistical processing of experimental results and mathematical modeling including «Turbo Dynamics», version 1.02 (long-term dynamics analysis, extrapolation prediction) and «Turbo Correlation», version 1.1 (non-linear and multiple correlation and regression analysis); we also used IBM SPSS Statistics («Statistical Package for Social Science») version 19.0 an expert statistic software package.

Results and discussion. It is truly vital to reveal potential carcinogenic risk factors in Taganrog, a city in Rostov region, with its population being approximately 250 thousand people as an existing situation regarding morbidity with malignant neoplasms is extremely bad there. Average long-term morbidity with MN over the last 15 years is equal to 486.42 $^{o}/_{oooo}$ which is 1.31 times higher than for urban population in Rostov region in general and it occupies the first rank place in the overall morbidity structure in the city. Average annual growth in long-term trend describing overall oncologic morbidity over the given period amounts to +1.07 %, and priority localizations in its structure are skin (without melanoma, 14.81 %), breast (13.08 %), trachea, bronchial tubes,

[1] GOST R 51392-99. Drinking water. Determining contents of volatile halogen-organic substances with gas liquid chromatography. Approved upon and made valid by the Order of the RF Gosstandart on issued on December 15, 1999 г. N 515-st. *KODEKS: an electronic fund for legal and reference documentation.* Available at: http://docs.cntd.ru/document/gost-r-51392-99 (03.08.2020) (in Russian).

and lung (9.22 %), middle intestine (6.94 %), and stomach (6.49 %).

The centralized water supply system in Taganrog is a mixed one as it supplies water taken both from surface sources (the Don, the Mius) and underground ones (two territorially separate water intakes). River water goes to treatment facilities where it undergoes two-stage treatment in horizontal tanks and fast filters with coagulation, pre-ammonization with ammonia sulfate, and double chlorination with chlorine water used as a reagent.

According to data obtained from the Center for Hygiene and Epidemiology in Rostov region, Taganrog office, hygienic assessment of drinking water quality revealed chloroform (trichloromethane), dichlorobrommethane, and dibromchloromethane in it; still, water quality can be considered relatively satisfactory. Thus, according to research results, 276 water samples were examined over 2012–2019, and chloroform contents higher than MPC were detected in a single one (0.36 %), and there were no samples with dichlorobrommethane or dibromchloromethane contents that exceeded MPC. Potential carcinogenic risk was assessed basing on well-grounded maximum exposure calculated as upper limits of 95 % confidence intervals of average trihalomethanes concentrations [25]. It was detected that total individual carcinogenic risk caused by oral exposure to trihalomethanes in water from centralized water supply system (CRwo) was estimated as maximum permissible over the whole 8-year period and was equal to $6.91 \cdot 10^{-6}$ with priority share contribution into it made by dibromchloromethane (55.8 %). A contribution made by the said parameter by chloroform ($7.09 \cdot 10^{-7}$) is negligible and corresponds to *De minimis* level. There was also maximum permissible level ($2.27 \cdot 10^{-6}$) detected for the total carcinogenic risk caused by inhalation exposure to trihalomethanes in water from centralized water supply systems (CRwi) with the greatest share contribution belonging to dichlorobrommethane (54.3 %). Individual carcinogenic risk caused by subcutaneous exposure to trihalomethanes (CRwd) turned out to be negligible ($6.11 \cdot 10^{-7}$). Therefore, we detected the maximum permissible total individual multi-exposure carcinogenic risks (TCRw) caused by trihalomethanes in ater taken from centralized communal and drinking water supply systems in Taganrog as per data collected over 2012–2019. The total carcinogenic risk amounted to $9.79 \cdot 10^{-6}$ with share contributions made by oral, inhalation, and subcutaneous exposure being equal to 70.6 %, 23.2 %, and 6.2 % accordingly. Total lifelong population multi-exposure carcinogenic risk (TPCRw) that occurred due to oral, inhalation, and subcutaneous exposure to chloroform, dichlorobrommethane, and dibromchloromethane amounted to 2.477 as per data collected over the examined 8-year period. Analysis of long-term dynamics regarding total population multi-exposure carcinogenic risk varying from $5.91 \cdot 10^{-3}$ to $1.16 \cdot 10^{-1}$ has revealed there is a descending trend in it with annual average growth rate being equal to –37.17 %. Therefore, the obtained results indicate that combined disinfection procedures applied at treatment faculties of the city centralized water supply system are highly efficient. These procedures involve both chlorination and pre-ammonization with ammonia sulfate that binds introduced chlorine; it results in chloramines occurrence that prevents trihalomethanes formation.

We continued experimental research on efficiency of preliminary ammonization applied in water treatment procedures and proceeded to quantitative modeling of dependence between trihalomethanes concentrations occurring in model water samples (chloroform, dichlorobrommethane, and dibromchloromethane) and parameters of pre-ammonization with ammonia sulfate during chlorination performed in laboratory conditions (from 0.7 to 3.0 mg/dm^3) taking into account chlorine absorption capacity of water and residual chlorine determination [26]. Simultaneously, we examined reference water

samples that were chlorinated with the same chlorine doses but without any preliminary ammonization. After 30-minute exposure we applied gas liquid chromatography to determine trihalomethanes contents in model water samples and we also measured total residual active chlorine contents. Research results prove that, first of all, trihalomethanes concentrations grow non-linearly depending on introduced chlorine doses and, secondly, trihalomethanes contents in reference water samples is substantially higher that the same parameters of water samples that have been through preliminary ammonization. Pre-ammonization was the most efficient under chlorination modes that provided total residual active chlorine contents remaining within hygienic standards (0.8–1.2 mg/dm^3). Thus, when total residual active chlorine contents in experimental water samples were equal to 1.2 mg/L, chloroform concentration was 7.29 times lower in them than in reference samples, and pre-ammonization efficiency turned out to be even higher for dichlorobrommethane and dibromchloromethane, 16.33 and 59.01 times accordingly.

Basing on the obtained experimental data, we revealed strong direct statistically significant correlations between trihalomethanes concentrations detected in model water samples and total residual active chlorine contents; these correlations are most adequately described with non-linear regression models built up as exponential curves for experimental samples that were pre-ammonized and logarithmic curves for reference samples that were not (Table 1).

Developed non-linear regression models clearly show a negative effect, that is, pre-ammonization efficiency regarding prevention of trihalomethanes occurrence is going down progressively when total residual active chlorine contents exceeds the hygienic standard (0.8–1.2 mg/dm^3); in particular, such a situation can occur when water is disinfected via hyper-chlorination procedure (Figures 1–3).

Table 1

Non-linear regression models showing dependence between trihalomethanes concentrations and total residual active chlorine contents after laboratory disinfections of river water samples

Trihalomethane	Laboratory conditions for a model solution chlorination	Non-linear regression models			
		Correlation coefficient (rYX)	Statistic significance (p-level)	Regression line type	Non-linear models showing dependence between trihalomethanes concentrations (Y) An total residual active chlorine contents in water (X)
Chloroform	pre-ammonized	0.838	$p < 0,01$	exponential curve	$Y=0.000737 \cdot X^{3.822}$
	without pre-ammonization	0.745	$p < 0,05$	logarithmic curve	$Y=0.023445+0.019443 \cdot log(X)$
Dibrom-chloromethane	pre-ammonized	0.808	$p < 0,01$	exponential curve	$Y=0.000024 \cdot X^{7.102467}$
	without pre-ammonization	0.817	$p < 0,01$	logarithmic curve	$Y=0.033443+0.051431 \cdot log(X)$
Dichloro-brommethane	pre-ammonized	0.739	$p < 0,05$	exponential curve	$Y=0.000551 \cdot X^{3.849085}$
	without pre-ammonization	0.851	$p < 0,01$	logarithmic curve	$Y=0.024353+0.027236 \cdot log(X)$

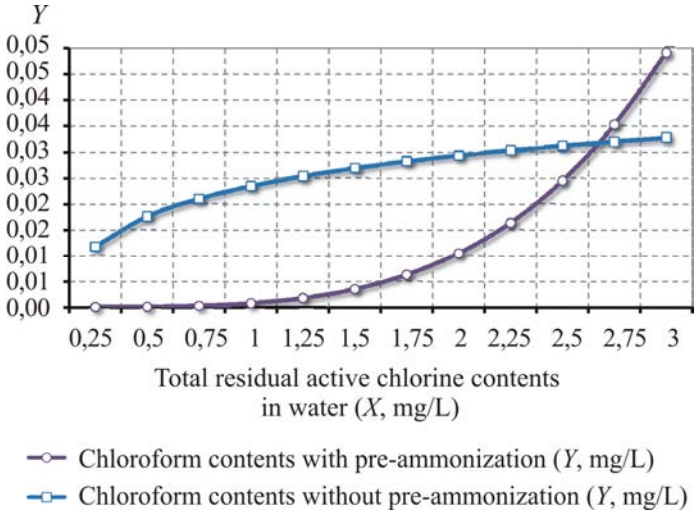

Figure 1. Non-linear regression models showing dependence between chloroform concentration and total residual active chlorine contents in model river water samples

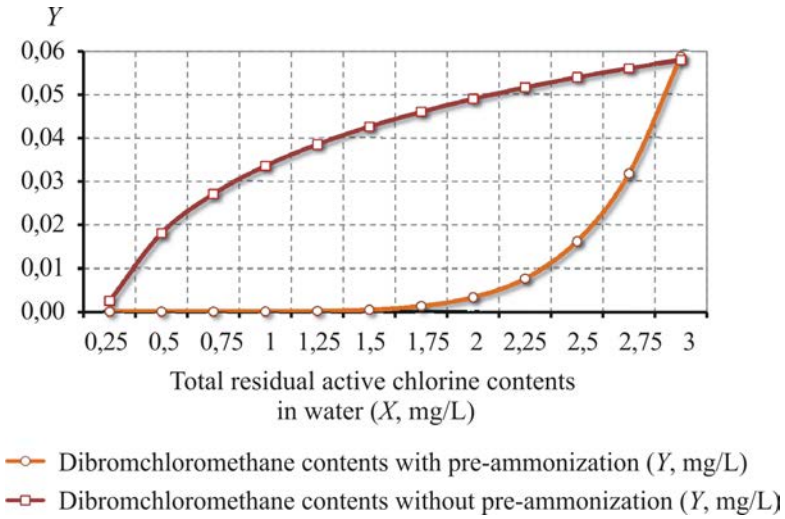

Figure 2. Non-linear regression models showing dependence between dibromchloromethane concentration and total residual active chlorine contents in model river water samples

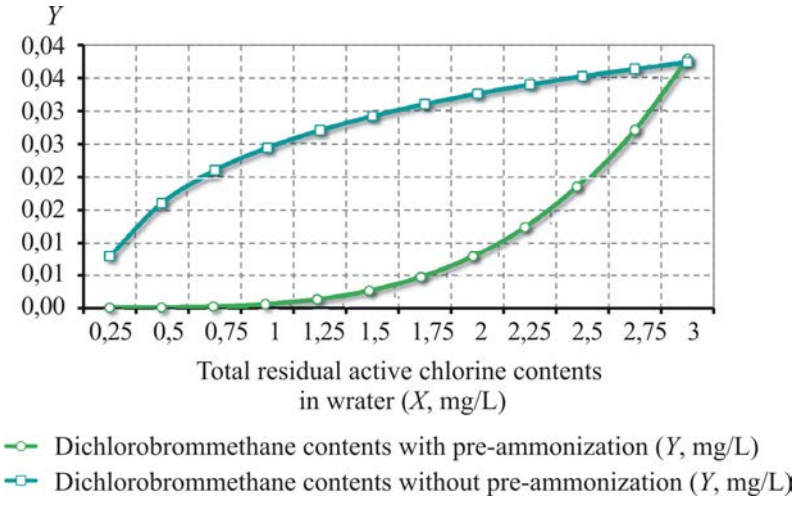

Figure 3. Non-linear regression models showing dependence between dichlorobrommethane concentration and total residual active chlorine contents in model river water samples

Therefore, experimental research results allow us to conclude that the most efficient pre-ammonization aimed at preventing or minimizing occurrence of the examined trihalomethanes (chloroform, dichlorobrommethane, and dibromchloromethane) during water treatment requires such chlorination procedures that do not result in total residual active chlorine contents being higher than hygienic standards. Pre-ammonization is efficient due to chlorine being bound as a result of chloramines occurrence; the procedure leads to a substantial decrease in redox potential of «natural water – chlorine» system and chlorine absorption capacity of water since chloramines possess much more humble oxidizing potential than free chlorine. An apparent decrease in pre-ammonization efficiency in situations when too high chlorine doses are applied can be related to a double effect that occurs in case chlorine absorption capacity of water is rather low. First of all, excessive active chlorine that remains in water after hyper-chlorination results in much more intense oxidation and destruction of monochloramine that occurred in it due to pre-ammonization; consequently, additional free active chlorine contents occur in water. Secondly, excessive free active chlorine interacts with organic compounds that can be found in natural water and it leads to increased trihalomethanes contents in it.

There are certain promising measures that can help decrease potential carcinogenic risks caused by trihalomethanes. Apart from systematic control over their contents in drinking water, including activities performed within social and hygienic monitoring, preliminary ammonization in water treatment, and maximum precise chlorine dosing in disinfection of water taken from natural sources, we can suggest considering, first of all, deep natural water purification prior to chlorination in order to minimize organic compounds contents in it as they are predecessor to trihalomethanes; secondly, we suggest applying post-chlorination at final stages in water treatment together with primary chlorination exclusion; and thirdly, we advise transition to reagentless disinfection of water in centralized water supply systems, for example, ultrasound radiation.

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

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Research article

INTEGRAL ASSESSMENT OF FOOD PRODUCTS CONTAMINATION WITH PRIORITY POLYAROMATIC HYDROCARBONS

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Polyaromatic hydrocarbons (PAH) occur in the environment as complex mixtures and each congener has different carcinogenic and mutagenic activity.

Our research goal was to accomplish an integral assessment of food products contamination with priority PAH basing on their determination with high precision procedures.

We validated a procedure for determining the said substances and hygienically assessed contamination of certain food products with benzpyrene, as well as with different carcinogenic and mutagenic PAH equivalents taking into account samples with low contamination. Quantitative determination limit for benz(a)anthracene and benzpyrene was fixed at 0.01 μg/kg; benz(b)fluoranthene and chrysene, 0.1 μg/kg. Detection limit for benz(a)anthracene and benzpyrene amounted to 0.003 μg/kg in our research; for benz(b)fluoranthene and chrysene, 0.03 μg/kg. A procedure for integral assessment of contamination with the examined compounds allowed us to calculate benz(a)anthracene, benzpyrene, benz(b)fluoranthene, and chrysene contents in certain food products taking into account mixture of the examined substances, their individual contributions into aggregated contamination, and their different toxic and mutagenic activity. Median food products contamination with benzpyrene amounted to 0.0065–0.42 μg/kg; PAH taking into account carcinogenic equivalents, 0.03–0.55 μg/kg; PAH based on mutagenic equivalents, 0.04–0.81 μg/kg. Maximum concentrations of benzpyrene and PAH based on carcinogenic and mutagenic equivalents are due to a combination of subsequent technological processes that make for occurrence of the examined substances and also due to physical and chemical properties of the examined food products.

Key words: *risk assessment, integral assessment, polycyclic aromatic hydrocarbons, contamination, food products, congeners, toxic equivalent, mutagenic equivalent.*

Food product safety is a key element in providing sanitary-epidemiologic welfare in Belarus. Food products may get contaminated with polyaromatic hydrocarbons (PAHs), substances with carcinogenic and mutagenic properties, due to surface contamination as well as due to these substances occurring when food products are being manufactured [1, 2].

PAHs are toxic organic compounds with two or more condensed aromatic rings. Experts established relations between exposure to PAHs mixtures and unfavorable outcomes at birth, neurologic and behavioral effects, and poorer fertility [3, 4]. Experiments performed on animals allowed revealing that certain PAHs were carcinogenic and made for occurrence of some oncologic diseases including breast cancer, lung cancer, and malignant neoplasms in distal intestines. More than 100 PAHs congeners have been examined so far and 16 out of them are determined as priority contaminants by the US Environmental Protection Agency due to their toxic

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properties; 7 PAHs are considered potentially carcinogenic for people [3]. According to a classification by the International Agency for Research on Cancer, benz(a)pyrene belongs to Group 1 carcinogens (is carcinogenic for humans); benz(a)anthracene, chrysene, and benz(b)fluoranthene belong to group 2B carcinogens (are possibly carcinogenic for humans) [4–8, 10].

There are multiple natural and anthropogenic PAHs sources in the environment. These substances occur when organic compounds are being burnt or during technological processes applied to produce food products [10–13]. PAHs contents in food products depend on procedures applied to treat and manufacture specific food products (smoking, grilling, application of smoking flavoring agents, frying, etc.) and on quantitative and qualitative characteristics of a technological process as well. Food products that are primary components in any ration (milk products and bread) get contaminated due to PAHs migration along food chains and surface contamination of grain cultures [1, 3, 6, 9–11].

When identifying hazards and describing risks related to PAHs alimentary introduction, it is necessary to take into account carcinogenic and mutagenic equivalence factors that are used to describe overall toxicity and mutagenicity of the chemicals being considered in this work [3, 4]. All the above mentioned indicates it is quite relevant to perform integral assessment of food products contamination with PAHs.

Our research goal was to integrally assess food products contamination with PAHs basing on their determination with high precision techniques.

Data and methods. PAHs were determined according to the State Standard GOST 31745-2012[1] . The said methodical guide contains the following parameters: quantitative determination limit amounts to 2.0 μg/kg, and detection limit varies from 0.1 to 5.0 μg/kg for specific PAHs, for example, 1.0 μg/kg for benz(a)anthracene; 1.0 μg/kg for chrysene; 0.25 μg/kg for benz(b)fluoranthene; and 0.5 μg/kg for benz(a)pyrene. Similar requirements are fixed to these PAHs contents in the European Union. However, according to the European Union legislation[2], detection limit for all the above mentioned PAHs should be ≤ 0.30 μg/kg and quantitative determination limit should be ≤ 0.90 μg/kg [3, 14, 15]. Given that, it seemed necessary to validate the procedure in order to achieve better sensitivity, as well as precision and accuracy of measurements aimed at determining benz(a)anthracene, benz(b)fluoranthene, chrysene, and benz(a)pyrene contents. We calculated linearity, repeatability, intermediate precision, accuracy (extraction), uncertainty, detection limit and quantitative determination limit of our procedure and compared them to the above mentioned EU Commission Regulation.

Contaminants were quantitatively determined via absolute calibration. All the obtained data were processed with Agilent Open LAB CDS software package. To build up a calibration curve, we established dependence between peak square and a corresponding concentration of benz(a)anthracene, benz(b)fluoranthene, chrysene, and benz(a)pyrene in calibration solutions. Contents of each substance in PAHs mixture amounted to 4 μg/cm^3. Calibration solutions of concentrations equal to 0.0004; 0.0008; 0.0040; 0.0100 and 0.0200 μg/cm^3 were prepared via diluting.

To calculate calibration curves, we applied the least-square procedure. Correlation coefficient R^2 was a linearity criterion.

Repeatability and intermediate precision as parameters showing actual precision of a procedure were determined in accordance with State Standard ISO 5725-2-2002, item 7, and

[1] GOST 31745-2012. Food products. Determining polycyclic aromatic hydrocarbons with high performance liquid chromatography. Minsk, Gosstandart Publ., 2014, 8 p. (in Russian).

[2] Commission Regulation (EU) No. 836/2011 of August 19 2011, that fixes procedures for sampling and analyzing aimed at official control over contents of lead, cadmium, mercury, non-organic tin, 3-MCPD and benz(a)pyrene in food products. *EuroLex*. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32011R0836&qid=1574851930841&from=EN (27.08.2019).

State Standard ISO 5725-3-2002, item 8.2[3, 4]. Shifting was assessed as per State Standard ISO 5725-4-2002, item 5[5]. To assess precision, we obtained statistic data via analyzing working samples of canned fish (sprats), vegetable oils, spread, and mayonnaise.

Accuracy of results obtained with the procedure was studied with validation examinations under repeatability conditions via analyzing samples containing benz(a)anthracene, benz(b)fluoranthene, chrysene, and benz(a)pyrene in a quantity equal to 0.01 mg/kg.

Extraction degree was calculated as a ratio of measured benz(a)anthracene, benz(b)fluoranthene, chrysene, and benz(a)pyrene contents in a sample with addition and calculated benz(a)anthracene, benz(b)fluoranthene, chrysene, and benz(a)pyrene contents in a sample with addition according to experimental data.

Contamination level is a variable used to assess exposure. And here PAHs can occur in food products in quantities lower than detection limit or quantitative determination limit. In such cases substitute values are required. Modeling is applied when a share of product samples with low contamination is higher than 60 %. Otherwise, non-significant contamination levels are considered to be equal to zero. We applied models that involved assessing upper and lower limits as well as an average level. Values for lower limit were equated with detection limit; for upper limit, with quantitative determination limit; and as for an average level, we took simple mean of the above mentioned parameters for it[6] [4, 10].

We examined benz(a)anthracene, benz(b)fluoranthene, chrysene, and benz(a)pyrene contents in 278 food product samples. PAHs contents in coffee and tea as drinks were calculated taking into account a percent of them that was transferred from coffee beans and tea leaves into liquid drinks [16, 17] (Table 1).

Table 1

A % of PAHs that is transferred from initial coffee beans and tea leaves into liquid drinks

Food product	% of transferred PAH
Dark roasted ground coffee	7.0
Light roasted ground coffee	9.0
Instant coffee	0
Black tea	0.86
Green tea	5.9
Tea drink	1.0

All the obtained data were statistically processed with STATISTICA 12.0 software program. We applied Shapiro-Wilkes test and Kolmogorov-Smirnov test with Lilliefors correction to assess normal distribution. When significance was $p < 0.05$, data distribution was considered to be non-parametric. Hygienic assessment of examined products contamination with PAHs was performed using median (Me), interquartile range (25 %÷75 %), and 95 % percentile (95P). Validity of discrepancies between upper and lower limits compared to an average food products contamination as per median was determined at $p < 0.05$ as per Mann-Whitney U-test.

Basing on application instruction No. 004-1618 and according to the research works [18, 19], we performed an integral assessment of food products contamination with PAHs mixture[6].

Results and discussion. Performed validation tests allowed assessing uncertainty in measured mass concentration of benz(a)anthracene, benz(b)fluoranthene, chrysene, and benz(a)pyrene that included the following (Table 2):

a) repeatability factor;

b) building up and using calibration curve;

c) sample preparation for analysis.

[3] GOST R ISO 5725-2-2002. Accuracy (correctness and precision) of measurement procedures and results. Part 2. The basic procedure for determining repeatability and reproducibility of a standard measurement technique. Moscow, Standartinform Publ., 2009, 42 p. (in Russian).

[4] GOST R ISO 5725-3-2002. Accuracy (correctness and precision) of measurement procedures and results. Part 3. Intermediate precision parameters of a standard measurement technique. Moscow, GOSSTANDART Rossii Publ., 2002, 29 p. (in Russian).

[5] GOST R ISO 5725-4-2002. Accuracy (correctness and precision) of measurement procedures and results. Part 4. Basic procedures for determining correctness of a standard measurement technique. Moscow, Standartinform Publ., 2009, 24 p. (in Russian).

[6] The procedure for hygienic assessment of polyaromatic hydrocarbons contents in food products: application guide No. 004-1618. Approved by the Deputy Minister, Chief Sanitary Inspector of Belarus on June 22, 2018. Minsk, 2018, 14 p. (in Russian).

Table 2

Uncertainty budget in PAH measurement

Source	Relative standard, %			
	Benz(a)anthracene	Benz(b)fluoranthene	Chrysene	Benz(a)pyrene
Repeatability of measurement results in a sample	5.28	4.20	2.16	6.29
Sample treatment	3.53	3.53	3.53	3.53
Extraction	2.35	1.72	1.11	2.31
Building up and using a calibration curve	10.3	6.2	8.6	10.8
Total standard uncertainty	21.46	15.65	15.4	22.93
Maximum extended measurement uncertainty ($k = 2$)	42.92	31.30	30.8	45.86

Table 3

Metrologic properties of the procedure for PAHs determination

Metrologic property	Benz(a)anthracene	Benz(b)fluoranthene	Chrysene	Benz(a)pyrene
QDL, μg/kg	0.01	0.10	0.10	0.01
Repeatability, %	5.69	5.94	3.05	8.90
Intermediate precision, %	6.92	7.11	4.57	9.18
Repeatability limit, %	20.89	16.63	8.54	24.92
Intermediate precision limit, %	26.71	19.91	12.80	25.70
Determination accuracy, %	86.38	90.24	94.24	89.17
Shifting, %	2.35	1.72	1.11	2.31
Extended uncertainty for a range of measurements, %	42.92	31.30	30.80	45.86

The performed research allowed establishing metrologic properties of the procedure for PAHs determinaiton; they are given in Table 3.

Therefore, performed validation of the procedure allowed establishing quantitative determination limit; it amounted to 0.01 μg/kg for benz(a)anthracene and benz(a)pyrene and to 0.01 μg/kg for benz(b)fluoranthene and chrysene. The European Food Safety Authority (EFSA) recommends the ratio of detection limit to quantitative determination limit to be not less than 3.3; or detection limit should be equal to 1/10 of a standard deviation from a background signal. Consequently, detection limit for benz(a)anthracene and benz(a)pyrene amounts to 0.003 μg/kg in our research; and it amounted to 0.03 μg/kg for benz(b)fluoranthene and chrysene. It corresponds to requirements fixed in the EU Commission Regulation.

Having applied the conventional procedure taking into account its validation, we quantitatively determined benz(a)anthracene, benz(b)fluoranthene, chrysene, and benz(a)pyrene in certain food products. Number of samples that contained these substances in quantities lower than quantitative determination limit varied from 0 to 81.4 % for oils and vegetable fats, processed cacao products, smoked fish and meat products and cheese [20]; from 0 to 90 % for bread and bakery; from 36.7 to 93.3 % for milk products; from 0 to 43.3 % for tea; from 50 to 100 % for coffee.

We modeled samples with low contamination via applying substitute values instead of contamination levels lower than quantitative determination limit and we also applied toxic and mutagenic equivalent factors to characterize benz(a)anthracene, benz(b)fluoranthene, and chrysene contents [20]. It allowed us to determine range of contamination levels for the examined food products with both benz(a)pyrene itself and in values equivalent for the contaminant.

Benz(a)pyrene contents in various food products are given in Table 4.

Contamination with benz(a)pyrene varied within 0.003–0.01 μg/kg range for processed cocoa products, milk products, and coffee (hereinafter meant as a ready drink) and within 0.009–0.0013 μg/kg range for smoked cheese. Discrepancies between lower and upper limits against the average level of contamination with benz(a)pyrene were statistically significant for processed cocoa products ($U = 584$, $Z = –2.94$, $p < 0.05$), milk products ($U = 58$, $Z = –5.79$, $p < 0.05$), and coffee ($U = 29.5$, $Z = –6.21$, $p < 0.05$). We didn't reveal any discrepancies between the examined level in other food products and it may be due to small size of examined samplings and a great number of values being higher than the quantitative determination limit chosen for the procedure applied in this work.

Average contamination with benz(a)pyrene taken as per median amounted to 0.42 μg/kg for tea (hereinafter meant as a ready drink); 0.20 μg/kg for vegetable oils and fats; 0.05 μg/kg for smoked fish products and bread and bakery; 0.02 μg/kg for smoked meat products; 0.01 μg/kg for smoked cheese; 0.0065 μg/kg for milk products, coffee, and processed cocoa products.

The highest (95P) benz(a)pyrene quantity reached 4.84 μg/kg in tea and 1.29 μg/kg in vegetable oils and fats.

Table 5 contains data on PAH mixture levels in various food products taking into account their carcinogenic equivalents.

Contamination with PAH mixture determined with using carcinogenic equivalents amounted to 0.03–0.04 μg/kg, 0.07–0.08 μg/kg, 0.05–0.06 μg/kg, and 0.01–0.03 μg/kg for processed cocoa products and milk products, smoked meat products, smoked cheese, and coffee accordingly. Discrepancies between upper and lower limits against average level of contamination with PAH mixture taking into account its carcinogenic equivalents were detected for processed cocoa products ($U = 636$, $Z = –2.49$, $p < 0.05$), milk products ($U = 311$, $Z = –2.05$, $p < 0.05$) and coffee ($U = 270$, $Z = –2.65$, $p < 0.05$).

Average levels of contamination with PAH mixture basing on its carcinogenic equivalents as per median amounted to 0.55 μg/kg for tea; 0.36 μg/kg for vegetable oils and fats; 0.14 μg/kg for bread and bakery; 0.10 μg/kg for smoked fish products; 0.08 μg/kg for smoked meat products; 0.06 μg/kg for smoked cheese; 0.04 μg/kg for milk products; 0.03 μg/kg for processed cocoa products; 0.02 μg/kg for coffee.

Table 4

Benz(a)pyrene contents in certain food products (μg/kg)

Food product	N	Me (25 % ÷75 %)			95P		
		Lower limit	Average level	Upper limit	Lower limit	Average level	Upper limit
Vegetable oils and fats	45	0.20 (0.12 ÷0.60)			1.29		
Processed cacao products	43	0.003* (0.003 ÷ 0.03)	0.0065 (0.0065 ÷ 0.03)	0.01* (0.01 ÷ 0.03)	0.28		
Fish products (smoked)	30	0.05 (0.02÷0.21)			0.58		
Meat products (smoked)	30	0.02 (0.003 ÷ 0.06)	0.02 (0.0065 ÷ 0.06)	0.02 (0.01 ÷ 0.06)	0.99		
Cheese (smoked)	10	0.009 (0.003 ÷ 0.05)	0.011 (0.0065 ÷ 0.05)	0.013 (0.01 ÷ 0.05)	0.61		
Bread and bakery	30	0.05 (0.003 ÷ 0.20)	0.05 (0.0065 ÷ 0.20)	0.05 (0.01 ÷ 0.20)	0.35		
Milk products	30	0.003* (0.003 ÷ 0.03)	0.0065 (0.0065 ÷ 0.0065)	0.01* (0.01 ÷ 0.01)	0.04		
Tea (ready drink)	30	0.42 (0.08 ÷ 1.64)			4.84		
Coffee (ready drink)	30	0.003* (0.003 ÷ 0.003)	0.0065 (0.0065 ÷ 0.0065)	0.01* (0.01 ÷ 0.01)	0.003	0.0065	0.01

N o t e : * means validity of discrepancy between lower limit, average level, and upper limit ($p < 0.05$).

Table 5

PAH mixture levels in certain food products basing on their carcinogenic equivalents (μg/kg)

Food products	Me (25 % ÷75 %)			95P		
	Lower limit	Average level	Upper limit	Lower limit	Average level	Upper limit
Vegetable oils and fats	0.36 (0.22 ÷0.73)			1.57		
Processed cocoa products	0.03* (0.02 ÷ 0.05)	0.03 (0.02 ÷ 0.06)	0.04* (0.03 ÷ 0.06)	0.36	0.38	
Fish products (smoked)	0.10 (0.04÷0.31)	0.10 (0.05÷0.31)		0.87	0.88	
Meat products (smoked)	0.07 (0.04 ÷ 0.15)	0.08 (0.05 ÷ 0.16)		1.68		
Cheese (smoked)	0.05 (0.03 ÷ 0.07)	0.06 (0.03 ÷ 0.08)		0.87	0.88	
Bread and bakery	0.14 (0.03 ÷ 0.28)			0.64		
Milk products	0.03* (0.01 ÷ 0.06)	0.04 (0.01 ÷ 0.07)	0.04* (0.02 ÷ 0.07)	0.09		0.10
Tea (ready drink)	0.55 (0.11 ÷ 2.14)			6.06		
Coffee (ready drink)	0.01* (0.01 ÷ 0.03)	0.02 (0.01 ÷ 0.04)	0.03* (0.02 ÷ 0.04)	0.48		0.49

N o t e : * means validity of discrepancy between lower limit, average level, and upper limit ($p < 0.05$).

Highest (95P) contamination levels reached 6.06 μg/kg in tea and 1.57 μg/kg in vegetable oils and fats.

Table 6 contains data on PAHs mixture contents in different food products using mutagenic equivalents.

Contamination with PAHs mixture taken as per its mutagenic equivalents varied within 0.03–0.05 μg/kg for processed cocoa products and milk products; 0.11–0.12 μg/kg for smoked fish products; 0.05–0.07 μg/kg for smoked cheese; 0.02–0.04 μg/kg for coffee. Discrepancies between upper and lower limits against average level of contamination with PAHs mixture taking into account its mutagenic equivalents were detected for processed cocoa products ($U = 418$, $Z = –4.37$, $p < 0.05$), milk products ($U = 278$, $Z = –2.54$, $p < 0.05$), and coffee ($U = 135$, $Z = –4.65$, $p < 0.05$). Average levels of contamination with PAH mixture basing on its mutagenic equivalents as per median amounted to 0.81 μg/kg for tea; 0.44 μg/kg for vegetable oils and fats; 0.14 μg/kg for bread and bakery; 0.12 μg/kg for smoked fish products; 0.11 μg/kg for smoked meat products; 0.07 μg/kg for smoked cheese; 0.03 μg/kg for smoked coffee; 0.04 μg/kg for milk products and processed cocoa products.

Maximum (95P) PAHs mixture contents recalculated as per its mutagenic equivalent reached 6.63 μg/kg in tea and 1.85 μg/kg in smoked meat products.

We didn't detect violated maximum permissible concentrations of benz(a)pyrene and mixture of benz(a)anthracene, benz(b)fluoranthene, chrysene, and benz(a)pyrene fixed in hygienic standards existing in Belarus, the Eurasian Economic Union, and in the European Union in all the examined food products samples[7, 8, 9].

[7] Commission Regulation (EU) No 835/2011 of 19 August 2011 amending Regulation (EC) No 1881/2006 as regards maximum levels for polycyclic aromatic hydrocarbons in food stuffs. *EuroLex*. Available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32002R0178&qid= %201429 076106145 (29.03.2019).

[8] The hygienic standard «Parameters of food products and food raw materials safety for human». Approved by the Order of the Belarus Public Healthcare Ministry on June 21, 2013 No. 52. Minsk, The Republican Center for Hygiene, Epidemiology, and Public health Publ., 2013. Available at: http://minzdrav.gov.by/ru/dlya-spetsialistov/normativno-pravovaya-baza/tekhnicheskie-normativnye-pravovye-akty/teksty-tekhnicheskikh-normativnykh-aktov/pishchevye-produkty-i-pishchevye-dobavki.php (29.03.2019).

[9] TR CU 021/2011. On food safety from 15.12.2011. Minsk, BelGISS Publ., 2015, 160 p. (in Russian).

Table 6

PAHs mixture levels in certain food products basing on their mutagenic equivalents (μg/kg)

Food products	Me (25 % ÷75 %)			95P		
	Lower limit	Average level	Upper limit	Lower limit	Average level	Upper limit
Vegetable oils and fats	0.44 (0.27 ÷0.78)			1.62		
Processed cocoa products	0.03* (0.02 ÷ 0.05)	0.04 (0.03 ÷ 0.06)	0.05* (0.04 ÷ 0.07)	0.45		
Fish products (smoked)	0.11 (0.05÷0.34)	0.12 (0.06÷0.34)		0.89		0.90
Meat products (smoked)	0.11 (0.07 ÷ 0.17)		0.11 (0.08 ÷ 0.17)	1.85		
Cheese (smoked)	0.05 (0.03 ÷ 0.08)	0.07 (0.04 ÷ 0.08)	0.07 (0.05 ÷ 0.09)	0.86		0,87
Bread and bakery	0.12 (0.03 ÷ 0.28)	0.14 (0.05 ÷ 0.29)	0.15 (0.06 ÷ 0.30)	0.89		
Milk products	0.03* (0.01 ÷ 0.09)	0.04 (0.02 ÷ 0.10)	0.05* (0.04 ÷ 0.11)	0.21		0,22
Tea (ready drink)	0.81 (0.12 ÷ 2.39)			6.63		
Coffee (ready drink)	0.02* (0.01 ÷ 0.03)	0.03 (0.02 ÷ 0.04)	0.04* (0.04 ÷ 0.06)	1.13		

N o t e : * means validity of discrepancy between lower limit, average level, and upper limit ($p < 0.05$).

Our results revealed that the highest contamination with benz(a)pyrene and PAHs mixture taking into account carcinogenic and mutagenic equivalents occurred in vegetable oils and fats and tea. It can be due to a sequence of technological processes that make for occurrence of the examined substances and to physical and chemical properties of the said food products. Greater contamination with the examined substances occurring in vegetable oils and fats can be due to high temperatures being applied when oil culture seeds are being dried and then roasted [1–3, 8]. Ether oils that are contained in tea can act as co-solvents for certain lipophilic compounds, PAHs included, and it results in greater contents of the examined substances in tea drinks [17, 18].

Lower benz(a)pyrene and PAH contents recalculated as per its carcinogenic and mutagenic equivalents in smoked meat, fish, and cheese are due to technological peculiarities typical for their production, namely, smoked flavoring agents or up-to-date equipment applied in production processes allowing to control conditions for smoked products manufacturing.

Bread and bakery, processed cocoa goods, and coffee get contaminated due to such technological operations as raw materials drying and roasting. These processes usually involve high temperatures for roasting [1–2, 8, 16]. Besides, cocoa and coffee beans get contaminated with PAH during their storage and transportation in jute or sisal bags treated with textile oil [1–2, 8, 16].

Milk products get contaminated due to PAH migration along food chains and surface contamination of grain cultures.

We didn't detect the examined substances in instant coffee; it is due to PAHs being hydrophobic and peculiarities of applied technological processes as ground coffee beans are treated with hot water under 15 atm (steam treatment), and then extracted soluble substances are dried with hot air. Therefore, the examined compounds that occur in ground coffee do not penetrate a ready product during extraction.

Conclusion. Validation of the procedure for quantitative PAH determination in food products allowed establishing lower detection limit for benz(a)anthracene and benz(a)pyrene,

namely, down to 0.003 μg/kg; and down to 0.03 μg/kg for benz(b)fluoranthene and chrysene. Average contamination with benz(a)pyrene as per median varied from 0.0065 μg/kg in processed cocoa products and milk products to 0.42 μg/kg in tea; from 0.03 μg/kg to 0.55 μg/kg basing on carcinogenic equivalents; from 0.04 μg/kg to 0.81 μg/kg basing on mutagenic equivalents. Contamination with benz(a)pyrene that was close to its maximum levels (95P) taking into account carcinogenic and mutagenic equivalents amounted to 4.84 μg/kg, 6.06 μg/kg, and 6.63 μg/kg in tea. We didn't detect maximum permissible concentrations of benz(a)pyrene and a mixture of benz(a)anthracene, benz(b)fluoranthene, and chrysene in any examined food product samples. Our research results revealed that the highest contamination with the examined substances was typical for food products manufactured via smoking, roasting, and drying as well as for products that contain fats and ether oils. Integral assessment of food products contamination with PAHs allowed determining contents of the examined substances as a mixture taking into account their individual contributions into overall contamination and degree of their carcinogenic and mutagenic activity.

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Research article

EXPOSURE ASSESSMENT AND RISK CHARACTERIZATION OF N-NITROSODIMETHYLAMINE (NDMA) IN THE DIET OF CHILDREN FROM 6 TO 36 MONTHS IN HANOI, VIETNAM

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N-Nitrosodimethylamine (NDMA) is a highly hepatotoxic compound and classified as group 2A according to IARC, which is probably carcinogenic to humans. The habit of consumption of grilled meat-based foods may lead to a health risk, especially in children. In this study, a food consumption survey was conducted in 4 districts (2 in urban and 2 in suburban areas) in Hanoi, Vietnam. Food samples in the diet of children from 6 to 36 months was collected and tested for NDMA by GC-MS/MS method. Total exposure dose was calculated and compared to the proposed tolerable daily intake (TDI) to characterize the risk. Among the food tested, NDMA was detected in canned puree, grilled meat and sausage. The average contents of NDMA were 1.50 µg/kg, 1.18 µg/kg and 0.20 µg/kg in grilled meat, sausage and puree, respectively. The average total daily exposure dose of NDMA was 8.23 ng/kg bw/day in all studied group, which were within the upper recommended TDI (9.3 ng/kg bw/day). With a certain assumption, the cancer risk caused by exposure to NDMA were higher than the recommended value of WHO.

Key words: *N-Nitrosodimethylamine, NDMA, exposure assessment, cancer risk, risk characterization, risk assessment, GC-MS/MS.*

N-Nitrosamine is a group of various compounds with N-Nitroso structure, which is formed from the reaction between a nitrosating agent with a secondary amine in the condition of temperature. The major N-Nitrosamine compound, N-Nitrosodimethylamine (NDMA), is a highly hepatoxic compound and a potential carcinogen and has been clas-

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sified as probably carcinogenic to human by International Agency for Research on Cancer from 1987 [1, 2]. According to U.S. Environmental Protection Agency (EPA) in a study in 1989, the lowest-observed adverse effect level (LOEAL) was established at 0.05 mg/kg bw/day for carcinogenic effect and the no-observed adverse effect level (NOEAL) was established at 0.5 mg/kg bw/day for non-carcinogenic effect [3]. In 2007, Fitzgeral and Robinson applied mathematical models to the incidence data for hepatocellular carcinomas and hemangiosarcomas, followed by arithmetic and exponential-weight averaging of the 5 % extra risk dose (mBMD 0.05) for the various models, produced an mBMD 0.05 range of 0.020–0.028 mg/kg bw/day. This was then divided by a range of modifying factors to account for seriousness of the carcinogenic endpoint, adequacy of the database, and inter- and intraspecies differences, generating a TDI range of 4.0 to 9.3 ng/kg bw/day [4].

Many researches have revealed the occurrence of NDMA as well as other N-nitrosamines in foods. Food products which go through heated processing steps such as frying or grilling may pose a risk of N-nitrosamines formed by reaction between amino acids from proteins decomposition and nitrate which is preservative in food. The amount of nitrosamine formed depends on the time of preparation, temperature, and the nitrates content in the sample [5]. The content of NDMA in meat products such as grilled meat, smoked meat, canned fish ... ranges from 1–100 ng/g [6–12].

Our previous study have described a method for determination of NDMA and other N-nitrosamines using QuEChERS extraction technique combined with EI-GC-MS/MS [13]. In this study, a food consumption survey will be performed together with food collection and testing for NDMA. These data will be used for exposure assessment and risk characterization of NDMA in the diet of Vietnamese children of age from 6 to 36 months.

Data and methods.

Food consumption survey.

The survey has been carried out in medical centers, nutritional centers and private houses in 4 districts in Hanoi including Dan Phuong, Thanh Tri, Bac Tu Liem and Dong Da, which are graphically representative for Hanoi habitants. Parents who had children of the given age (n = 480) were questioned in May and June of 2019. All children were divided into three age groups according to their age (group 1 – 6–12 months (29.7 %); group 2 – 12–24 months (46.2 %) and group 3 – 24–36 months (24.1 %)). Overall distribution of children as per gender was as follows: 48.9 % were girls and 51.1 % were boys and this is equal to the general gender proportion for Hanoi.

Food sampling.

A total of 400 samples including rice porridge (with various kinds of meat), cereal based foods, canned purees, sausages, and processed meats were randomly collected from markets, grocery stores and supermarkets in the four studied districts. Each sample was collected at least 1 kg, placed in air-tight sealed plastic bags, encoded and transported to National Institute of Food Control for analysis of NDMA.

Analysis of NDMA.

The method for determination of NDMA content was described previously, which contain a QuEChERS extraction step and GC-MS/MS analysis. Five grams of homogenized sample was added with internal standard (NDMA-d6) of 1 µg/mL (50 µL) and extracted with 10 mL of acetonitrile: water (1:1, v/v) with the addition of ammonium chloride (5.5 g). The extract was cleaned-up with dispersive solid phase extraction containing 300 mg of anhydrous magnesium sulfate and 100 mg of C18 sorbent. n-Hexane (2 mL) was used to remove the fat and then acetonitrile layer was diluted with dichloromethane (1:1) then analyzed by GC-MS/MS.

The GC-MS/MS system was a GC 7890A and a triple-quadrupole mass spectrometer

7000B (Agilent Technologies, USA). Chromatographic separation was done on a DB 1701 column (15 m length·0.25 mm i.d.·0.25 μm film thickness) with a temperature ramp. The MS condition included an electron impact source and multiple reaction monitoring mode with the transitions of NDMA and the IS were 74 → 44; 74 → 42.0 and 80 → 50; 80 → 48, respectively.

The method was internally validated and showed good performance to be used for food analysis with the limit of detection (LOD) of 0.15 ng/g.

Exposure assessment.

The exposure dose of NDMA from studied food products was calculated as follows:

$$(\text{Exposure dose}\left(\text{ng/kg bw/day}\right) = \quad (1)$$

$$= \frac{\text{NDMA level (ng/g)} \cdot \text{Consumption}\left(\text{g/day}\right)}{\text{Body weight}\left(\text{kg bw/person}\right)}).$$

Since the left-censored data (not detected samples) of some matrices was higher than 50 %, LOD was used for not detected samples. However, for the matrices that no samples were detected with NDMA, these will be withdrew from the exposure dose calculation.

Risk characterization.

The health risk of NDMA was assessed using non-carcinogen effect assessment, the exposure dose was directly compared to the TDI of 4.0 to 9.3 ng/kg bw/day which was proposed by Fitzgeral and Robinson [4].

Besides, assuming that people get exposure to the NDMA for the whole life, the cancer risk contribution of this age group due to ingestion of NDMA in food was calculated using following equation:

$$(\text{Cancer risk} =$$

$$= \frac{\text{Exposure dose (ng/kg bw/day)}}{10^6 \cdot \text{Life time}} \times \quad (2)$$

$$\times \frac{\text{Slope factor} \cdot \text{Exposure duration}}{10^6 \cdot \text{Life time}}).$$

Since liver cancer is the major problem induced by NDMA consumption, this was chosen as the end point of health risk in this study. According to US EPA, the slope factor was estimated of 51 per mg/kg bw/day [14], while another slope factor reported by California Office of Environmental Health Hazard Assessment was 16 per mg/kg bw/day [15]. These was used as the upper-bound and lower-bound of cancer slope factor. The average life time of 70 years was used. In this study, the exposure duration was only 2.5 years, which will show the contribution of this period to the whole risk of cancer. However, the exposure duration of 30 years can be used assuming the exposure dose will not change over the period. The lifetime excess cancer risk level is 10^{-5}, which based on the World Health Organization (WHO) recommendation [16].

Data analysis.

The food consumption was analyzed statistically using SPSS 16.0. The exposure dose and risk characterization were performed using Microsoft Excel.

Results and discussion.

Occurrence of NDMA.

NDMA was found in 76 out of the 80 sausages samples (95.0 %) with the concentration from 0.15 to 2.20 μg/kg and the average value of 1.18 μg/kg; 79 out of the 80 grilled or fried meat samples (95 %), with the concentration from 0.15 to 2.80 μg/kg and the average value of 1,50 μg/kg. For canned puree samples, only 7 of 80 samples was detected with NDMA. Using LOD for not detected samples, the average concentration was 0.20 μg/kg, ranged from 0.15 to 0.84 μg/kg. NDMA was not detected in samples of rice porridge and cereal based foods.

Food consumption data.

The intake of studied foods for each age group are summarized in table 1.

It was obvious that the main foods used for children from 6 to 36 months in Hanoi, Vietnam were from rice and other cereals. The proportion of meat-based ingredients in

Table 1

The daily consumption of food products in Hanoi, Vietnam (mean, g/day)

Age groups (month)	N (%)	Rice porridge	Instant cereals	Canned purees	Sausages	Process meats
6 to 12	142 (29.5)	174.4	42.8	20.7	34.8	30.5
> 12 to 24	223 (46.5)	204.1	69.3	27.4	36.4	33.7
> 24 to 36	115 (24.0)	216.4	110.6	27.6	32.9	48.6
All: 6 to 36	480 (100)	191.8	66.3	25.2	35.2	37.6

Table 2

Average exposure dose of children from 6 to 36 months

Age groups (month)	Exposure dose (ng/kg bw/day)				TDI (ng/kg bw/day)
	Canned purees	Sausages	Process meats	Total	
6 to 12	0.38	3.87	4.30	8.55	4.0-9.3
> 12 to 24	0.46	3.67	4.31	8.45	
> 24 to 36	0.38	2.72	5.10	8.20	
All: 6 to 36	0.40	3.32	4.51	8.23	

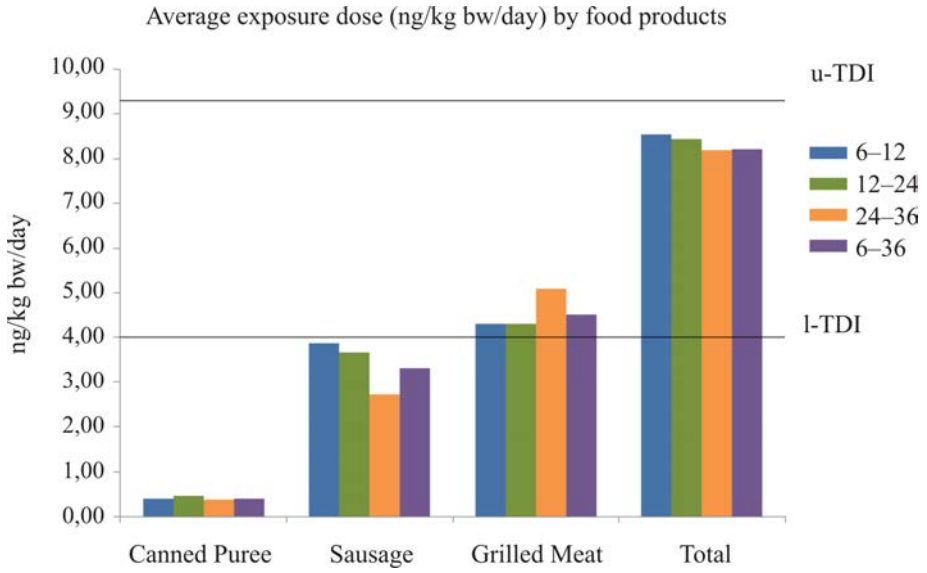

Figure. Average exposure dose by food products compared to TDI

rice porridge and instant cereals were small, which leads to a very low risk of NDMA contaminant. For this reason, these two food groups were eliminated from risk assessment. The average daily consumption of canned purees, sausages and processed meats were 25.2, 35.2 and 37.6 g/day, respectively. It was a surprise that children start to use sausages and grilled or fried meats from very young age (6–12 months of age).

Exposure dose and acute health risk.

The exposure doses of different age groups of children from 6 to 36 months were presented in table 2 and figure.

Table 3

Cancer risk contribution by exposure to NDMA

Food groups	Contribution of the studied period to cancer risk		Estimated cancer risk with assumption	
	Lower cancer risk	*Upper cancer risk*	*Lower cancer risk*	*Upper cancer risk*
Canned purees	$0.023 \cdot 10^{-5}$	$0.072 \cdot 10^{-5}$	$0.273 \cdot 10^{-5}$	$0.869 \cdot 10^{-5}$
Sausages	$0.190 \cdot 10^{-5}$	$0.605 \cdot 10^{-5}$	$2.28 \cdot 10^{-5}$	$7.26 \cdot 10^{-5}$
Processed meats	$0.257 \cdot 10^{-5}$	$0.821 \cdot 10^{-5}$	$3.09 \cdot 10^{-5}$	$9.85 \cdot 10^{-5}$
Total	$0.470 \cdot 10^{-5}$	$1.49 \cdot 10^{-5}$	$5.64 \cdot 10^{-5}$	$18.0 \cdot 10^{-5}$

The results of the study showed that the total exposure doses of NDMA for all food groups were in the range from 8.20 to 8.55 ng/kg bw/day. In particular, the group of processed meats gave the highest value (4.51 ng/kg bw/day). According to the recommendations from the study of Fitzgerald and Robinson [4], the recommended TDI for NDMA ranges from 4.0 to 9.3 ng/kg bw/day. The average exposure dose of NDMA in the Vietnamese children's study showed that the values for all age groups of processed meat were greater than 4.0 ng/kg bw/day, exceeding the lower TDI (l-TDI) as recommended. The total exposure doses of NDMA were as highest as 8.55 ng/kg bw/day, which did not exceed the upper recommended TDI (u-TDI) level. This indicates that the exposure to NDMA in the products does not pose an acute health risk to children from 6 to 36 months in Hanoi, Vietnam.

Cancer risk.

The contribution to cancer risk and the estimated cancer risk with the assumption that the people will be exposure to NDMA for 30 years and the exposure dose will not change is presented in Table 3.

According to table 3, the contribution of the studied period to cancer risk were lower than the recommended value of WHO (reference value of 10^{-5}) except for the total value of upper cancer risk. However, with the certain assumption, the cancer risk when consuming sausages and processed meats were higher than the reference value, which were 2.25 and 3.09 times higher, respectively (if used lower cancer slope factor) and were 7.26 and 9.85 times higher, respectively (if used upper cancer slope factor). This means that the consumption of sausages and processed meats for a long time (30 years) can be a reason for liver cancer risk.

Conclusion.

An exposure assessment and risk characterization of NDMA has been performed and show the daily intake of NDMA from foods in Vietnamese children of 6 to 36 months was within the recommended tolerable daily intake. However, the values can pose a cancer risk higher than the recommendation of WHO. These results can be used for risk communication and risk management of consuming these kinds of products in Vietnam.

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

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Research article

CONSUMPTION OF UNREGULATED FOOD ITEMS (FALSE MORELS) AND RISK FOR NEURODEGENERATIVE DISEASE (AMYOTROPHIC LATERAL SCLEROSIS)

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Unknown environmental factors are thought to contribute to the etiology of sporadic forms of amyotrophic lateral sclerosis (ALS). Strong evidence supporting this view is found in the post-World War decline and disappearance of high-incidence ALS in three Western Pacific populations that formerly utilized neurotoxic cycad seed as a traditional source of food and/or medicine. The principal toxins in cycads (cycasin) and in False Morel mushrooms (gyromitrin) generate methyl free radicals that damage DNA and cause mutation and uncontrolled division of cycling cells and degeneration of late-/post-mitotic neurons. Since False Morels are scavenged for food in Finland, Russia, Spain, and USA, research studies are underway in Western Europe and USA to determine if the practice is associated with sporadic ALS.

Key words: *Amyotrophic lateral sclerosis, cycad seed, cycasin, gyromitrin, DNA damage, Guam, Finland, Russia, USA.*

While a small percentage of human neurodegenerative diseases has a genetic origin, the large majority occurs sporadically. Disorders such as amyotrophic lateral sclerosis (ALS) are believed to result from the action of unknown environmental factors on individuals with an underlying genetic susceptibility [1]. Evidence for the primary or exclusive role of an environmental trigger comes from longitudinal observation of Western Pacific ALS [2]. This neurodegenerative disorder was formerly present in very high incidence among populations in the Mariana Island of Guam (USA), the Kii Peninsula of Honshu Island (Japan), and Papua Province, west New Guinea (Indonesia). However, over the past seven decades, the incidence of ALS has declined in all three populations, with disappearance of the disease on Guam [3]. This has coincided with population development and acculturation to modernity during which traditional practices progressively declined. Discontinued practices include use of the neurotoxic seed of cycad gymnosperms (*Cycas spp.*) for food (Guam) and/or medicine (Guam, Kii, Papua). These traditional practices have been associated with ALS in all three pockets of neurodegenerative disease, although the strongest epidemiological evidence comes from Guam [2].

Cycad Toxins. Cycad seed linked to Western Pacific ALS contain cycasin (2–4 % w/w) and smaller amounts of the nonprotein amino acid β-*N*-methylamino-L-alanine (L-BMAA), both of which have genotoxic and neurotoxic potential. The concentration of cycasin (but not of L-BMAA) in flour derived from washed cycad seed used by Guamanians for food was strongly associated with ALS among males and females [4]. Cycasin (methylazoxymethanol-β-D-glucoside) is metabolized by plant, animal and human glucosidases to form methylazoxymethanol (MAM), which in turns forms methyl free radicals that damage cellular DNA [5]. MAM-induced DNA damage in cycling cells

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may trigger mutations that lead to uncontrolled mitosis and tumorigenesis, a property used experimentally to generate an animal model of colon cancer. MAM is also a potent developmental neurotoxin that disrupts the development of rodent brain and activates cellular pathways associated with both cancer and neurodegeneration [6].

False Morel Toxins. Methyl (carbon-centered) free radicals are also generated by hydrazine compounds that are mechanistically related to MAM [7]. Hydrazine is used in agricultural chemicals (pesticides), chemical blowing agents, pharmaceutical intermediates, photography chemicals, boiler water treatment for corrosion protection, textile dyes, and as fuel for rockets, spacecraft and emergency power units in certain military jet aircraft [8]. For present purposes, however, the most relevant potential exposure to hydrazine compounds is from the consumption of certain fungal species. The commercially available and widely eaten Button Mushroom (*Agaricus bisporus* Lange) contains up to 0.04 % agaritine (*β*-*N*-[*γ*-L-(+)-glutamyl]-4-hydroxymethylphenylhydrazine) and 4-hydroxymethylphenylhydrazine) [9]. Of interest here, however, are the highly poisonous False Morel mushrooms (*Gyromitra*, *Helvella* and *Verpa* spp.), notably *Gyromitra esculenta* Pers. (Figure); this species contains 0.3 % gyromitrin (acetaldehyde-*N*-methyl-*N*-formylhydrazone), the hydrolysis of which forms DNA-damaging methylating agents, namely *N*-methyl-*N*-formylhydrazine (MFH) and N-monomethylhydrazine (MMH), by further hydrolysis of MFH [10]. The risk of long-term adverse health effects from consumption of *Gyromitra esculenta* may be greater in individuals with genetic slow acetylation rates, which would result in larger amounts of MMH formed from gyromitrin [10]. Since hydrazines and MAM induce the same type of DNA damage, it is hypothesized that single or repeated exposure to methyl free-radical-generating hydrazines might trigger long-latency neurodegeneration culminating in ALS or a related brain disease [11].

Food Use of Certain Ascomycetes Fungi.

Distribution. The False Morel *G. esculenta* has a very wide distribution, including the entire continent of Europe, especially Germany and Poland. It is also found throughout Asia, everywhere from Russia to Indonesia. In North America, it occurs from Mexico to Alaska, especially in the U.S. Midwest, Pacific Northwest, and the Rockies. *G. esculenta* also occurs in North Africa and the Middle East regions around the Mediterranean Sea.

Europe and USA. Consumption of wild mushrooms, which include False Morels (*Gyromitre*, *fausse morille*, *morille brun*e) and True Morels (*Morchella spp.*), has been identified as a risk factor for a cluster of 12 ALS patients in a small community in Savoie in the French Alps [11]. While True Morels (*morille*) are highly prized as a delicacy in Europe and beyond, it can be difficult to distinguish them anatomically from poisonous False Morels. Consumption of False Morels is also documented elsewhere in Europe (Finland) and the USA, especially in the State of Michigan, where the local Poison Control Center historically has received the highest number of MMH mushroom-related calls [13, 14]. Eight to ten species of *Gyromitra* exist on the North American continent, including *G. montana Harmaja* (possibly *G. gigas*), which reportedly has been collected from the West Coast of the USA and sold through intermediaries for use in restaurants in the State of Florida [15, 16].

Finland. False Morels are considered a delicacy in Finland [10]. The Finnish Food Authority recommends extensive washing and double boiling prior to their ingestion and advises against ingestion by children and pregnant and breastfeeding women because of «residues of the toxin gyromitrin despite processing» [17]. However, in previous dec-

ades, dried, or once-boiled fresh False Morels were considered safe to eat. During and after the Finnish Winter War with Russia (November 30, 1939 – March 12, 1940), there was a mass migration of Karelians to Finland and particularly to the southeast (Itä-Suomi) where there is a strong mushroom-eating culture, including MMH-generating *G. esculenta* (*Korvasieni*) among Karelians. Between 1914 and 1945, one quarter of the number of acute poisonings attributed to *G. esculenta* occurred in southeastern Finland [18]. Consumption of *Gyromitra spp.* can trigger acute gastrointestinal (nausea, vomiting, diarrhea) and neurotoxic effects (headache, vertigo, ataxia, fever, muscle fasciculation, seizures, coma, death) [19]. Notably, the birth location of a cluster of ALS subjects in Finland corresponds to a region of False Morel consumption [20]. The cluster involved a population of half a million subjects residing in parts of the Finnish provinces of Kuopio, Mikkeli, and Pohjois-Karjala, as well as parts of present-day Russian Karelia. ALS rates were 225 % higher among Finnish WWII evacuees from Karelia (18 per 100,000) compared with non-evacuees (8 per 100,000). As noted by the authors, these data speak against a genetic etiology for ALS and for exposure to one or more environmental factors that made the evacuees more liable to develop motor neuron disease later in their lives.

Russian Federation. *G. esculenta* (*strochok*, *Строчок*) grows wild in the pine-tree forests near St. Petersburg (Dibuny-Pesochny, Kannelyarvi, Kuzmolovo, Lounatjoki, Orekhovo, Petiayarvi, notably close to the Lenin Trail proximate to Razliv near Dibun, northwest of the city (Figure).

Precise locations, sighting dates and photographs of *G. esculenta* are recorded on *Google Earth*, which suggests they are collected and used for food, as in Karelia. G.N. Zaraf'iants, Saint-Petersburg State Medical University, has described fatalities from the gyromitrin syndrome triggered by ingestion of *G. esculenta* (May) or, in August-September, *G. gigas* Krombh (Snow or Russian Autumn Morel) [21, 22]. Another False Morel, *Verpa bohemica* Krombh, is said to be sold frozen in Russia and eaten by many Russian people [23, 24]. Consumption of large amounts of *V. bohemica* in a single sitting, or on successive days, has been reported to cause a gyromitrin-like syndrome in susceptible individuals [25]. *G. korshinskii* Jacz. (Round Spored False Morel) has been described across the entire Russian Federation [26].

Figure. False morel mushroom (*Gyromitra esculenta*, *Strochok*) near Lenin Trail in area of Razliv near Dibuny, north-west from Saint Petersburg, Russia. Leninskaya Tropa, Pesochny, Sankt-Peterburg, Russia

There are no data to suggest any long-term adverse health of consuming MMH-containing fungi in Russia but the question may never have been addressed. Given evidence of their acute neurotoxic potential, the DNA-alkylating properties of MMH, and the tentative association of these properties with long-latency motor neuron disease and/or cancer, the question has merit [9, 11]. While causes are unknown, cancer rates in Russia greatly exceed those in Europe and the USA [27]. Colorectal cancer is the second cause of cancer death (after breast cancer) in women and the third for men (after lung and stomach cancers), and both the incidence and mortality have increased since 2000 [28]. With respect to neurodegenerative disease,

Russian research has focused mainly on genetic risk factors for ALS [29, 30]. While Bunina bodies, the neuronal inclusions named for Russian neuropathologist Tat'yana Bunina [31], are seen in familial, sporadic and Guam cases of ALS [32], the epidemiology of ALS in the Russian Federation is not well developed [1].

Conclusions. Research is underway in Europe and the USA to determine if there is any relationship between ALS and food use of False Morels, with or without an acute poisoning event attributable to MMH, which forms a methyl free radical that alkylates DNA. Research on this question has been triggered by evidence of a similar molecular mechanism underlying the neurotoxic property of MAM, the aglycone of the principal toxin in cycad seed that is associated with Western Pacific ALS. Since clinical evidence of Guam and Kii ALS may surface years or decades after migration to or from affected populations in the first part of life [5], it is evident that dietary practices must be scrutinized from childhood onward to test for an association between food use of False Morels and long-latency neurological disease (or cancer), whether in Europe, the USA or the Russian Federation.

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Research article

COMBINED EXPOSURE TO CHEMICAL FACTORS AND FACTORS RELATED TO EDUCATIONAL PROCESS

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Hygienic assessment of combined effects produced by heterogeneous factors on comorbid diseases in the nervous system and digestive organs in children is vital for early detection and prevention of health disorders given existing risks and threats.

Our research goal was to estimate probability of comorbid diseases in the nervous system and digestive organs in children attending primary schools under combined exposure to chemical factors and factors related to the educational process.

Our research objects were factors related to the educational process that produced their effects on children aged 7–10 who attended primary schools with different educational programs; chemicals contents in ambient air and air inside classrooms as well as in children's blood; biochemical parameters of negative effects; models showing cause-and-effect relations.

Our research results allowed us to identify priority influencing factors and their share contributions into negative effects development in case there was comorbidity with nervous system diseases and digestive organs diseases; to give grounds for biological markers of negative effects applied for early diagnostics and development of activities aimed at preventing comorbid disorders for schoolchildren. Implementation of an algorithm for calculating and estimating probability of comorbid diseases in the nervous system and digestive organs under combined exposure to heterogeneous factors involves determining additional comorbidity cases among children who attend schools with more comprehensive educational programs in comparison with children attending ordinary schools.

Timely and adequate correction of detected influencing factors and development of activities aimed at preventing comorbid health disorders will allow minimizing risks of comorbid diseases in the nervous system and digestive organs in school children under combined exposure to chemical factors existing in the environment and inside classroom and factors related to the educational process.

Key words: *chemical environmental factors, factors related to the educational process, comorbidity of diseases, biomarkers of negative effects, cause-and-effect relations.*

At present environmental objects tend to be of poor quality and educational processes at schools are rather stressful and intense; they involve much less physical activity than they used to. All this can exert combined negative impacts on the state of schoolchildren's leading vital systems. It can result in functional disorders in the digestive organs, first of all, motility disorders due to changes in nervous regulation caused by vegetative dysfunction as a pathogenic mechanism of diseases occurrence is common in this case (comorbidity) [1–5].

Results obtain in several Russian research works indicate that children living in industrially developed regions have technogenic chemicals in their blood that are simultaneously tropic to the central and vegetative nervous system and digestive organs [6, 7]. And such negative effects as functional disorders of the nervous system and motility disorders in the gastroduodenal and biliary systems occur

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together with oxidative stress and lower non-specific resistance of the gastrointestinal tract mucosa [8–11].

Health of children who attend primary schools operating in the contemporary innovative educational space is influenced not only by environmental factors but also by prevailing mental work together with lower physical activity, high static loads, and combined basic and additional education without taking into account aggregated volumes of studying a primary school child has to face [12, 13]. Children have to spend a lot of time under excessive educational loads and it creates neurotic disorders with the subsequent clinical manifestation, functional disorders in the gastrointestinal tract and other critical organs and systems [14].

As a result, there are additional diseases cases among children simultaneously in the gastrointestinal tract and nervous system, and this comorbid pathology tends to become chronic more frequently [15, 16]. There are rather alerting negative trends such as a 2-time growth in prevalence of gastric diseases among children, especially those who attend primary school; these diseases are chronic gastroduodenitis, stomach ulcer, and biliary dysfunction combined with functional disorders of the nervous system such as neurotic and asthenic disorders and vegetative-vascular dystonia [17–20].

Chronic somatic pathology in adults can actually occur as early as at pre-school age or during primary school years and later on it results in poorer life quality and lower labor activity. Bearing that in mind, it seems vital to detect and prevent additional comorbidity of the nervous system and digestive organs in primary school children under combined exposure to heterogeneous factors. In this relation it is especially important to substantiate biological markers showing negative effects produced by comorbidity among schoolchildren in order to provide early diagnostics and prevent health disorders caused by the existing risks and threats.

Our research goal was to assess probability of comorbid diseases in the nervous system and digestive organs in children attending primary school under combined exposure to chemical factors and factors related to educational process.

Data and methods. To achieve this goal, we performed a profound examination of 60 schoolchildren (boys) aged 7–10 who attended the 1^{st}–4^{th} grades. Our test group was made up of 34 children who simultaneously had a disease of the nervous system and digestive organs as a basic or a concomitant disease (ICD–10: G00–G99; K00–K93); they attended a primary school with additional educational programs involving intense physical and military training. Our reference group included 26 children with the same diseases who attended a primary school providing only basic educational programs without any additional training. Children's samplings were comparable in terms of sex and age, psychological climate in a family, social conditions at home, welfare, and frequency and types of bad habits and occupational hazards their parents had.

We hygienically assessed ambient air as per data collected via field observations at school territories and inside classrooms and also used a direct relevant model showing dependence between a chemical concentration in blood and its concentration in environmental objects. It allowed us to select phenol out of 11 analyzed chemical factors and to substantiate its concentration in blood being higher than 0.014 mg/dm^3 as aerogenic exposure marker.

We revealed that educational processes at the examined schools deviated considerably from the Sanitary-Epidemiologic Requirements 2.4.2.2821-10 and they were much more intense than it was fixed by the Federal recommendations FR ROSHUMZ-16-2015; and we also used a model that revealed direct dependence between nervous system and digestive organs diseases in children and exposure to factors related to educational processes. It allowed us to analyze 18 factors and select 4 of them as exposure markers related to educational process, namely intellectual loads, emotional loads, monotony of loads, and a period during

which technical teaching aids (TTA) were used uninterruptedly[1, 2].

We created a list of approximately 30 laboratory parameters as per data taken from scientific literature; these parameters showed a pathogenetic mechanism of negative effects occurrence in the nervous system and digestive organs. We modeled the following dependence: «exposure marker – response indicator – a negative effects as a disease of the nervous system and digestive organs»; it allowed us to substantiate increased acetyl cholinesterase and pepsinogen I contents in blood serum as biomarkers showing comorbidity in schoolchildren under combined exposure to phenol, intellectual, emotional, and monotonous loads and a period during which TTA were used uninterruptedly.

We calculated total probability of comorbid diseases in the nervous system and digestive organs with subsequent quantitative assessment of an extent to which they were caused by combined exposure to heterogeneous factors. The procedure was performed according to an algorithm developed together with experts from the Department for mathematical modeling of systems and processes.

The calculation algorithm included several stages. The 1st stage involved calculating a probability of *k*-th biomarker of an effect related to increased phenol contents in blood and exposure to educational process factors deviating from the physiological standard. The calculation was based on estimating «exposure marker – biomarker of an effect» dependence which was established separately for each *k*-th biomarker with each influencing *i*-th factor as per the following formula:

$$P_i^k = \frac{1}{1+e^{-(b_0^k + b_1^k x)}}, \text{ where} \qquad (1)$$

P_i^k is a calculated probability that there is a deviation from physiological standard in *k*-th biomarker of an effect related to increased phenol contents in blood and exposure to educational process factors;

x is phenol concentration in blood (mg/dm^3) or a factor related to educational process (arbitrary units);

e is exponent or an exponential function with its base being equal to an irrational number;

b_0^k, b_1^k are mathematical model parameters determined via least square technique with applied software for statistical data analysis (Statistica, SPSS, SAS etc.).

The 2nd stage involved calculating a probability of a negative effect occurrence as syntrophy in the nervous system and digestive organs (as a disease) when *k*-th biomarker of an effect deviated from physiological standard; the calculation was performed as per the following formula:

$$P_k^n = \frac{1}{1+e^{-(b_0^n + b_1^n x)}}, \text{ where} \qquad (2)$$

P_k^n is a calculated probability of a negative effect occurrence as syntrophy in the nervous system and digestive organs (as a disease) when *k*-th biomarker of an effect deviated from physiological standard;

x is a value of *k*-th biomarker of an effect (ng/ml or μg/L);

e is exponent or an exponential function with its base being equal to an irrational number;

b_0^n, b_1^n are mathematical model parameters.

The 3rd stage involved calculating an overall probability that comorbid diseases occurred in the nervous system and digestive organs under isolated exposure to phenol, intellectual loads, monotonous loads, emotional loads, and uninterrupted use of technical teaching aids; the calculation was performed as per the following formula:

$$P_i^n = 1 - \prod_k (1 - P_k^n \cdot P_i^k), \text{ where} \qquad (3)$$

[1] SER 2.4.2.2821-10. Sanitary-epidemiologic requirements to educational process conditions and organization in secondary schools. Approved by the RF Chief Sanitary Inspector on December 29, 2010 No. 189. *KODEKS: an electronic fund for legal and reference documentation.* Available at: http://docs.cntd.ru/document/901765645 (20.04.2020) (in Russian).

[2] FR ROSHUMZ-16-2015. Hygienic assessment of educational activities intensity for students: federal recommendations on providing medical aid to students. Moscow, 2015, 18 p. (in Russian).

P_i^n is an overall probability that comorbid diseases occurred in the nervous system and digestive organs under isolated exposure to a factor;

P_i^k is a probability that *k*-th biomarker deviates from physiological standard in case there is elevated phenol contents in blood or under exposure to one of the analyzed factors related to educational process;

P_k^n is a probability of a negative effect occurrence as syntrophy in the nervous system and digestive organs (as a disease) at an established values of *k*-th biomarker of an effect;

$\prod_k$ is a product of values obtained via an operation $(1-P_k^n \cdot P_i^k)$, that is, the formula looks as follows for k biomarkers ($k = 2$):

$$\prod_{k=1}^{2} =(1-P_{k_1}^n \cdot P_i^{k_1}) \cdot (1-P_{k_2}^n \cdot P_i^{k_2})$$

The 4th stage involved calculating total probability that comorbid diseases occurred in the nervous system and digestive organs under combined exposure to the analyzed factors as per the following formula:

$$\sum P_i =1-(1-P_{i_1}^n) \cdot (1-P_{i_2}^n) \times$$

$$\times (1-P_{i_3}^n) \cdot (1-P_{i_4}^n) \cdot (1-P_{i_5}^n), \text{ where} \quad (4)$$

$\sum P_i$ is total probability that comorbid diseases occurred in the nervous system and digestive organs under combined exposure to heterogeneous factors;

$P_{i_1}^n$ is an overall probability that comorbid diseases occurred in the nervous system and digestive organs under isolated exposure to phenol;

$P_{i_2}^n$ is an overall probability that comorbid diseases occurred in the nervous system and digestive organs under isolated exposure to intellectual loads;

$P_{i_3}^n$ is an overall probability that comorbid diseases occurred in the nervous system and digestive organs under isolated exposure to monotonous loads;

$P_{i_4}^n$ is an overall probability that comorbid diseases occurred in the nervous system and digestive organs under isolated exposure to emotional loads;

$P_{i_5}^n$ is an overall probability that comorbid diseases occurred in the nervous system and digestive organs under isolated exposure to uninterrupted use of technical teaching aids.

Calculated values, such as overall probability under isolated exposure ($P_i^n > 0{,}05$) and total exposure under combined exposure ($\sum P_i > 0{,}05$), were taken as criteria showing that such negative effects as comorbid diseases of the nervous system and digestive organs were caused by long-term aerogenic exposure to phenol and impacts exerted by intellectual, emotional, and monotonous loads and a period of time during which technical teaching aids were used uninterruptedly. An extent to which the negative effects were caused by the combined exposure to the analyzed factors was estimated according to the following scale: $0.05 \le \Sigma P_i$ or $P_i^n \le 0.3$ meant weak causality; $0.31 \le \Sigma P_i$ or $P_i^n \le 0.6$, average causality; $0.61 \le \Sigma P_i$ or $P_i^n \le 1.0$, strong causality.

Results and discussion. We assessed «exposure marker – biomarker of an effect» dependence and determined its parameters; it allowed us to establish how probable was a deviation in each biomarker of an effect (acetyl cholinesterase and pepsinogen I) from its physiological standards caused by increased phenol contents in blood and exposure to intellectual, emotional, and monotonous loads, as well as a period of time during which technical teaching aids wee used uninterruptedly (P_i^k) (Table 1). We also assessed «biomarker of a negative effect – syntrophy negative effect» dependence and determined its parameters; it allowed us to establish how probable was a syntrophic negative effect (P_k^n) in the nervous system or digestive organs in case acetyl cholinesterase and pepsinogen I contents exceeded their physiological (Table 2).

Overall probability that comorbid diseases of the nervous system and digestive organs would occur under isolated aerogenic exposure to phenol in school children attending a school

Table 1

Parameters b_0^k and b_1^k used for calculating probability (P_i^k) that a negative effect biomarker deviated from its physiological standard under increased phenol concentrations and exposure to factors related to educational process

Exposure marker (i)	Biomarker of a negative effect in blood serum (k)	Parameters of «exposure marker – negative effect biomarker» model		Probability (P_i^k) that a negative effect biomarker deviates from its physiological standard
		b_0^k	b_1^k	
Phenol in blood	Acetyl cholinesterase	–5.22	89.14	0.022
	Pepsinogen I	–6.43	184.73	0.030
Intellectual loads	Acetyl cholinesterase	–4.49	1.35	0.200
	Pepsinogen I	–3.05	1.11	0.379
Monotonous loads	Acetyl cholinesterase	–4.22	1.35	0.200
	Pepsinogen I	–2.94	0.74	0.200
Emotional loads	Acetyl cholinesterase	–4.22	2.02	0.200
	Pepsinogen I	–2.94	1.11	0.200
Duration of TTA uninterrupted use	Acetyl cholinesterase	–2.59	0.74	0.250
	Pepsinogen I	–2.42	0.34	0.150

Table 2

Parameters b_0^n and b_1^n used to calculate a probability (P_k^n) that a syntrophic negative effect would occur in case of deviation in each k-th biomarker of an effect

Biomarker of a negative effect in blood serum (k)	Negative effect (n)	Parameters of «biomarker of an effect – negative effect (disease model)»		Probability (P_k^n) that a syntrophic negative effect would occur
		b_0^n	b_1^n	
Acetyl cholinesterase	Comorbidity of the nervous system diseases (G00-99) and digestive organs diseases (K00-93)	–0.38	0.09	0.844
Pepsinogen I		–4.38	0.03	0.320

with additional training programs amounted to 0.028; overall probability under exposure to isolated influence exerted by specific factors related to educational process varied from 0.221 to 0.248 depending on an analyzed factor. We assessed calculated values and determined that causality was rather weak. A share contribution made into negative effects occurrence solely by a chemical factor (phenol) amounted to 2.8 %, and that made by exposure to factors related o educational process varied from 22.4 % to 27.2 %.

We comparatively analyzed total probability that comorbid diseases of the nervous system and digestive organs would occur in children attending primary schools under combined exposure to chemical environmental factors and factors related to educational processes. The comparative analysis revealed that the total probability amounted to $\sum P_i = 0.55$ for school children attending ordinary primary schools without any additional training programs and it meant that causality was average. The total probability amounted to $\sum P_i = 0.68$ for schoolchildren attending primary schools with additional physical and military training and it meant strong dependence between the analyzed factors and comorbid diseases occurrence. A probability that comorbid diseases of the nervous system and digestive organs would occur in schoolchildren without exposure to any factor (P_0^n) amounted to 0.38, in other words, causality was weak. This causality value was the lowest one and it allowed us to consider it as «background causality».

Table 3

Additional cases of cop morbid diseases in the nervous system and digestive organs under combined exposure to environmental factors and factor related to educational process among schoolchildren in Perm region

Parameter	Additional physical and/or military training	Ordinary educational programs
Number of schools*	2	8
Average number of children in a class**	20	25
Overall number of classes in primary school	4	4
Number of classes belonging to the same grade	3	5
Overall number of children in primary school	480	4,000
Additional calculated probability of comorbid diseases in the nervous system and digestive organs under combined exposure to examined factors (ΔP_i^n)	0.298	0.172
Number of additional comorbid diseases cases	143	688
Number of additional comorbid diseases cases, cases/1,000 primary school children per year	298	172

Note:
*data on a number of primary schools with different educational programs are taken from the Unified information-analytical system (UIAS) on education;
**data on an average number of children in a class are given according to the Order issued by the Perm Regional Educational Department on June 29, 2001 No. 509 «On approval of typical staff standards for administrative, educational, auxiliary, and junior maintenance staff in educational establishments in Perm»[3].

The suggested algorithm for calculating and assessing probability that comorbid diseases in the nervous system and digestive organs in children were caused by combined exposure to heterogeneous factors allowed determining a number of additional co-morbid diseases cases in children attending primary schools with different educational programs. We comparatively analyzed comorbidity among children who attended primary schools in Perm region; the analysis allowed revealing that there were 0.2 additional disease cases among children attending primary schools with ordinary educational programs without any additional training and 0.3 additional diseases cases among children who attended schools with additional physical and military training (a 1.5-time discrepancy) (Table 3).

Therefore, we can predict approximately 298 additional cases of comorbid diseases in the nervous system and digestive organs per 1,000 people per year under combined exposure to heterogeneous factors among children attending schools with additional physical and military training; there can be up to 172 additional cases of comorbid diseases per 1,000 persons per year among children attending schools with ordinary educational programs.

Conclusion. If we want to reduce number of comorbid diseases in schoolchildren under combined exposure to environmental factors and factors related to educational process, we should determine and substantiate priority exposure factors and their share contribution into negative effects occurring simultaneously in the nervous system and digestive organs. These factors are subject to relevant correction depending on an extent to which comorbid diseases are caused by heterogeneous factors; substantiated biomarkers of negative effects are to be taken into account in order to make early diagnostics more efficient and to develop relevant prevention activities.

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

[3] On approval of typical «staff standards for administrative, educational, auxiliary, and junior maintenance staff in educational establishments in Perm: the Order issued by the Perm Regional Educational Department on June 29, 2001 No. 509. *Garant: information and legal support*. Available at: http://base.garant.ru/43079860/#friends (20.04.2020) (in Russian).

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Research article

HYGIENIC ASSESSMENT OF CONTRIBUTION MADE BY COOLING METEOROLOGICAL FACTORS INTO OCCUPATIONAL RISKS OF HEALTH DISORDERS FOR WORKERS WHO HAVE TO WORK OUTDOORS IN COLD SEASON

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Effects produced by hazardous occupational factors on workers employed in oil extraction often occur under low temperatures when workers have to perform their tasks outdoors.

Our research goal was to assess a contribution made by cooling meteorological factors into health risks for workers performing their job tasks outdoors during a cold season in order to substantiate priority prevention activities.

The research was performed on workers employed by a large oil extracting company who spent different amount of time outdoors during a cold season. A posteriori group risk was assessed according to the Guide[1] as per results obtained via periodical medical examinations in 2017–2018. Working conditions were assessed basing on a report obtained via special assessment of working conditions and industrial control results. Cooling microclimate was assessed according to G 2.2.2006-05[2] .

Basing on the results of a priori group risk assessment, work places were ranked as per health disorders probability. It was shown that in-plant noise was the leading factor causing health risks. Besides, when working experience exceeded 20 years, cooling meteorological conditions also made a substantial contribution into risks occurrence.

Obtained results indicate that it is necessary to develop medical and prevention activities for workers who have to spend a lot of time outdoors in areas with cold climatic conditions.

Key words: *workers' health, health disorders prevention, hazardous working conditions, assessment o working conditions, risk assessment, occupational risks, risk management, outdoor work.*

State guarantees aimed at providing health consider population safety as complete absence of unacceptable risks for life and health; any risk management has an ultimate goal which is consistent reduction in risks related to impacts produced by adverse factors on population, industrial and social infrastructure and environmental objects until such risks become acceptable [1]. Any labor or activity performed in industry and the environment involves probable adverse effects on health; their quantitative assessment is determined by

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a value of a risk [2]. Occupational risks assessment as a component in the whole risk assessment system aimed at prevention and preservation of workers' life and health during their occupational activities is becoming more and more vital every year. It is to a great extent determined by changes that are happening now in the country including stronger competition on traditional goods, technologies, and labor markets. And new technologies tend to cause new health risks for workers [1, 3–6].

Obviously, occupational risks assessment is significant for enterprises operating in various brunches. As a tool applied to quantitatively assess levels of threats to health, it provides an opportunity to rank objects and workplaces and to determine priorities when accomplishing preventive activities taking into account actual risks levels. Risk assessment can give grounds for working out systems and means for individual and collective protection and determination of their efficiency as well as for finding solutions to other important tasks [3–4, 7, 8].

Physical factors including vibration, noise, labor hardness, and unfavorable microclimate typical for certain seasons occupy the leading place among adverse occupational factors existing at oil-extracting enterprises [9]. A lot of technological processes and related work tasks involve a necessity for a worker to constantly or periodically stay either in a cold room without any heating or outdoors under dangerous exposure to cooling meteorological factors.

We should note that apart from low temperatures workers, as a rule, are exposed to a set of other adverse meteorological conditions (drops and rises in temperature, relative air humidity and mobility, precipitations, etc.); intensity of such factors is determined by climatic and geographic conditions existing in a region where a specific oil-extracting enterprise operates.

At present a considerable part of employable population in the West Siberia work in oil extraction. In most cases, workers employed in oil extraction are exposed to adverse occupational factors under specific natural and climatic conditions existing in the Polar region where cold season is long and air temperatures are low [10]. Unfortunately, despite technologies applied at oil extraction enterprises are constantly modernized and developed, it results in only slightly improved working conditions for oil industry workers. Moreover, working conditions assessments tend to neglect assessment of impacts exerted by microclimate on a human body on an open territory under exposure to cooling meteorological conditions [11].

At the same time, a role that microclimate plays in human activities is predetermined by the latter being possible only provided that temperature homeostasis is preserved and it is reached due to proper functioning of various systems in a body (cardiovascular, respiratory, endocrine, excretory system, energy, water-salt, and protein metabolism). Strain occurring in these systems functioning under exposure to adverse microclimate (heating or cooling one) can be a cause for body defenses inhibition and pre-pathology occurrence; they in their turn exacerbate effects produced by other adverse occupational factors. Consequently, there is a risk that morbidity will grow[3]. Therefore, in our opinion, the subject of the present work is vital and certainly worth considering.

Our research goal was to assess a contribution made by meteorological factors into occupational risks occurring when work tasks are performed outdoors in cold season and to substantiate priority of prevention activities.

Data and methods. There were 794 participants in our research; they were all workers employed by «Samotlorneftegaz» JSC, an oil extraction company. They had the following occupations: desalting and dewatering unit (DDU) operators; compressor units (CU) operators; operators responsible for working substance pumping into a bed (WSPB); repairmen. Working on an open territory (outdoors) was a criterion for selecting workers (occupa-

[3] Guide on occupational hygiene. In 2 volumes. Vol. I. In: N.F. Izmerov ed. Moscow, Meditsina Publ., 1987, 368 p. (in Russian).

tions) to be included into the research. Workers from the examined occupational groups had to stay outdoors in cold season for different amounts of time. We created three occupational groups to analyze a contribution made by occupational factors into health risks occurrence. To properly compare occupational groups as per parameters characterizing workers' health depending on exposure to cold, we had to exclude impacts exerted by occupational factors existing only at certain workplaces and for workers with specific occupations and therefore being able to distort research results. Due to welding aerosol being a leading adverse occupational factor causing occupational pathology occurrence in electrogas-welders and repairmen, this occupational group was excluded from the overall sampling selected for a posteriori risk assessment [12].

Cooling microclimate outdoors and in cold rooms was assessed according to Guide R 2.2.2006-05. Equivalent temperature determination was based on daily meteorological parameters (air temperature and mobility) over three winter months (December 2018, January and February 2019) as per data obtained from Laryakskaya meteorological station. A posteriori group risk was assessed as per the Guide[1] basing on data taken from the ultimate report on chronic diseases prevalence among workers employed at the examined enterprise as per results obtained via periodical medical examinations performed in 2017–2018. We calculated the following parameters: relative risk (RR), sensitivity (Se), specificity (Sp), and etiological fraction (EF) using contingency tables.

A priori occupational risks caused by exposure to in-plant noise, chemicals, overall vibration, labor hardness, and microclimate, as well as combined risks were assessed taking into account concentration/exposure dose and working experience. Working conditions were assessed basing on reports issued as per results of special assessment of working conditions and industrial control results. We took into account measured levels of in-plant noise and overall vibration, adverse chemicals contents in working area air (saturated aliphatic hydrocarbons), and factors related to labor process. All the examinations (measurements) were performed by laboratory centers certified according to established procedures. A priori occupational risk caused by exposure to adverse microclimate in cold season when work tasks were performed outdoors and in cold rooms was calculated basing on minimal air temperatures and average wind speed.

Data were statistically processed with OfficeStd 2013 RUSOLPNLAcdmc: 021-10232; and Statistica 10. Student's test and Mann-Whitney test were applied when parameters were distributed in stratified samplings. Discrepancies in the structure of qualitative properties distribution were assessed with χ^2. A confidence interval being not lower than 95 % ($p < 0.05$) was taken as statistical reliability criterion.

Results and discussion. Adverse occupational factors can cause not only occupational diseases but also occurrence and development of common diseases related to an occupation [2]. Results of occupational risks assessment performed for workers from different occupational groups revealed that in-plant noise was the leading factor causing both occupational and non-specific pathology development (Figure 1).

But still, there was just an insignificant probability that occupational pathology could develop due to exposure to overall vibration and factors related to labor processes at all workplaces of workers from the examined occupational groups.

Exposure to microclimate in cold (winter) season when work tasks were performed either outdoors or in cold rooms made a substantial contribution into occupational and non-specific morbidity growth among workers regardless of their occupational group. We should note that according to the Guide R 2.2.2006-05, a territory where «Samotlorneftegaz» JSC is located belongs to the climatic zone II (III) (with average air temperature in winter being -18^0C and average wind speed calculated basing on the most probable values in winter months being 3.6 m/sec). Our results revealed that risks causedby exposure

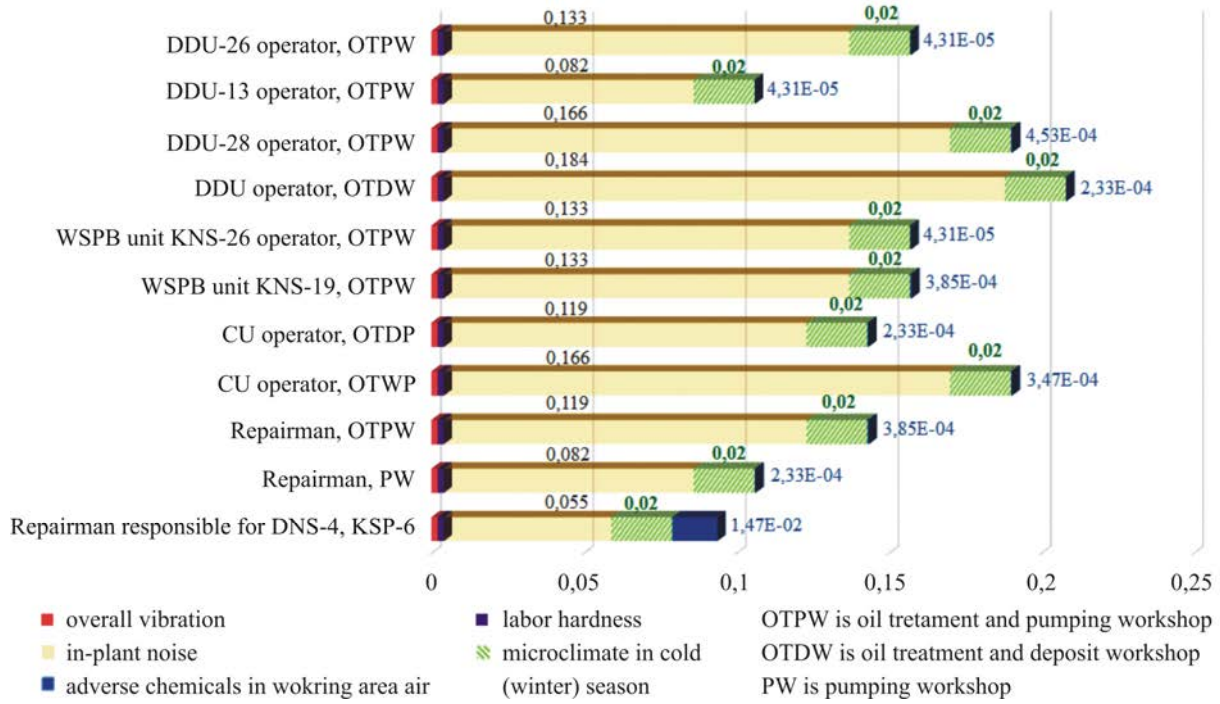

Figure 1. Contribution made by occupational factors into combined occupational risks occurrence over 10 years of working experience

to adverse microclimate in cold (winter) season amounted to 0.02 for workers with their working experience being equal to 10 years; it meant there was a conditional growth in morbidity equal to 2 cases per 100 workers for 10-year working experience. Values of a priori risks caused by exposure to cooling microclimate on an open territory determined that 20-year working experience was a significant one for non-specific pathology occurrence (Figure 1).

When working experience reaches 20 years, a contribution made by exposure to cooling meteorological conditions existing outdoors in cold season into health disorders increases and corresponds to conditional growth in morbidity equal to 5 cases per 100 workers. Exposure to adverse chemicals in working area air (aliphatic hydrocarbons), overall vibration, and labor process factors remains insignificant for occupational and non-specific pathology development.

When working experience reaches 40 years, risks caused by exposure to cooling meteorological conditions existing outdoors in cold season grow up to 0.33 and it corresponds to conditional morbidity growth equal to 33 cases per 100 workers.

Work places were comparatively characterized basing on calculated values of health risks over certain working experience. Working experience equal to 10 years was selected as an evaluative parameter. Working experience duration varied from 7 years (WSPB KNS-6 operator at oil treatment and pumping workshop No. 1) to 20 years (DDU operator at oil treatment and deposit workshop No. 1).

Basing on a priori group risk assessment, we ranked workplaces of workers from the examined occupational groups as per health risk probability. The highest rank place was taken by workplaces of DDU operators working in oil treatment and deposit workshop No. 1 (OTDW-1). It was due to value of combined health risks (caused by exposure to in-plant noise, overall vibration, adverse chemicals in working area air, labor hardness, and microclimate in cold (winter) season when work tasks were performed outdoors or in cold rooms).

The second rank places belonged to workplaces of CU VKS-28 operators and DDU DNS-28 operators working in oil treat-

ment and pumping workshop No. 2 (OTPW-2). Combined risk amounted to 0.18 and it corresponded to a conditional growth in morbidity equal to 18 cases per 100 workers. The third rank place was taken by workplaces of WSPB operators working with KNS-19 and KNS-1 units in OTPW-2 and KNS-26 and KNS-13 in oil treatment and pumping workshop No. 1 (OTPW-1). Combined risks amounted to 0.15 and it corresponded to conditional growth in morbidity equal to 15 cases per 100 workers.

Figure 2 shows dynamics of changes in risks caused by exposure to in-plant noise and microclimate in cold season with working experience growing from 1 year to 40 years at workplaces of DDU operators working in oil treatment and deposit workshop No. 1 (OTDW-1).

As working experience becomes longer, risks of occupational and non-specific pathology is also rising. And it is interesting to note that exposure to cooling meteorological conditions leads to growth in risks. Thus, for example, when working experience of DDU operators working in oil treatment and deposit workshop No. 1 (OTDW-1) is equal to 20 years, risk of health disorders caused by in-plant noise is equal to 0.245, and health risk caused by exposure to adverse microclimate in cold season is equal to 0.05, and totally it corresponds to conditional growth in morbidity equal to 30 cases per 100 workers. When working experience was as long as 40 years, risks caused by exposure to microclimate in cold season grew substantially and amounted to 0.33; it corresponded to conditional growth in morbidity equal to 33 cases per 100 workers, and combined risks caused by exposure to both in-plant noise and microclimate in cold season reached 0.646; it corresponded to conditional growth in morbidity equal to 65 cases per 100 hundred workers (Figure 2).

Basing on accomplished time study of a working shift typical for the examined occupations, we distributed the examined workers into 3 groups as per different amount of time spent outdoors in cold season taking into account exposure to a set of adverse occupational factors; the groups were as follows: the 1st one, 30 % of a working shift spent outdoors; the 2nd group, 50 %; the 3rd group, 60–75 %.

Prevalence of chronic diseases among workers was analyzed taking into account amount of time spent outdoors during a working shift. As workers from the examined occupational groups had either 8- or 12-hour working shifts, a 40-hour working week was taken as an integral parameter; basing on it, we determined one risk group and two reference

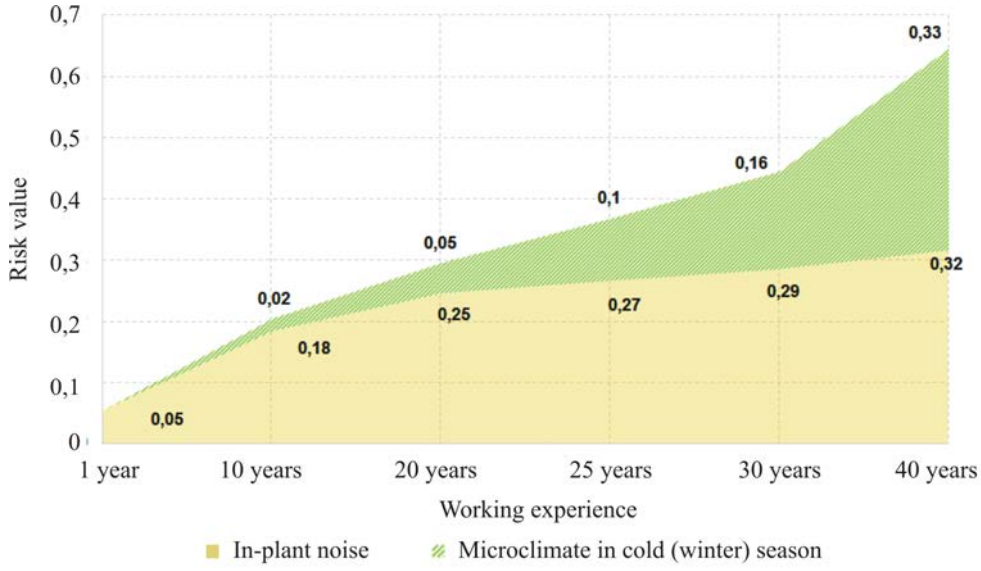

Figure 2. Occupational health risks caused by exposure to in-plant noise and adverse microclimate in cold season depending on working experience at a workplace of DDU operators working in oil treatment and deposit workshop No. 1 (OTDW-1)

groups. The 1st reference group was made up of CU operators and WSPB operators; workers from this group had to spend outdoors from 10.8 to 15.7 hours during a 40-hour working week and it amounted to approximately 30 % of the total working time. The 2nd group included DDU operators who had to spend out doors from 18.5 to 20.05 hours during a 40-hour working week, and it amounted to approximately 50 % of the total working time. The risk group was made up of repairmen who had to perform their work tasks mostly outdoors thus spending a lot of time on open territories; overall amount of time spent outdoors varied from 25.5 to 31 hours per a 40-hour working week for this group.

All three groups were homogenous as per age and sex and there were no authentic discrepancies between them as per these parameters ($p > 0.05$). Male workers prevailed in all three groups.

Workers form the risk group had to spend authentically the longest amount of time outdoors, 28.4±0.2 hours per a 40-hour working week in comparison with the 1st and 2nd occupational groups ($p < 0.001$). Average number of diseases per 1 worker (0.4±0.06) was also authentically higher in the 3rd (risk) group than in the 1st ($t = 2.36$; $p = 0.02$) and the 2nd one ($t = 3$; $p = 0.003$). Also the share of practically healthy workers was the lowest in the 3rd group (70.4 %) against the 1st ($\chi^2 = 5.07$; $p = 0.025$) and the 2nd one ($\chi^2 = 10.3$; $p = 0.02$) (Table 1).

We assessed a cause-and-effect correlation between health disorders and exposure to cold with different amounts of time spent outdoors; the assessment results are given in Table 2.

Obtained values of relative risks are higher than 1.0 with statistic significance being within 95 % range; it means that diseases of the ear and mastoid, circulatory system diseases, digestive organs diseases, respiratory diseases and diseases of the nervous system can probably occur due to exposure to cold associated with long periods of time spent outdoors in cold season.

According to published data, the respiratory and cardiovascular systems take active part in thermoregulatory processes; it results in certain strain in them and determines specific structure of morbidity among workers. The most substantial shifts occur in the respiratory, blood-making, circulatory, immune, endocrine, reproductive, and nervous systems; there has been a concept designed specifically for such cases, namely, «polar» metabolic syndrome [13–19].

Relative risk (RR) shows how a risk of a specific outcomes grows (by how many times) in case there is an influencing risk factor against a situation when this influencing risk factor is absent[4].

Relative risk (RR) calculation revealed an authentically high risk of nervous system diseases (RR = 4.66) among workers who had to spend the longest periods of time outdoors. Etiological fraction (EF) amounted to 78.5 % and it meant that an extent to which those diseases were work-related was very high[5].

Also workers form this group ran authentically high risks of digestive organs diseases (RR = 3.96, EF = 74.7 %), diseases of the ear and mastoid (RR = 2.99; EF = 66.6 %), and increased dextrose contents in blood (RR = 3.55; EF = 71.8 %).

Sensitivity as a parameter shows a share of those who actually falls sick in a risk group; the fact that workers are sick is usually detected during periodical medical examinations and specificity parameter shows how probable is the correct identification of people who do not have any disease[1]. Specificity as per certain nosologies was rather high with the highest value being equal to 72.2 % and it means a share of workers who fell sick and were detected as being sick during a periodical medical examination was significant in a risk group.

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Table 1

Age and sex characteristics of workers from the examined occupational groups depending on working experience, number of diseases per 1 worker, number of practically healthy workers, and average amount of time spent outdoors in cold season ($M \pm m$)

Parameter	Group 1 $n = 201$	Group 2 $n = 461$	Group 3 $n = 132$	Significance of discrepancies
Sex: males, abs. / %	140 (69 %)	271 (59 %)	131 (99.2 %)	$p < 0.001$
females, abs. / %	61 (31 %)	190 (41 %)	1 (0.8 %)	
Average age, years	38±0.6	37.08±0.4	36.06±0.8	$p > 0.05$
Average working experience, years	10±0.4	9.8±0.3	9.05±0.3	$p > 0.05$
Number of practically healthy workers, abs. / %	163 (81 %)	383 (83.1 %)	93 (70.4 %) *	1 and 3: $\chi^2 = 5.07$; $p = 0.025$ 2 and 3: $\chi^2 = 10.3$; $p = 0.02$
Average number of diseases per 1 workers	0.23±0.04	0.21±0.02	0.4±0.06*	1 and 3: $t = 2.36$; $p = 0.02$ 2 and 3: $t = 3$; $p = 0.003$
Average amount of time spent outdoors in cold season during a 40-hour working week (hours)	13.7±0.13	20.7±0.13	28.4±0.2*	$p < 0.001$

Note: * means discrepancies are statistically significant as $p < 0.05$.

Table 2

A posteriori risk assessment regarding health disorders among workers form the examined occupational groups with different amount of time spent outdoors

ICD-10, nosologies	Relative risk (RR) (95 % CI)	Sensitivity Se, %	Specificity Sp, %	Etiological fraction EF, %	Statistics
Diseases of the ear and mastoid	2.99 (1.02–8.75)	46.2	78.3	66.6	$\chi^2 = 4.40$; $p = 0.037$
Diseases of the circulatory system	1.99 (1.00–3.96)	56.7	52.0	49.8	$\chi^2 = 3.90$; $p = 0.046$
Increased dextrose contents in blood	3.55 (1.40–9.01)	70.0	62.3	71.8	$\chi^2 = 8.20$; $p = 0.005$
Diseases of the digestive organs	3.96 (1.44–10.80)	72.2	62.2	74.7	$\chi^2 = 8.40$; $p = 0.004$
Diseases of the respiratory organs	5.23 (0.88–31.02)	60.0	78.1	80.9	$\chi^2 = 4.15$; $p = 0.042$
Diseases of the nervous system	4.66 (1.05–20.55)	57.1	78.2	78.5	$\chi^2 = 4.98$; $p = 0.026$

Analysis of relative risk (RR) with statistic significance being within 95 % confidence interval indicates there is a high risk of a disease due to exposure to cold as a risk factor as the parameter is higher than 1.0 both as per its average value, and its upper and lower limits.

Conclusions.

1. A priori occupational risk assessment allowed revealing that in-plant noise was the leading factor causing occupational and non-specific pathology occurrence.

2. Cooling meteorological conditions existing on open territories in cold season also make their contribution into pathology development; this contribution grows considerably when working experience exceeds 20 years.

3. Obtained values of relative risks with statistic significance being within 95 % confi-

dence interval are higher than 1.0; it means that diseases of ear and mastoid, circulatory system diseases, digestive organs diseases, respiratory diseases and diseases of the nervous system can probably occur due to exposure to cold associated with long periods of time spent outdoors in cold season.

Therefore, the results we obtained indicate that it is necessary to work out medical and preventive activities for workers who have to spend a lot of time outdoors in regions with cold climate. These activities should be aimed at preserving warmth within acceptable levels including workers being provision with additional heat-saving clothing and adapted work and rest regimes. Workers who perform their tasks under exposure to cold should be informed about its influence on a body and measures aimed at preventing overcooling. Besides, any performed hygienic assessment of occupational factors and factors related to labor process should take into account impacts exerted on a worker's body by climatic and weather conditions of a region where workers live and work.

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Research article

COMPLEX APPROACH TO ASSESSING RISKS AND PREVENTING VARIOUS SOMATIC DISEASES IN WORKERS (EMPLOYED AT FURNITURE PRODUCTION)

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At present a number of contemporary furniture production enterprises is growing fast in Saratov region. And simultaneously there is a growth in number of working places that require adequate sanitary-hygienic assessment of their safety.

Our research goal was to perform complex assessment of somatic diseases risks for workers employed at furniture production.

We examined 323 workers employed at «Maria» furniture factory. To perform assessment, we applied sanitary-hygienic, laboratory-instrumental, and statistic research techniques. It was established that 23 % workers had to work under hazardous working conditions (hazard category 3.2); 37 % workers had to work under conditions belonging to hazard category 3.1; 39 % examined workers had optimal and acceptable conditions at their workplaces (category 1–2). Having examined workers' age groups, we revealed that workers aged 21–30 prevailed among the examined ones and average working experience amounted to 5.4 years for people of this age. The second in number were workers aged 31–40 with their working experience being equal to 8.5 years. At the next stage in our research we examined morbidity among workers employed at furniture production. Thus, it was established that diseases of the nervous system were the most frequent among the examined workers (33.3 %); they were followed by respiratory diseases (20.4 %), cardiovascular diseases (12.1 %), and digestive organs diseases (10.2 %).

The third stage involved examining hereditary burdens on morbidity among workers employed at furniture production. Thus, 108 workers were established to have various diseases and 79.6 % of them had hereditary predisposition.

At the final stage in our research we examined retrospect data on changes in workers' life quality over 2015. The obtained data were compared with occurrence or absence of new diseases cases over the next three years.

Key words: *furniture production, working experience, age, life quality, morbidity, hereditary predisposition, working conditions, workers.*

Russia possesses huge amounts of timber occupying a leading place in the world as per this parameter. More than 2 million people work in forestry and wood-processing, 50 % out of them being employed at furniture productions. Over the last decades new workshops have been built and new production lines installed; it has led to qualitative changes in working conditions and processes at most workplaces in the branch. At present furniture productions are being equipped with more powerful and safer Russian and foreign machinery but still certain peculiarities of technological processes applied in wood processing do not allow eliminating adverse impacts exerted on workers' health completely and they make efficient primary diseases prevention harder to achieve [1–3].

Given rapid industrial growth and economic development, issues related to occupational hygiene and preservation of employable population's health in the country are especially vital for wood processing industry. And not enough attention has been paid to dependence between health risk parameters and hazardous working conditions taking into account

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not only leading adverse factors but also complex influence exerted by occupational factors and factors related to labor process existing at workplaces in furniture production. At the same time, models for assessing occupational health risks for workers in wood processing are applied only occasionally and described in very few scientific works[1, 2, 3] [4–10].

Occupational peculiarities in wood processing are determined by production technologies, production equipment, automation and mechanization at a given enterprise; all this results in negative effects produced by adverse factors and predetermines their range and intensity. Issues related to preserving employable population's health remain extremely vital given contemporary economic development and it is also true for forestry and wood processing. Over the recent years there has been a growth in population mortality, in particular, among workers employed at such productions and it highlights the necessity to examine the issue in greater details [10]. A lot of authors mention a cause-and effect relation between high morbidity among workers employed in the branch and adverse occupational factors existing at their workplaces; this high morbidity includes cardiovascular diseases, diseases of the nervous system, respiratory and gastric diseases[4] [5, 11–13]. Up to now, hygienic standards have been basic tools applied to hygienically assess impacts exerted by adverse occupational factors on workers' health. Violation of these standards means simultaneous violation of sanitary legislation and it is taken into account when economic and social protection activities are developed. But the basic focus here is not on reducing potential risks but on compensatory measures. Given that, it is advisable to assess working conditions basing on complex analysis of occupational factors (hygienic and psychophysiological parameters) and detection of health disorders, occupational and work-related diseases as per medical criteria [13]. Occupational risk assessment is a promising technique applied to examine influence exerted by occupational factors on workers' health. But still, life quality (LQ) assessment is a promising additional technique that can be applied in the sphere since recently both Russian and foreign experts have been paying more and more attention to examining various aspects of dependence between health and life quality, both for population in general and specific population groups as well [14, 15]. Life quality predetermines a person's health to a great extent. But health in its turn also influences life quality considerably. This thesis has been used in developing HRQL (Health–related quality of life) concept [16, 17].

At present many doctors and genetics adhere to an opinion that all the diseases are hereditary ones[5] [18]. Such wide-spread chronic diseases as stomach and duodenum ulcer, hemophilia, pancreatic diabetes, ischemic heart disease, bronchial asthma, schizophrenia, hypercholesterolemia, and some others are diseases with poly-functional predisposition [18, 19]. However, we should note that such a factor as predisposition to a disease in this or that system has not been analyzed at all within assessing influence exerted by adverse factors on working population's health, in particular on health of workers employed at furniture production. It is important to note that most hygienic conditions are analyzed in retrospect, that is, the analysis assesses a disease that has already occurred. At the same time, to optimize organizational and prevention activities, one requires prospective examinations aimed at

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assessing risks occurring in specific working conditions when a medical and social status of a particular person is determined. However, very few works have focused on this issue in relation to furniture production [14].

Therefore, all the above mentioned issues existing within assessment of adverse working conditions at furniture production have not been given much attention; the same is true for predicting health risks existing in the brunch. Given that, the present work seems truly vital and of practical importance as it focuses on a specific example, namely, «Maria», a furniture mill located in Saratov region, one of the largest manufacturers in the country that produces furniture for kitchens.

Our research goal was to apply a complex approach to assessing risks of somatic diseases occurrence in workers employed at contemporary furniture production and to outline necessary stages in prevention.

Data and methods. Overall, we examined 323 workers employed at «Maria» furniture mill. We took only data on morbidity among men since women employed at the enterprises didn't have to work under hazardous working conditions. We also excluded workers who had already suffered from chronic diseases prior to being employed at the mill. We detected that at the moment the examination was taking place, 23 % workers had to work under hazardous working conditions belonging to 3.2 hazard category; also, 37 % had to work under working conditions belonging to 3.1 hazard category. But still, 39 % workers had optimal and permissible working conditions at their workplaces (hazard category 1 and 2). People aged 21–30 prevailed among workers with average working experience being equal to 5.4 years for this age group. The second rank place belonged to workers aged 31–40 with their average working experience being 8.5 years. We applied sanitary-hygienic, laboratory-instrumental and statistic research techniques in this work. Occupational factors were assessed as per Sanitary-Epidemiological Rules 2.2.4.3359-16[6]. We determined noise and vibration at workplaces with «Assistent-S1V3RT» noise and vibration analyzer No. 102212. Working conditions were classified according to occupational hazards and threats, labor hardness and intensity as per Guide R.2.2.2006-05[7]. Health-related life quality was assessed with Health Status Survey SF-36, a standard questionnaire. SF-36 contains 36 questions that are distributed into eight groups represented by 8 scales; they characterize physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). Research results were statistically processed with «Microsoft Excel 2010» and «STATISTICA-6.0» applied software packages. When performing statistical processing, we applied variations statistics techniques. Kolmogorov-Smirnov criteria assessment revealed that the examined sampling was normal; as a result, we applied parametric analysis technique given as M±m. Validity of discrepancies between groups was assessed with Student's t-test. Discrepancies were considered valid at $p<0.05$. To calculate relative and absolute risk, we applied results obtained via assessing risk factors (working experience, hereditary predisposition, a decrease in life quality during one year, and a worker's age) producing their effects on 131 workers employed at furniture production; 17 workers didn't face any risk factors; 18 workers had to face one risk factor; 26 workers, two; 47 workers, three, and 40 workers, all four factors. Absolute and relative health risks were assessed according to conventional techniques in all the above mentioned groups.

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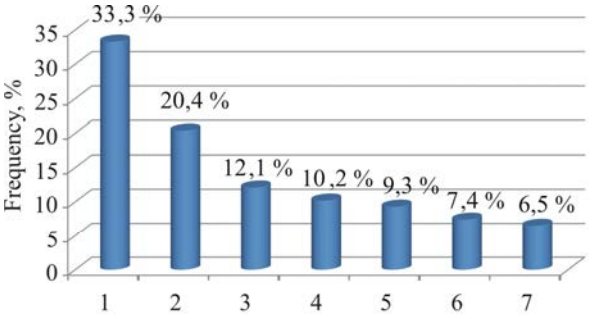
Results and discussion. We analyzed occurrence of various diseases among workers employed at contemporary furniture production and possible relations between them and working conditions using results obtained via profound medical examinations performed in 2018. Overall, 323 workers employed at «Maria» were examined.

Figure 1 illustrates the structure of detected diseases. Diseases of the nervous system prevailed among workers employed at furniture production (33.3 %); they were followed by respiratory diseases (20.4 %), diseases of the cardiovascular system (12.1 %), and gastric diseases (10.2 %). There were no sufficient data on other nosologies for statistical processing; therefore, the further analysis was performed as per functional systems only.

Figures 2 and 3 show the structure of the diseases diagnosed for the first time taking into account working experience and working conditions as per nosologies.

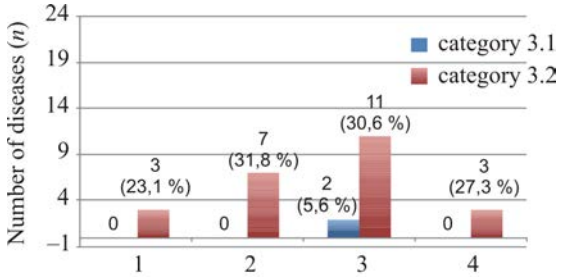
Having analyzed morbidity with diseases of the cardiovascular system (CVS), we established that there were no new disease cases among workers with their working experience being equal to 2–3 years and with working conditions belonging to category 3.1 at their workplaces. However, four new disease cases were registered among workers with their working experience exceeding three years. Morbidity among workers who had to work under working conditions belonging to hazard category 3.2 grew by 3 times from 2-year experience to 3-year one; it doubled further for workers with their working experience exceeding three years as a number of new cases amounted to six.

Morbidity with respiratory diseases grew by 5 times among workers with their working experience exceeding 5 years and working under hazardous conditions (hazard category 3.1). Morbidity among workers who had to work under conditions belonging to 3.2 hazard category already grew when working experience was from two to three years as there were seven new disease cases; when working experience under these conditions exceeded 3 years, morbidity grew further by 42.8 % and reached 10 new disease cases.



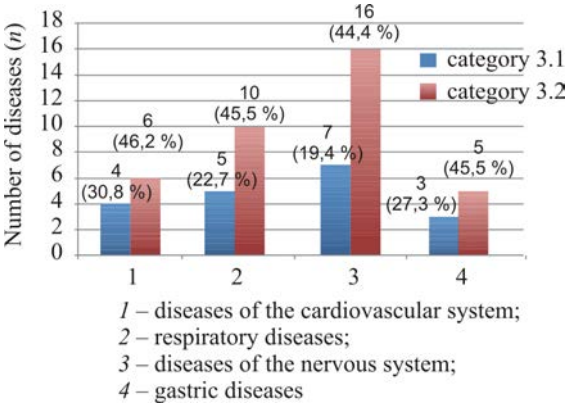
1 – diseases of the nervous system; *2* – respiratory diseases; *3* – diseases of the CVS; *4* – gastric diseases; *5* – diseases of the musculoskeletal system; *6* – diseases of the endocrine system; *7* – idseases of the eye and its accessory apparatus

Figure 1. Frequency of various diseases among workers employed at furniture production



1 – diseases of the cardiovascular system;
2 – respiratory diseases;
3 – diseases of the nervous system;
4 – gastric diseases

Figure 2. Structure of diseases diagnosed for the first time with working experience being equal to 2–3 years distributed as per working conditions category



1 – diseases of the cardiovascular system;
2 – respiratory diseases;
3 – diseases of the nervous system;
4 – gastric diseases

Figure 3. Structure of diseases diagnosed for the first time with working experience being longer than 3 years distributed as per working conditions category

Morbidity with diseases of the nervous system also tended to grow. Two new disease cases were detected among workers who had to work under hazardous conditions belonging

to 3.1 hazard category and with their working experience being from 2 to 3 years. Morbidity grew by 2.5 times (seven new cases) among workers with their working experience exceeding 3 years. 11 new disease cases were registered among workers with their working experience being from 2 to 3 years who had to work under conditions belonging to hazard category 3.2. Morbidity grew further by 45.5 % and reached 16 cases among workers with their working experience exceeding 3 years.

As for gastric diseases, 3 new disease cases were detected among workers with their working experience exceeding 3 years and working conditions at their workplaces belonging to hazard category 3.1. Morbidity grew by 3 times among workers who had to work under conditions belonging to hazard category 3.2 and with their working experience being from 2 to 3 years. Morbidity grew by 66.7 % among workers having the same conditions at their workplaces but with working experience exceeding 3 years and reached 5 new cases of gastric diseases.

If we sum up all the data, given on Figures 2 and 3, we can conclude that risks of various diseases for workers employed at furniture production grow in proportion to their working experience and labor hardness. The most adverse effects are produced by these factors on the nervous system.

108 workers out of 323 examined ones employed at «Maria» furniture mill had various diseases; 79.6 % of them were caused, among other things, by hereditary predisposition. We examined influence exerted by hereditary predisposition on frequency of diseases occurrence in workers employed at furniture production and working under adverse working conditions belonging to hazard categories 3.1 and 3.2 and their working experience exceeding 3 years (Figure 4).

Having analyzed the obtained data, we came to a conclusion that hereditary predisposition was an unfavorable factor causing various diseases in workers employed at furniture production in case labor hardness and intensity were comparable (hazard category 3.1 and 3.2) and working experience was the same (longer than 3 years). In particular, diseases of the

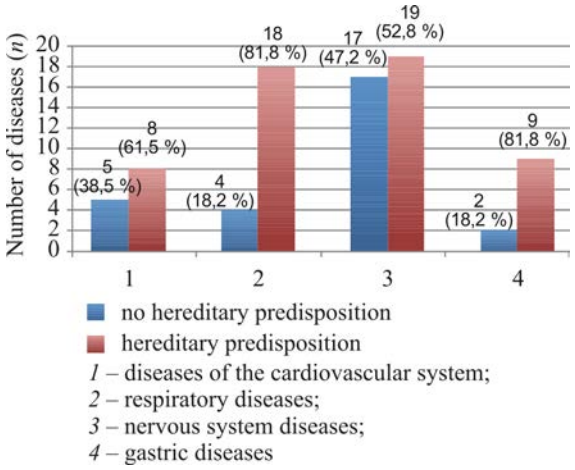


Figure 4. Morbidity among workers taking into account absence/occurrence of hereditary predisposition and given hazardous working conditions (3.1 or 3.2 hazard category) and working experience exceeding 3 years

cardiovascular system occurred only in 5 workers without hereditary predisposition after working experience exceeded 3 years; when it was present, 8 new cases were registered. Overall, we can conclude that workers employed at furniture production with hereditary predisposition and working experience longer than 3 years run a risk of cardiovascular diseases that is by 60.0 % higher than that for their counterparts without hereditary predisposition.

The same situation was detected when it came down to respiratory diseases. 18 new disease cases were registered among workers with hereditary predisposition to such diseases and it was by 77.8 % higher than among workers who had no hereditary predisposition to them. If we look at morbidity with diseases of the nervous system, we can see than 17 new disease cases were registered among workers who didn't have any hereditary predisposition to such diseases. However, in case hereditary predisposition was present, a number of hew cases amounted to 19 and it was by 11.8 % higher than among workers without it. 2 new gastric diseases cases were registered in workers without hereditary predisposition and with working experience exceeding 3 years. But frequency of gastric diseases was by 3.5 times higher among workers with hereditary predisposition.

To sum up our analysis of influence exerted by hereditary predisposition on this or

that disease among workers employed at furniture production, we should note that growth in morbidity is more apparent among workers with hereditary predisposition with working conditions and experience being comparable.

The final stage in our research involved examining retrospect data on changes in life quality of workers employed at the examined furniture mill that occurred in 2015; the obtained data were then compared with absence or occurrence of new disease cases during the following 3 years.

Analysis of data given in Table 1 indicates that a decrease in life quality of workers employed at furniture production that is equal to 30 % and higher during 1 year is an unfavorable factor that predicts various diseases occurrence in the next 3 years. In particular, people who were diagnosed a cardiovascular disease in the examined period had a 29.4 % decrease in their life quality in a year prior to the examined period; 32.1 % decrease in case a disease of the nervous system occurred; 31.8 % for a respiratory disease; and a 33.5 % decrease for a gastric diseases. At the same time, workers who didn't have any new disease registered during the examined period had less significant decrease in their life quality, by 15.1 %, 13.3 %, 10.6 % and 13.3 % accordingly ($p \leq 0.05$). Taking all the obtained data into account, we can conclude that a different decrease in workers' life quality during 1 year indicates that greater decrease in life quality results in greater growth in risks of various pathologies occurrence during the next 3 years (30 % and higher).

We determined absolute and relative risks of various somatic diseases taking into account all the above-mentioned parameters (Table 2).

The 1st group didn't have any risk factors; it was made up of 17 workers employed at furniture production with only one new disease case among them. The following groups given

Table 1

Changes in life quality parameters of workers in 2015 depending on absence or occurrence of a disease during the next 3 years, taken in dynamics in scores

Nosology	LQ parameters as per SF-36 scales, Sn (integral index)					
	No disease *n*=126			A disease occurred *n*=82		
	Initial data	1 year after	Changes, %	Initial data	1 year after	Changes, %
Cardiovascular system	68.3±8.6	59.3±6.8	-15.1 %	68.3±8.6	**48.2±4.3***	-29.4 %
Respiratory organs	67.2±7.8	60.1±7.1	-10.6 %	67.2±7.8	**45.8±5.2***	-31.8 %
Nervous system	70.1±6.9	60.8±5.8	-13.3 %	70.1±6.9	**47.6±6.1***	-32.1 %
Gastrointestinal tract	69.3±6.3	60.1±4.8	-13.3 %	69.3±6.3	**46.1±5.1***	-33.5 %

N o t e : * means $p < 0.05$ against the pervious group.

Table 2

Contingence of risk factors for a disease occurrence and their realization during the next 3 years

Analyzed groups	Observation results		Absolute risk in the test group	Absolute risk in the control group	Relative risk (RR)	Discrepancy	Sensitivity (Se)	Specificity (Sp)
	Outcome	No outcome						
No risk factors / A number of risk factors	1	16						
1	2	16	0.11	0.05	1.88	0.05	0.66	0.5
2	8	18	0.32	0.05	5.23	0.24	0.88	0.47
3	21	26	0.47	0.05	7.5	0.38	0.95	0.38
4	24	16	0.62	0.053	11.4	0.54	0.96	0.52

in Table 2 had risk factors, from one to all four. The group with only one risk factor consisted of 18 workers and 2 out of them actually fell sick during 3 years of working and 16 workers employed at the examined furniture mill didn't have any disease diagnosed in them during this period. Therefore, absolute probability of a disease occurrence in this group amounted to 0.11; relative probability was 1.88. Similarly, results obtained for groups with two, three or four risk factors are given in Table 2. In particular, in case there were two risk factors, two workers employed at furniture production had a disease diagnosed in them and other 18 in the same group didn't. Therefore, absolute risk of diseases occurrence in this group amounted to 0.32, and relative probability was equal to 5.23. The next group consisted of 47 workers who had three risk factors; 21 out of them had a diseases while the rest 26 didn't; therefore, absolute probability of a diseases occurrence amounted to 0.47 in this group whereas relative risk grew up to 7.5. The group with four risk factors consisted of 40 workers and 24 out of them had a disease while the rest 16 didn't. Absolute risk amounted to 0.62 in this group; relative one, 11.4. Therefore, as we can see from this table, a probability of a disease occurrence grows substantially if a number of risk factors increases.

Conclusions:

1. Morbidity among workers employed at furniture production depends on working conditions and working experience. Morbidity is 1.4 times higher among workers older than 40 than among those aged from 21 to 30.

2. Morbidity growth is 3.9 times more apparent among workers with hereditary predisposition than among those without it even if their working conditions are the same.

3. Various somatic pathologies developing in workers employed at furniture production are to a great extent caused by impacts exerted by such adverse factors as hazardous working conditions, hereditary predisposition, age, working experience, and a decrease in life quality by more than 30 % during 1 year.

4. A decrease in workers' life quality during 1 year by 30 % or more indicates there is high risk of various diseases occurrence in the next three years.

5. Our research allows assessing risks of various somatic diseases taking into account working experience, hereditary predisposition, decrease in life quality, and age of a specific worker.

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Research article

INFLUENCE EXERTED BY SOMATIC PATHOLOGY ON RISKS OF OCCUPATIONAL LUNG FIBROSIS IN WORKERS EMPLOYED AT REFRACTORY PRODUCTION

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Occupational lungs and bronchial pathology occurs not only under exposure to dusts, their aerosol structure and aggression, but also depends on individual properties of a body. The latter can determine either increased body resistance or susceptibility to occupational pathology occurrence.

Our research goal was to determine influence exerted by somatic pathology on occupational lung fibrosis occurrence as well as to estimate prevalence of risk factors for cardiovascular and metabolic pathology occurrence in workers employed at refractory production.

At the first stage 449 workers employed at refractory production were examined at a periodical medical examination (PME). Patients' average age was 41.59 ± 0.45 and average work experience was 14.47 ± 0.39 years. At the second stage 172 workers were examined at an occupational pathology center; 75 out of them were workers who had silicosis and were included into the test group and the remaining 97 workers didn't have any occupational pathology and were included into the reference group. Both groups were comparable as per sex (p = 0.0052) and work experience under exposure to dusts (p = 0.862).

Workers examined at a PME most frequently had overweight and obesity (68 %). Arterial hypertension (AH) prevalence amounted to 19.5%; carbohydrate metabolism disorders, 19.8 %; 48.1 % workers had hypercholesterolemia. Patients with silicosis had certain disorders significantly more frequently than workers with long work experience but without any occupational pathologies; those disorders were AH, cardiac muscle hypertrophy in the left ventricle, ischemic heart disease, heart rate disorders, as well as mixed (obstructive and restrictive) breath mechanics disorders. We determined some factors that authentically produced certain effects on occupational lung fibrosis occurrence in workers employed at refractory production. Median time of silicosis occurrence was significantly shorter (by 11.5 years) among workers with severe AH, arrhythmia (by 13 years), lower hemoglobin in blood (by 11.5 years). Besides, silicosis occurred significantly earlier (by 10.8) among women than among men.

Key words: *refractory production, fibrogenic dust, silicosis, somatic pathology, median work experience, arterial hypertension, hypercholesterolemia, obesity, metabolic disorders.*

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Respiratory diseases are among the most significant issues for contemporary occupational medicine as they account for more than one fifth of all the occupational diseases[1] [1]. Lung diseases with damage to the lungs caused by exposure to industrial aerosols hold the 2nd rank place as per their prevalence in occupational morbidity structure; such diseases result in substantial social and economic losses due to lower working capacity or total loss of it by workers[2, 3]. It occurs due to both insufficient control over exposure to industrial dusts under adverse working conditions and late diagnostics of the diseases caused by their long latent period. Dust diseases in the lungs lead to working capacity loss and make patients' life shorter[3] [2].

At present it is obvious that a nature of pathology developing in the bronchial tubes and lungs, its clinical course and complications are determined not only by dust loads, industrial aerosol structure, and their aggressive properties, but also by individual characteristics of a body including its elevated sensitivity to effects produced by fibrogenic dusts. It can be due to differences in biochemical reactions, in regulation mechanisms of physiological systems, humoral and endocrine factors, and immune reactions of a body. Special significance here belongs to a range of activity for biochemical processes behavior based on genetic polymorphism [3].

Experimental works revealed that silicon dioxide dust caused changes in membrane phospholipids structure with a decrease in amount of phospholipids with unsaturated fatty acids; it resulted in improper membranes penetrability, changes in lipid-dependent enzymes activity, and, consequently, in disorders in metabolic processes in a cell. Chronic introduction of fibrogenic dust into the respiratory organs makes for lipid metabolism disorders. Contents of all lipid fractions grow together with an increase in lung tissue weight. As per data taken form literature, there are elevated lipid contents in blood of workers who have long contacts with quartz dust, workers with «suspected» silicosis and patients already suffering from the disease[3].

At present it is beyond any doubts that dust pathology develops in the lungs due to critical mass of dusts being present in the organ [4, 5]. Pathogenesis of pneumoconiosis and silicosis in particular involves cellular cooperation between macrophages, fibroblasts, and leukocytes, and it stimulates excessive immune system activation thus leading to chronic inflammation development. This inflammation is determined by immune-modulating effects produced by quartz on the immune system. Long-term excessive formation of active oxygen forms is known as oxidative stress that is considered to be the key component in dust pathology development and plays the leading role in pathogenesis of interstitial diseases in the lungs. When dusts enter a human body, oxidative stress occurs prior to silicosis and other dust diseases in the respiratory organs[3]. At the same time fibrogenesis, as a response to damage, occurs via complex cellular interactions that become possible due to specific molecular routes[4]. Pathological process is based on long-term retention of dust particles in the lungs caused by inefficient self-purification mechanisms of the respiratory tracts. And here different susceptibility can be caused by different self-purification efficiency; thank to it, occupational lung fibrosis develops in different time in different workers even under the same exposure to dust [6].

Development of pathologic process caused by exposure to dust particles and their effects on lung tissue is accompanied with changes in cellular structures of lung tissue,

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changes in cellular structure of bronchial and alveolar secretion, and changes in immune reactivity [7]. Coniophages death results in aseptic inflammation and its development involves participation of both phagocytes activation products and phagocytes decay products; there is also a drastic increase in synthesis of anti-inflammation mediators [2, 8, 9]. At the same time there are research works with data on systemic nature of a body response to a long-term exposure to industrial dusts confirmed by registered morphological changes in various organs [1]. Several experimental works contain data on damage to the kidneys, heart, and vessels as well as on disorders in various metabolic processes in a body [10, 11].

Clinic practice shows that risks of occupational diseases are determined by not only hygienic criteria but also hereditary factors, living conditions, nutrition peculiarities, bad habits, and concomitant somatic pathology [12].

As there are unfavorable trends in contemporary society showing an increase in prevalence of risk factors that cause cardiovascular and metabolic pathology such as obesity, carbohydrate and lipid metabolism disorders, and arterial hypertension [13–16], one should assume that somatic pathology can exert its influence on occupational pathology occurrence.

Our research goal was to establish to what extent somatic pathology influenced a period of time during which occupational lung fibrosis developed as well as to assess prevalence of risk factors that could cause cardiovascular and metabolic pathology occurrence in workers employed at refractory production.

Data and methods. Our research had two stages. At the first stage we analyzed prevalence of cardiovascular and metabolic pathology among workers employed at refractory production as per results obtained via periodical medical examinations (PME) according to the Order No. 302 n[5]. At the second stage patients were examined at the clinic of the Occupational Pathology Center and influence exerted by somatic pathology on terms of silicosis occurrence in workers employed at refractory production was analyzed. To do that, we compared median working experience (it is predicted that an occupational disease will occur in a half of workers who reach this length of their working experience) in patients with different somatic pathologies.

449 workers were examined during a PME; their average age was equal to 41.59 ± 0.5 (from 18 to 66), average working experience at the examined enterprise was equal to 14.47 ± 0.39 (from 1 to 43). There were 304 males among the examined workers (67.7 %). The test group included 311 workers with basic occupations existing at fire-clay silica refractory production (mixing rollers operators, grinder operators, press operators, repairmen, and carrier operators) with their average age being 41.51 ± 0.54 and average working experience being 14.53 ± 0.51. There were 211 males among the examined workers (69 %). When performing their work tasks, workers were exposed to a set of adverse occupational factors and the basic one was highly fibrogenic dust with crystalline silicon dioxide contents accounting for more than 70 % in its structure ($MPC_{w.a.air} = 1$ mg/m^3). Average group concentration of crystalline silicon dioxide dust in working area air amounted to 1.05 ± 0.02 mg/m^3. The reference group was made up of 53 people (31 of them or 58 % were males) who were not exposed to silicosis-hazardous dust at their workplaces. Average age of people included into the reference group was 44.13 ± 1.37 and their average working experience was 16.25 ± 1.18 years. Basic occupations in the group were engineers, loader drivers, painters, foremen, sorter operators, and inspectors. Both groups were compa-

[5] On approving the list of adverse and (or) hazardous occupational factors and work tasks which require obligatory preliminary and periodical medical examinations and the Procedure for accomplishing obligatory preliminary and perifocal medical examinations of workers employed at workplaces with hard labor and adverse and (or) hazardous working conditions (amended and supplemented): The RF Public Healthcare Ministry Order No. 302n issued in 2011. *KonsultantPlus.* Available at: http://www.consultant.ru/document/cons_doc_LAW_120902/ (04.08.2020) (in Russian).

rable as per age ($p = 0.068$), sex ($p = 0.149$), and working experience under adverse working conditions ($p = 0.201$).

We analyzed prevalence of metabolic disorders, AH, and changes in external breath function (EBF) depending on length of working experience under adverse occupational conditions for workers from the test group. We examined frequency of fat, carbohydrate, and lipid metabolism disorders, AH, as well as EBF parameters for workers distributed into subgroups as per working experience starting from one not exceeding 5 years; from 6 to 10 years; from 11 to 20 years; from 21 to 30 years; from 31 to 40 years; longer than 40 years.

Then we analyzed case histories of 172 workers employed at refractory production who had been examined at the clinic in 2000–2017. The basic group included 75 patients with diagnosed silicosis and the reference group was made up of 97 workers with long working experience who didn't have occupational diseases diagnosed during the PME accomplished at the 1st stage. Both groups were comparable as per sex ($p = 0.052$) and working experience under exposure to dust (21.11 ± 1.03 and 20.85 ± 1.05 years accordingly, $p = 0.862$). Workers from the basic group were older (55.84 ± 0.96 and 49.72 ± 0.84 accordingly, $p = 0.000$). Average concentration of crystalline silicon oxide dust over a shift in working area air amounted to 3.19 ± 0.26 mg/m^3 for workers from the basic group and to 1.87 ± 0.12 mg/m^3 for workers from the reference one. We analyzed prevalence of cardiovascular pathology and risk factors that could cause it among workers employed at refractory production; we also analyzed influence exerted by cardiovascular pathology on silicosis occurrence.

To perform mathematic analysis, we used SPSS applied software (version 20) [17, 18].

Results and discussion. Only 25 workers (5.57 %) among those employed at refractory production and examined during the PME didn't have any changes in their somatic health. AH was diagnosed in 90 workers from the examined group (20 %). There were no ischemic heart disease cases in the group. 9 people (2 %) had type-2 diabetes and there was high prevalence of hyperglycemia as 90 workers (20 %) had elevated dextrose level in their blood on empty stomach. It should be noted that practically half of workers (216 people or 48.1 %) had elevated levels of total cholesterol (TC) in their blood.

On average workers in the group tended to have increased body mass index (BMI) that amounted to 26.43 ± 0.23 kg/m^2 (from 17.7 to 49.1). Only 112 people (24.9 %) had normal weight. 337 people (75.1 %) had their BMI deviating from the physiological standard. 167 people (37.2 %) had overweight and 170 people (37.9 %) had obesity with different manifestation. Therefore, more than a half of the examined workers had overweight.

Having compared workers from subgroups with working experience not exceeding 5 years and from 6 to 10 years, we revealed a significant decrease in all EBF parameters in patients with their working experience being from 6 to 10 years, as well as a significant increase in total cholesterol (TC) contents in blood ($p = 0.012$) and dextrose in blood ($p = 0.016$), an authentic increase in number of cases when there were elevated TC contents in blood ($p = 0.018$) and dextrose in blood on empty stomach ($p = 0.021$). Having compared sub-groups with working experience being from 6 to 10 years and from 11 to 20 years, we revealed not only a significant difference in age but also an authentic increase in average BMI value, from 25.60 ± 0.44 kg/m^2 to 26.89 ± 0.39 kg/m^2 ($p = 0.038$). Besides, there was a considerable growth in number of AH cases, from 13 % to 21 % ($p = 0.113$). There was no dynamics in EBF parameters detected when these two sub-groups were compared. Next, we compared sub-groups with working experience being 21–30 years and 31–40 years; apart from difference in age, there was a significant decrease in such EBF parameters as lung capacity (LC) ($p = 0.013$) and forced expiratory volume (FEV) during the 1st second ($p = 0.034$); it could mean there were mixed (restrictive and obstructive) disorders in breathing mechanics. That is, workers who were exposed to silicon dioxide dust already had a de-

crease in their EBF parameters even when their working experience hadn't yet reached 10 years. During the following 10 years (a subgroup with working experience 11–20 years) there was a significant increase in dextrose contents in blood, BMI, and a number of workers with obesity.

172 workers employed at refractory production had more profound examination at the clinic where prevalence of cardiovascular and metabolic pathology was considered. AH was authentically more frequently detected among patients with silicosis (65 % and 43 % accordingly, $p = 0.005$). Besides, patients with silicosis had cardiac muscle hypertrophy in the left ventricle authentically more frequently, 48 % and 20 %, accordingly ($p = 0.002$); the same was true for ischemic heart disease (20 % and 7 % accordingly, $p = 0.010$), heart rhyme disorders (15 % and 1 % accordingly, $p = 0.006$), and chronic heart failure (25 % and 2 % accordingly, $p = 0.000$). Also patients with silicosis had hemoglobin levels in their blood lower than reference values authentically more frequently (21 % and 8 %, accordingly, $p = 0.022$).

Having compared time of respiratory pathology occurrence, we revealed that occupational lung fibrosis occurred authentically earlier in patients with stage-3 AH in comparison with other patients. Thus, median working experience prior to a moment when silicosis was diagnosed amounted to 31.64 years for workers without stage-3 AH and to 22.7 years for workers with stage-3 AH ($p = 0.047$).

In case there were heart rhyme disorders, dust pathology also occurred significantly earlier as median working experience prior to a moment when silicosis was diagnosed amounted to 18.0 years for patients with arrhythmia and to 34.0 years for those without it ($p = 0.011$).

Silicosis occurred authentically earlier among patients with low hemoglobin; thus, media working experience prior to a moment when silicosis was diagnosed amounted to 31.65 years among patients with normal hemoglobin and to 20.23 among those with low hemoglobin ($p = 0.044$). Besides we revealed certain gender-related differences in silicosis occurrence. Thus, median working experience under exposure to dust prior to silicosis was diagnosed amounted to 33.06 years for men and to 22.27 for women ($p = 0.008$).

As PME were usually performed on workers without any occupational diseases, it provided an opportunity to detect primary health disorders in them which in future could exert their influence on occupational pathology occurrence. High prevalence of lipid metabolism disorders is rather alerting as they were detected in 216 workers (48.1 %) and it is significantly higher than on average in the country [19].

Individual reactions a body might have as a response to the same exposure to dust can be due to impacts exerted by regulatory systems, in particular, due to prevalence of sympathotonic or parasympathotonic influence exerted by the vegetative nervous system and due to a ratio between pro- and anti-inflammatory hormones produced by the adrenal cortex. This factor can also explain more rapid silicosis occurrence in patients with grave AH and hypertrophy in the left ventricle detected in our research.

Detected gender-related differences in silicosis occurrence do not contradict literature data. Thus, basing on multi-factor analysis of results obtained via examining workers employed at fire-clay silica refractory production, the authors showed that a female body was more susceptible to silicosis [20].

We can assume that metabolic disorders already existing in a body potentiate chronic systemic inflammation caused by exposure to fibrogenic dust and in future it leads to more rapid silicosis development in patients with somatic pathologies.

Conclusion.

1. We determined somatic pathologies in workers employed at refractory production that had significant influence on overall and occupational health. As per data obtained via PME workers most frequently had obesity (up to 68 %). Arterial hypertension prevalence amounted to 19.5 %; hypercholesterolemia was detected in 48.1 % cases; and carbohy-

drate metabolism disorders were detected in 19.8 % cases.

2. Workers employed at refractory production with their working experience being less than 10 years already had a significant decrease in EBF parameters. Besides, as working experience at refractory production grew longer, a significant increase in average BMI occurred ($p = 0.025$), average dextrose contents in blood also grew ($p = 0.045$), and obesity became more frequent ($p = 0.041$). Therefore, there is a necessity to adjust these factors associated with occupational and somatic diseases occurrence for workers with different working experience under adverse working conditions.

3. Patients with silicosis more frequently suffered from AH, hypertrophy in the left ventricle, IHD, heart rhyme disorders as well as mixed (obstructive and restrictive) breath disorders in comparison with workers with long working experience who didn't have this occupational pathology.

4. We revealed gender-related differences in occupational lung silicosis occurrence among workers employed at refractory production: silicosis occurrence was expected to occur significantly earlier (by 10.8 years) among women in comparison with men.

5. Concomitant somatic pathology authentically influences time in which an occupational pathology occurs: silicosis occurs much earlier due to grave AH (by 11.5 years), arrhythmia (by 13 years), and low hemoglobin (by 11.5 years). Therefore, active prevention and treatment of somatic pathology will make for occupational diseases prevention.

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Research article

ANALYSIS OF INDIVIDUAL OCCUPATIONAL HEALTH RISKS FOR WORKERS WITH BASIC OCCUPATIONS TYPICAL FOR OIL PROCESSING ENTERPRISES

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At present a systemic approach based on occupational risk assessment methodology is a key to adequate detection of cause-and-effect relations between a disease and working conditions.

Our research goal was to calculate and assess individual occupational health risks for operators and drivers employed at an oil processing enterprise.

Our research object were parameters revealed via special assessment of working conditions and data obtained via periodical medical examinations performed on 198 operators and 160 drivers employed at an oil processing enterprise.

A procedure for calculating individual occupational health risks took into account working conditions, individual health, working experience, and workers' age. Influence exerted by working experience duration on health of workers from the examined occupational groups was estimated in three groups: working experience shorter or equal to 5 years; working experience equal to 6–10 years; working experience being longer than 10 years. Integral assessment of working conditions was obtained taking into account impacts exerted by occupational factors with different hazard categories, assessed risks of injuries and assessment of workers' protection with individual protection means. We calculated integral parameters of working conditions assessment, hazard parameters at workplaces, and one-number integral values of individual occupational risks.

We determined that 91 % drivers and 34.9 % operators ran high and extremely high occupational risks of diseases; those risks changed individually depending on hazard occupational factors at workplaces, age, working experience, and a worker's health. It was shown that high individual occupational risks were much more frequent among drivers and operators with long working experience (6–10 years and longer) who had III–IV health groups and worked under hazardous conditions.

Key words: *occupational hazard, integral assessment of working conditions, operators, drivers, Individual occupational risks.*

There have been significant achievements in occupational hygiene and workers' health protection that allow preventing injuries and morbidity among employable population. Despite that, a lot of industrial enterprises still face serious problems related to managing health risks for workers [1, 2]. Occupational risks create substantial threats for workers' health and working capacities, equipment, and working environment; they produce adverse effects on competitiveness and economic performance indicators in a brunch. Occupational diseases and industrial accidents lead to grave social, economic, and medical consequences [3]. According to international statistic data, occupational diseases and industrial accidents result in almost 2.5 million deaths per year and in more than 2.8 trillion USD expenses all over the world [4]. These data clearly indicate that health risks for workers are a serious problem and are subject to proper regulation [5]. Raising awareness among workers about adverse outcomes occupational diseases and industrial accidents might have has led to more efficient implementation of prevention activities aimed at reducing occupational health risks [6, 7]. Given that, OHSMS (Occupational Health and Safety Management Systems) are being actively implemented in many countries all over the

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world as they are an efficient tool that allows industrial enterprises to manage their occupational risks and to control problems existing in labor protection [8, 9]. Such a system focuses on occupational safety at workplaces whereas contemporary issues indicate it is also necessary to take medical aspects into account [10]. International practices in occupational risks assessment and management at workplaces are actively involving a system for Personal Exposure Monitoring; its fundamental role is to comprehensively assess not only physical, chemical, biological and ergonomic target threats but also medical factors determining how sensitive workers' bodies are to occupational hazards [10, 11]. However, up to now experts have still been searching for efficient approaches and techniques that can be used to quantitatively assess occupational health risks for workers[1] [12–14].

In domestic studies recently there has been search for efficient systems aimed at managing occupational health risks for workers via influencing exposure to occupational factors, their intensity, and taking into account individual sensitivity of a specific worker's body to occupational hazards [15–17]. Quantitative calculation of damage to a worker's health that can occur during his or her occupational activities is considered an efficient procedure within a systemic approach to managing occupational health risks at production[2] [18–20]. Prediction given for preservation of a worker's life span, health, functional abilities, and his or her children's health is considered a key criterion in quantitative health risk assessment[3, 4].

Our research goal was to calculate and assess individual occupational health risks for operators and drivers employed at an oil processing enterprise.

Data and methods. Individual occupational health risks were assessed for 198 operators and 160 drivers employed at an oil processing plant; the assessment was performed as per the procedure developed by N.F. Izmerov, L.V. Prokopenko, N.I. Simonova et al. (2010) and approved by the Scientific Council held by the RF Public Healthcare Ministry and Russian Academy of Medical Sciences «Medical and ecological issues for employable population» [20]. Individual occupational risks were calculated basing on results obtained via assessing working conditions at a workplace, workers' health at the beginning of the year, their age and working experience as well as data on injuries and occupational morbidity among operators and drivers. Occupational factors influencing operators and drivers were examined as pre data obtained via special assessment of working conditions and workers' health examined during periodical medical examinations. Influence exerted on health of workers from the examined occupational groups by length of their working experience was estimated in three groups, workers with working experience up to 5 years; the 2nd group, 6–10 years; the 3rd group, longer than 10 years. One-figure value of an individual occupational risk (IOR) was calculated via multiplying summed weighted values of parameters (working conditions assessment, operators' and drivers' working experience, workers' age, and workers' health) reduced to relative values by indexes showing injuries and occupational morbidity at workplaces (1):

$$IOR = (w_i K_i IAWC + w_3 k_3 He + + w_в k_в A + w_c k_c WE)\, I_{in} \cdot I_{om} \quad (1)$$

where:

IAWC is integral assessment of working conditions at a workplace;

[1] CCPS.Guidelines for Hazard Evaluation Procedures. New York, American Institute of Chemical Engineers Publ., 2008, 576 p. (in Russian).

[2] Occupational health risks for workers: guide. In: N.F. Izmerov, E.I. Denisov eds. Moscow, Trovant Publ., 2003, 448 p. (in Russian).

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He is workers' health;

A is workers' age

WE is working experience;

I_{in} is index showing injuries at a workplace;

I_{om} is an index showing occupational morbidity at workplace;

w_i,w_3, $w_в$, w_c are weighted coefficients that allow taking significance of certain parameters into account;

k_i,k_3, $k_в$, $k_c$are coefficients used to recalculated parameters from their absolute values into relative ones.

Integral assessment of working conditions (IAWC) at operators' and drivers' workplaces was performed taking into account exposure to occupational factors with different hazard categories, assessing risks of injuries, and assessing workers' protection with personal protective equipment depending on hazard index (HI) values as per the formula (2):

$$IAWC = \frac{100 \cdot [(HI-1) \cdot 6 + R]}{2334} \qquad (2)$$

where:

HI is a calculated hazard index for working conditions at a specific workplace;

R is a rank determined in accordance with injuries risks (IR) and protection assessment (PA) for a specific workplace;

100 is a proportionality coefficient;

2334 is a number that characterizes all theoretically possible combinations of HI, IR, and PA values.

We calculated how hazardous operators' and drivers' working conditions were following a certain sequence via determining total hazard (TH):

$$TH = \sum^{m} Vi,$$

where:

m is a number of occupational factors existing at a workplace;

Vi is a score number that depends on working conditions category for the i-th occupational factor existing at a workplace.

Then, we calculated total scores (TS) for a workplace:

$$TS = 2 \cdot m,$$

where m is a number of occupational factors existing at a workplace.

Then we calculated working conditions hazard (WCH) as per the following formula:

$$WCH\ (TH-TS)/2,$$

where TH and TS were calculated as per the formulas given above, and

2 is a coefficient equal to 2 scores and used to transfer Hi into a dimensionless value.

Integral assessment of working conditions gave us the following ranks for working conditions:

IAWC≤0.04 means working conditions are acceptable;

IAWC 0.04–0.51, hazardous;

IAWC 0.52–1.54, extremely hazardous;

IAWC 1.55–3.60, unacceptably hazardous;

IAWC 3.61–7.50, dangerous;

IAWC ≥ 7.50, extremely dangerous.

One-figure integral values of individual occupational risk were estimated as per the following scale:

IOR = 0.13 means low risk;

IOR = 0.13–0.21, average risk;

IOR = 0.22–0.39, high risk;

IOR ≥ 0.4, extremely high risk.

Statistical analysis was performed with Statistica 12/0 applied software for Windows. Numerical data are given as simple mean and its standards error ($M \pm m$). To reveal statistically significant discrepancies between the examined groups, we applied Student's parametric procedure with coefficient calculation and a non-parametric procedure with Mann-Whitney coefficient determination. Discrepancies were considered statistically significant at $p \leq 0.05$.

Results and discussion. We determined that integral hazard index (HI) amounted to 1.6±1.8 scores at operators' workplaces, and to 2.4±2.1 scores at drivers; workplaces ($p \leq 0.05$) and was considered to be dangerous. HI was determined at operators' workplaces by such occupational factors as microclimate, infrasound, and labor hardness that were considered to be optimal (2.0 hazard category) and corresponded to 6 scores; elec-

tromagnetic radiation and noise belonged to 3.1 hazard category (hazardous working conditions) and corresponded to 8 scores; chemical factor and labor intensity belonged to 3.2 hazard category and corresponded to 10 scores (Figure 1). Hazard index at drivers' workplaces was determined by labor intensity (hazard category 2.0, 2 scores); microclimate, electromagnetic radiation, and labor hardness belonging to 3.1 hazard category (12 scores); chemical factor, noise, and infrasound (3.2 hazard category, 24 scores).

Working conditions as their integral assessment (IAWC) revealed turned out to be hazardous and amounted to 0.38 ± 0.0006 units for operators and to 0.43 ± 0.005 units for drivers, $p \leq 0.05$. Basing on initial data obtained via integral assessment of working conditions, workers' health, age, and working experience, we calculated individual occupational risks (Figure 2). We determined that 55 % operators ran average occupational risks; 32 %, high occupational risks; 2.9 %, extremely high occupational risks; and only 10.1 % operators ran low individual occupational risks. It is important to note that 78.6 % drivers ran extremely high occupational risks, and only (% ran average risks; there were no drivers who ran low individual occupational risks.

Analysis of data given in Table 1 revealed that individual occupational risk for workers from the examined occupational groups grew depending on their working experience in the sphere and at the examined enterprise. It was shown that individual occupational health risks grew for both operators and drivers as their working experience got longer. Thus, 64.0 % operators with their working experience at the examined enterprise being shorter than 5 years ran low individual occupational risks; 28.2 %, high risks; and only 7.8 %, high risks. There was a 1.2-time growth in number of operators running high individual occupational risks among those with working experience being form 6 to 10 years (15.1 % of the examined workers); and 1.9 % operators in this group ran extremely high occupational health risks. As working experience exceeded 10 years, there was a 2-time growth in a number of operators who ran high occupational health risks.

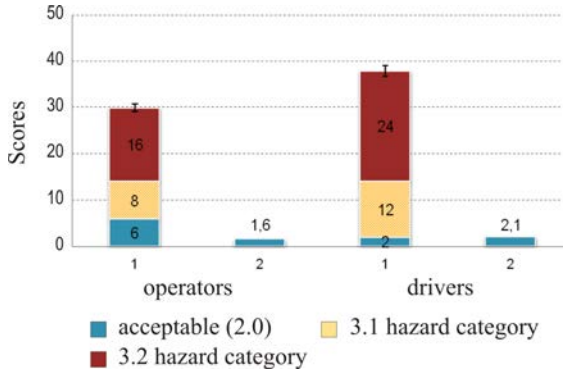

Figure 1. Weighted values of occupational factors (1) and hazard indexes (2) at operators' and drivers' workplaces

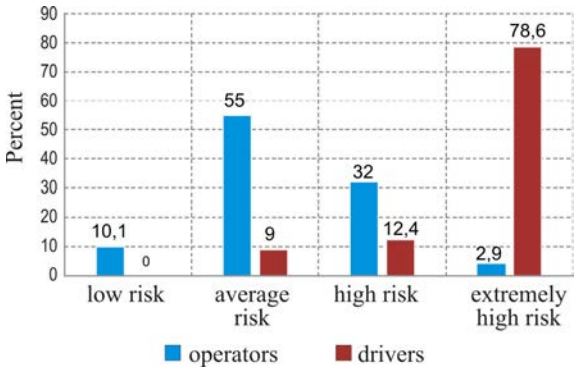

Figure 2. Operators and drivers distributed depending on their individual occupational risks

Table 1

Workers running different individual occupational risks and distributed depending on their working experience (%)

Individual occuaptional risk	Working experience		
	Shorter than 5 years	6–10 years	≥10 years
Operators			
Very low	–	–	–
Low	64.0	22.6	31.5
Average	28.2	60.4	35.2
High	7.8	15.1	32.4
Extremely high	–	1.9	0.9
Drivers			
Very low	–	–	–
Low	–	–	–
Average	24.0	15.8	3.8
High	38.0	26.3	3.8
Extremely high	38.0	57.9	92.4

Unlike operators, 76 % drivers with short working experience (shorter than 5 years) ran high and extremely high occupational risks, and only 24 % drivers in this group ran average occupational health risk. Occupational health risks for drivers also grew as their working experience got longer and the growth rate was more significant than for operators. Thus, 57.9 % drivers with working experience being 6–10 years ran extremely high occupational risks, and the figure was much higher (92.4 %) among drivers with working experience exceeding 10 years (Table 1).

We determined that workers' health was significant for individual occupational risk. It was detected that 73 % operators and 43 % drivers belonged to I and II health groups as per data obtained via periodical medical examinations (Figure 3).

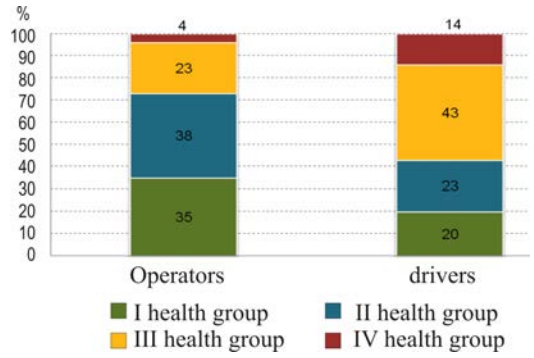

Figure 3. Workers distributed depending on their health group

Workers from I health group didn't have any complaints about their health, their case histories didn't contain any data on any disease or functional disorders and periodical medical examinations didn't reveal them either. Such workers fell sick not more than 2 times a year and it was usually a respiratory disease; overall duration of temporary disability for workers from this health group amounted up to 7 days per year. Workers who had certain functional disorders and therefore ran a risk of a disease occurrence belonged to II health group; they fell sick with respiratory diseases more than 2 times a year, and their temporary disability varied from 7 to 14 days a year. At the same time, 43% drivers and 23 % operators belonged to III health group. They all had a compensated non-communicable chronic disease; they had a respiratory disease 2 or 3 times a year; and their temporary disability varied from 14 to 21 day. All this, together with impacts exerted by adverse occupational factors and long working experience, resulted in high and extremely high occupational health risks for workers form this health group.

Conclusions.

1. According to integral assessment, working conditions for operators and drivers are hazardous. Integral hazard index was 1.3 times higher for drivers' workplaces than for operators' ones and it was determined by such adverse occupational factors as noise, infrasound, air being contaminated with a set o adverse chemicals, unfavorable microclimate, and significant labor hardness.

2. It was shown that 34.9 % operators and 9% drivers ran high and extremely high individual occupational health risk that changed depending on occupational factors hazards at workplaces, working experience, workers' age and health.

3. Individual occupational health risks were more frequent among drivers and operators with long working experience, workers belonging to III–IV health groups, and workers who were exposed to not less than 3 adverse occupational factors belonging to 3.2 hazard category.

4. Therefore, our calculation results and results obtained via analyzing individual occupational health risks for operators and drivers are a basic instrument for substantiating, developing, and selecting a sequence for implementation of managerial decisions necessary to reduce occupational health risks and to preserve workers' health.

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Research article

ISOLATION AND CHARACTERIZATION OF *STAPHYLOCOCCUS AUREUS* FROM TWO LARGE-SCALE FOOD POISONING OUTBREAKS IN VIETNAM

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In Vietnam and around the world, Staphylococcus aureus remains a major hazard of food safety and food poisoning. S. aureus is present in many places and easily contaminates food production during processing chains.

In this study, we successfully isolated S. aureus strains from suspected samples of two food borne poisoning outbreaks in Ha Giang and Vinh Phuc in 2017 and 2018, respectively. The collected samples were examined for presence of staphylococcal enterotoxins (SEs) by using 3M™TECRA™ Staph Enterotoxin kit, from there all the samples were positive with SEs. Different strains of S. aureus were isolated and then confirmed by MALDI-TOF technique. Those strains then were stored in Brain heart solution with 15 % glycerol until further analysis.

Our results identified three STs, ST96, ST88 (spa type t7558), and ST72 (spa type t3092), were responsible for two outbreaks. Two virulence genes detected from the above strains were sea and sec. Furthermore, these strains are test for antibiotic resistance susceptibility with commonly antibiotics. Penicillin are found to be resisted by all three STs, in particularly, ST96 and ST88 are both resistant to erythromycin while ST72 is resistant to gentamicin.

Taken together, our study highlights the usefulness of molecular characterization to study and monitor bacterial pathogens associated with food poisoning outbreaks in Vietnam.

Key word: *antibiotic-resistant, food poisoning, β-lactamase, ESBL, ampC β-lactamases, Staphylococcus areus, MLST, Spa genes, staphylococcal toxins.*

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According to the WHO annual report in 2014, there are 40 million food poisoning cases reported worldwide. The Asia-Pacific region reports up to more than 50 % of total cases [1]. After *Salmonella* and *Campylobacter*, the two most common bacteria associated with food poisoning, *Staphylococcus aureus* is also a major foodborne pathogen which is identified in up to 241,000 cases each year globally. Along with that, reports from Europe showed that 5 % of food poisoning outbreaks in the continent were caused by *S. aureus*, which led to an annual rate of infection from 0.6 to 0.7/100,000 people (data from 2010 and 2011) [2, 3]. In Vietnam, the situation has not been under control with a total of 677 outbreaks involving 21,002 patients in the four-year period from 2011 to 2014 [4]. In the first 4 months of 2016, half of the outbreaks counted in Ho Chi Minh city, the largest city in Vietnam, happened in school canteens, and 50 % of them were caused by *S. aureus* [5].

Staphylococcus aureus is a Gram-negative bacterium belonging to the *Staphylococcus* genus, which to date includes more than 30 species. Among those, *S. aureus* is the most frequently associated with food poisoning and the most common causative of foodborne diseases in human and animal in general [6, 7]. Approximately, 25–30 % of healthy adults carry *S. aureus* asymptomatically, mostly in the nasopharynx and on the skin. *S. aureus* normally cannot compete with other type of bacteria naturally exist in food, however, due to their ability to withstand living conditions such as high salt concentration (up to 15 %) and low humidity, *S. aureus* can survive on human skin or the surface of clothes and multiple apparatus [8–10]. Therefore, for most cases of staphylococcal food poisoning, the contamination route is through contact with infected food handlers, or infected food preparation surface [11].

S. aureus causes food poisoning by producing staphylococcal enterotoxins, which lead to symptoms such as nausea, abdominal pain, vomiting and diarrhea. Up to now, more than 20 types of staphylococcal enterotoxins (SEs) and SE-related toxins have been described, among these SEA, SEB, and SED are the most prevalent in food poisoning cases [11].

In Vietnam, food is still mostly manually prepared by traditional ways all over local markets, restaurants or school canteens before it reaches consumers, increasing the chance of *S. aureus* transmission during food preparation. It is thus necessary to monitor and characterize *S. aureus* strains involved in outbreaks in the region. Multilocus Sequence Typing (MLST) – a technique utilizes variations in several housekeeping genes to group isolates into common sequence types (STs) – has been successfully handle to quickly and accurately identify and characterize pathogenic bacterial and viral strains worldwide. Besides MLST, variations of the virulent gene *spa* of *S. aureus* have been used successfully to study the prevalence and diversity of this bacterial species [12]. In this study, we employed both MLST and *spa* typing, together with enterotoxin and antibiotic susceptibility assays to characterize and elucidate the phylogenetic relationship of *S. aureus* strains involving in two food poisoning outbreaks in Vietnam.

Data and methods.

Food samples. Food samples were collected after the two food poisoning outbreaks had been reported. The first food poisoning outbreak happened at a wedding reception in 2017, in Vinh Phuc province and caused more than one hundred people to be hospitalized. Food items were collected for further investigation and glutinous rice cake was identified as the suspected causative food. The second outbreak was documented in a school canteen in Ha Giang province. The suspected food was minced pork, which might be the reason for the hospitalization of almost two hundred students. All food samples were collected, kept in ice boxes, and transferred to the National Institute for Food Control for bacterial isolation and characterization.

Detection of SEs in food samples. The presence of five major SEs (SEA to SEE) in food samples was detected using 3M^{TM}TECRA^{TM} Staph Enterotoxin kit (Novatek, Russia, 16215008) following the manufacturer's instruction [13]. In detail, the amount of 25 g of

each food sample was homogenized with Tris buffer, pH 8.0 and the supernatant was collected by centrifugation. All samples were confirmed for the presence of peroxidase before 200 µL of sample was mixed with test suspension additive solution (containing 2 g Tween 20 and 0.001 g thimerosal in 6.0 mL H2O) and incubated at 35–37 °C for 2 hours, followed by washing and conjugating with distinctive antibody for each type of SEs. Results were interpreted by measuring absorbance values at 414±10 nm.

Bacterial isolation. Food samples were homogenized in sterile saline buffer at 1:10 ratio, diluted up to 10^{-4} fold and 0.1 mL of each dilution was plated on Bair Packer (BP) agar (Becton, Dickinson, USA, 276840). Plates were incubated at 37°C ± 1°C in 24–48 hours and black colonies were chosen for coagulase tests.

The identification of coagulase-positive colonies was, then, performed strain by Vitek®-MS (bioMérieux Clinical Diagnostics, France). Confirmed *S. aureus* isolates were kept at -80 °C in Brain heart infusion (BHI, Difco, USA, 1104930500) broth supplemented with 15 % glycerol until further analyses.

Antibiotic susceptibility test. Isolates were recovered on blood agar and one pure colony was transferred to BHI broth. Antibiotic susceptibility tests were performed following the Clinical and Laboratory Standards Institute (CLSI) guideline [14]. Of seven antibiotics tested, susceptibilities to oxacillin (OX; 1 µg), erythromycin (E; 15 µg), gentamicin (CN; 10 µg), tetracycline (TE; 30 µg), and penicillin (P; 10 µg) were determined using disc diffusion assay. Where disc diffusion assay was not applied, resistance to methicillin (MET; 5 µg) and vancomycin (VA; 30 µg) was instead determined by minimum inhibitory concentration (MIC) method. Isolates were classified as sensitive, intermediate or resistant in accordance with CLSI breakpoints for each tested antibiotic. Multidrug resistance (MDR) was defined as non-susceptibility to at least one agent in three or more antimicrobial categories [15].

Genomic DNA extraction. Stored isolates were recovered on blood agar before growing overnight in BHI broth at 37 °C for DNA extraction. From 3 mL of overnight *S. aureus* culture, genomic DNA was extracted by using GeneJET Genomic DNA Purification Kit (Thermo Fisher Scientific, USA, K0721) in accordance with the manufacturer's instruction. The quality of extracted DNA was assessed using the Nanodrop 1000 instrument (Thermo Fisher Scientific, USA, I594).

Identification of virulence genes. Five classical SE genes *sea, seb, sec, sed* and *see* were identified from genomic DNA of *S. aureus* isolates by PCR using primer sequences reported by Johnson and colleagues [16]. Each 25 µL polymerase chain reaction (PCR) contained 12.5 µL 2x DreamTaq MasterMix (Thermo Fisher Scientific, USA, K0171), 10 pmol of each primer, 100 ng DNA, and sterile water up to the final volume. Final PCR products were analyzed by agarose electrophoresis to detect the presence or absence of specific amplicons. The presence of classical enterotoxins was confirmed by 3M^{TM}TECRA^{TM} Staph Enterotoxin kit (Novatek, Russia, 16215008) according to the manufacturer's instruction as described above. The presence of *mecA* and *femA* was detected by PCR using the specific primers from previous publications (Table 1).

Molecular typing and phylogenetic analyses (MLST). MLST and *spa* typing were done as previously described in Jolley et al. 2018. In detail, primer sequences and PCR conditions used for amplification of the seven housekeeping genes in the MLST scheme were referred from PubMLST [17]. The polymorphic region of *spa* gene was amplified using the primer pair spa-1113f (TAA AGA CGA TCC TTC GGT GAG C) and spa-1514r (CAG TAG TGC CGT TTG CTT) [18]. PCR products were purified and sequenced using Sanger method by 1st Base DNA Sequencing Services (Singapore). Sequence type (ST) assignment and clustering were done using PubMLST and eBURST, respectively [1, 19]. Geographical distribution and phylogeography analysis were done using Microreact [20]. *Spa* types were assigned by the SpaServer website and clustered using Based Upon Repeat Pattern (BURP) [21, 22].

Table 1

PCR primers for staphylococcal enterotoxin genes, methicillin-resistance genes, and *spa* typing

Gene	Primer	Primer sequence (5′–3′)	References
sea	SEA Fw	GCA GGG AAC AGC TTT AGG C	(Veras, et al., 2008)
	SEA Rv	GTT CTG TAG AAG TAT GAA ACA CG	
seb	SEB Fw	GTA TGG TGG TGT AAC TGA GC	(Veras, et al., 2008)
	SEB Rv	CCA AAT AGT GAC GAG TTA GG	
sec	SEC Fw	CTT GTA TGT ATG GAG GAA TAA CAA	(Veras, et al., 2008)
	SEC Rv	TGC AGG CAT CAT ATC ATA CCA	
sed	SED Fw	GTG GTG AAA TAG ATA GGA CTG C	(Veras, et al., 2008)
	SED Rv	ATA TGA AGG TGC TCT GTG G	
femA	FemA Fw	AAA GCA CAT AAC AAG CG	(Veras, et al., 2008)
	FemA Rv	GAT AAA GAA ACC AGC AG	
mecA	MecA Fw	TGCTATCCACCCTCAAACAGG	(Yoshida, et al., 2003)
	MecA Rv	AACGTTGTAACCACCCCAAGA	
spa	spa-1113f	TAA AGA CGA TCC TTC GGT GAG C	(Strommenger, et al., 2006)
	spa-1514r	CAG TAG TGC CGT TTG CTT	

Results and discussion.

Case description and isolate characterization. Two staphylococcal food poisoning outbreaks occurred independently in north Vietnam between 2017 and 2018 (Table 2). The first outbreak happened at a wedding in Vinh Phuc province in 2017, causing 152 guests to be hospitalized. The other outbreak, occurred at a primary school, happened in October 2018. At the second outbreak in Ha Giang, 279 students were at risk while 170 were hospitalized. Common symptoms in all outbreaks included diarrhea, nausea and vomiting, reported from 2 to 6.5 hours after eating. All patients successfully recovered. Three presumptive *S. aureus* isolates were identified from remaining food samples. Isolates found in samples were kept for further investigation.

Virulence genes and antibiotic resistance pattern of isolates. According to our results, two isolates, designated 388 and 389, were identified from the first outbreak, while, only one isolate, 24ND, was identified in the second outbreak (Table 3). All isolates were coagulase positive. Furthermore, PCR was performed in order to detect the presence of classical SE genes in all isolates. The first outbreak appeared to be caused by two different *S. aureus* strains, one carrying *sea* toxin genes and *femA*, and the other having *sec* and *femA*. The only *S. aureus* strain identified in the second outbreak also carried *femA* gene, besides *sec*. The presence of classical SE toxins in all isolates was confirmed by 3M^{TM}TECRA^{TM} Staph Enterotoxin kit.

Table 2

Epidemiological data from food poisoning outbreaks

Outbreak	Date (DD/MM/YY)	No. of patients at risk / No. of hospitalized patients / No. of deaths	Location / Site	Incubation period (hour)	Symptoms (no. of cases)	Causative Food
1	20/10/17	152/109/0	Vinh Phuc/ Wedding/House	5	N,V,S,D	Glutinous rice cake
2	03/10/18	279/170/0	Ha Giang/ Primary school	2	N,V,S,D	Minced pork

Note: N – nausea; V – vomiting; S – Stomachache; D – diarrhea.

Table 3

Characterization of isolates from food poisoning outbreaks

Outbreak	Isolate	Origin (No. of isolates)	MLST	*spa* type		Classical toxins	Virulence genes	Antibiotic resistance phenotypes
				ST's mapped [a]	This study			
1	388	FD	96	NA	NA	+	*coa, sea, femA*	E, P
	389	FD	88	t186	t7558	+	*coa, sec, femA*	E, P
2	24ND	FD	72	t126	t3092	+	*coa, sec, femA*	CN, P

N o t e : FD – food; E – Erythromycin; P – Penicillin; CN – Gentamicin; [a] ST(s) known associated *spa* type(s), by Ridom Spa Server [22].

In order to examine the extent of antibiotic resistance of all *S. aureus* isolates, antibiotic susceptibility was tested using disc diffusion method and where required, MIC method was perform as instructed in the Clinical and Laboratory Standards Institute (CLSI) 2018 guideline. The tested antibiotics consisted of those commonly used for treatment of staphylococcal food poisoning (oxacillin, erythromycin, gentamicin, tetracycline, penicillin, and vancomycin) in Vietnam. All isolates were found resistant to at least two antibiotics, one of which was penicillin. Both isolates from the first outbreak were also resistant to erythromycin. 24ND, the isolate from the second outbreak, showed resistance to gentamicin and penicillin.

Molecular typing and phylogenetic analysis. Genotyping was performed on all isolates using MLST and *spa* typing. MLST profiling revealed there were three sequence types (STs), ST96, ST88, and ST72, among three isolates in this study. ST96 and ST88 were responsible for the first outbreak, and ST72 were responsible for the second one. eBURST analysis showed that none of the detected STs formed clonal complexes with one another or any other known STs, even though all three STs were the central most prevalent ST of their respective group, which were formed by known single-locus variants in PubMLST database. Based on the group definition of PubMLST, ST72 formed a group with 50 others known STs, ST88 and ST96 respectively formed groups with 48, 66 and 7 other STs. ST72 was the most abundant with 120 isolates recorded in PubMLST, followed by ST88 (n = 108) and ST96 (n = 3) (Figure 1). An

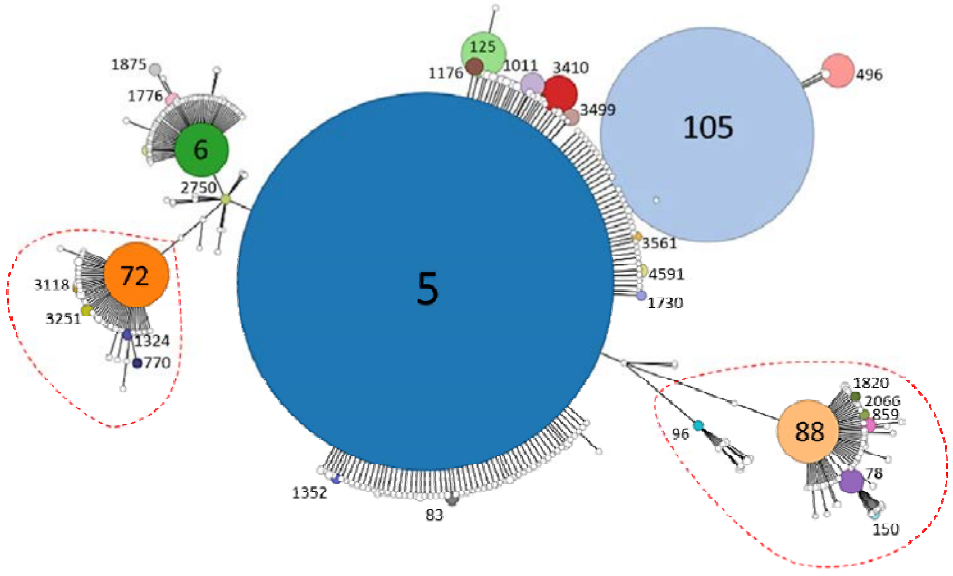

Figure 1. Groups of STs found in this study and their respective single-locus and double-locus variants. STs with more than two known isolates were colored and labeled. Node sizes were numerically correlated with numbers of isolates in each ST. For ST72, ST88 and ST96, all related STs with fewer than two reported isolates were unlisted

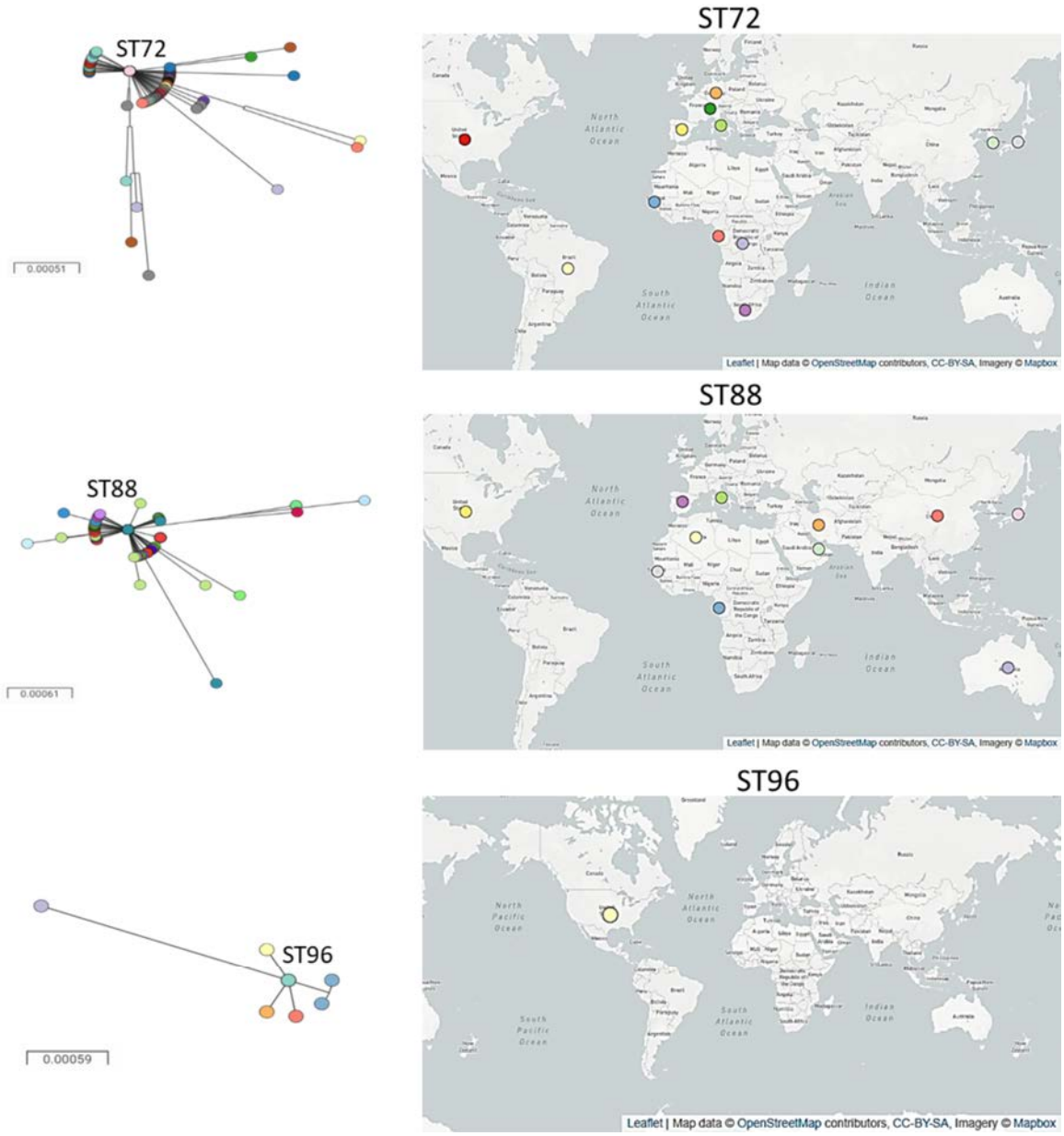

Figure 2. Visualization of phylogeographic trees and geographical distributions of the three STs identified from food poisoning cases in Vietnam between 2017 and 2018: A – phylogeographic trees of each ST showing evolutional relationship and color-labels according to country; B – geographical distribution of the three STs in this study

examination of external nodes, defined as STs sharing at least five identical loci, identified no immediate ancestor of ST72, ST88 and ST96. ST72 has not evolved into any major ST, while ST88 was the ancestor of ST78. ST96 showed branching-out of three STs evolved from it.

Geographical mapping explained the globally distribution of ST88, recorded in all continents. ST72 was found in all continents except for the Oceania. ST96 was the rarest, with only three isolates reported in the USA so far (Figure 2).

In this study, we characterized the causative *S. aureus* strains of two foodborne outbreaks in Vietnam in 2017 and 2018 that led to more 109 and 170 people hospitalized, respectively. Glutinous rice cake and minced pork

were identified as the causative food, and transmission likely happened during the food preparation process. Using MLST and *spa* typing methods, three sequence types (STs) involved in two outbreaks were identified, namely ST77, ST88, and ST96. All strains showed resistance to penicillin. In addition, two strains from the outbreak in Vinh Phuc were resistant to erythromycin while the one from the second outbreak in Ha Giang exhibited resistance to gentamicin. Results showed that classical toxins, SEA and SEC, are presented in glutinous rice cake and minced pork. These classic SEs have been recorded as the main toxins causing foodborne outbreaks among more than 20 of SET groups. SEA is predominantly determined around the world in 56.9 % of outbreaks. However, only a small percentage of outbreaks was caused by SEA in conjunction with SEC. In our study, SEA and SEC were identified from the first foodborne outbreak. On the other hand, only SEC was found on minced pork in the second one. This is similar to other reports on staphylococcal food poisoning worldwide [11].

In the United Kingdom, *S. aureus* led to 359 foodborne outbreaks during the period from 1969 to 1990. Meat and poultry were the main sources of poisoning [11]. According to European Food Safety Authority report, *S. aureus* caused 5.5 % of outbreaks in the European Union [23].

In this study, we employed both housekeeping genes of MLST scheme and *spa* variants to analyze strains' phylogenetic relationship. MLST scheme utilized genes encoded for primary metabolism enzymes, while *spa* is a typical virulence gene, which is normally subjected to higher selection pressure. By combining both schemes, we can accurately estimate strains' evolution. MLST and *spa*-typing databases are not fully inclusive.

Conclusions. In this study, three STs, including of ST77, ST88, and ST96, were successfully isolated. All isolated strains carry *sea* gene that produces SEA. According to antibiotic susceptibility testing, all three strains are resistant to penicillin. Moreover, both ST88 and ST96 are resistant to erythromycin, while ST77 is non-susceptible to gentamicin. Geographical mapping data demonstrated that ST96 seems to be an emerging ST which has only been described in outbreaks in the US, whereas the two other STs have been recorded in almost all continents. *S. aureus* remains a major pathological hazard that rapidly evolves and develops antibiotic resistance, thus continual monitoring of the genetic and antibiotic resistant profiles of circulating *S. aureus* strains in Vietnam is crucial for outbreaks prevention and response.

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

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Research article

UP-TO-DATE TECHNIQUES FOR EXAMINING SAFETY AND PHYSIOLOGICAL EFFICIENCY OF INDUSTRIAL EXOSKELETONS

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Occupational morbidity caused by physical overloads and certain organs and systems being overstrained ranks second among occupational pathologies depending on an influencing adverse occupational factor. Given that, it seems vital and promising to develop industrial exoskeletons as they are able to protect a worker's musculoskeletal system from excessive physical loads. And absence of a relative regulatory and technologic base is a challenge here as it imposes substantial limitations on industrial exoskeletons implementation in productions both in Russia and in other countries.

A significant role in creating regulatory and technological base belongs to a possibility to accomplish an objective medical and biological examination of industrial exoskeletons safety and physiological efficiency. Developed and properly tested procedures for examining physiological and ergonomic properties of industrial exoskeletons will make a substantial contribution into a system of complex ergonomic tests accomplished at stages when exoskeletons are developed, created, and put into trial operation.

The present paper dwells on up-to-date medical and biological procedures for examining safety and physiological efficiency of industrial exoskeletons. There are examples on using a «movement seizure» procedure performed with inertial sensors, ergospirometry, electromyography, and myotonometry for estimating physiological and ergonomic properties of industrial exoskeletons at a modeled working place.

Results obtained via this research involving all the above mentioned procedures confirmed that it was safe and quite efficient to apply industrial exoskeletons for workers who had to deal with physical labor when performing work tasks similar to those used in developed models. Applied procedures can substantially enhance approaches to examining a worker's functional state and obtained results will make a significant contribution into development of a regulatory and technological base for promising individual protection means used to protect the musculoskeletal system within the existing System of occupational safety standards.

Key words: *industrial exoskeletons, individual protection means, biomechanical analysis of movements, ergospirometry, electromyography, myotonometry.*

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Occupational morbidity caused by physical overloads and certain organs and systems being overstrained ranked 2nd among occupational pathologies in 2018 depending on an influencing harmful occupational factor and amounted to 24.7 %[1]. And at present there are no personal protective equipment (PPE) that can prevent negative effects produced by labor hardness on a worker's musculoskeletal system (MSS). Given that, it seems promising to implement industrial exoskeletons (IE) that can protect a worker's musculoskeletal system from overstrain caused by physical loads. World IE market is growing and a lot of enterprises are trying to implement them, both abroad [1, 3–5], and in the Russian Federation as well [7–9].

A major problem that imposes certain limitations on IE implementation at production facilities, both in Russia and abroad, is an absence of a proper regulatory and technological base with requirements to them [1].

At present, according to the Order by the Federal Technical Regulation and Metrology Agency No. 962 issued on May 21, 2020 «On organizing activities of the technical committee (TC) on standardization "Personal protective equipment" «a production committee (PC) 11 (Industrial exoskeletons) was created within the TC 320 structure. It was organized at Izmerov's Research Institute of Occupational Health (hereinafter called the Institute). The Institute, together with IE designers, large enterprises, and scientific and research organizations, is working out two draft national standards that regulate requirements to IE as a new type of MSS PPE; the work is being accomplished within the National Standardization Program for 2020[2].

It is beyond any doubts that objective medical and biological assessment of IE plays a significant role in making conclusions on their safety and physiological efficiency. We analyzed up-to-date approaches to examining a person's functional state that are applied in occupational medicine, sport medicine, functional diagnostics, rehabilitation, and other spheres. Procedures selected for the present work included:

– «movement seizure» with inertial sensors as the most acceptable procedure for assessing biomechanics of movements in joints[3];

– ergospirometry (ESM) as a non-invasive procedure for complex assessment of the cardiorespiratory system state [1–11];

– electromyography (EMG) as a basic procedure for assessing bioelectrical muscle activity [11–16];

– myotonometry (MTM) as an up-to-date procedure for muscle tone assessment.

Besides, our research included conventional procedures that are widely used in clinical and preventive medicine such as dynamometry[4], stabilometry, mental and physiological testing, questioning, interviewing, as well as functional tests [17, 18].

Experts from the Institute, together with the Robotechnics Laboratory of Sberbank, «Poleznye roboty» LLC, and «Exoatlant» LLC, performed a scientific research work in order to examine safety and physiological efficiency of IE application. The most significant results are outlined in the present paper.

The research goal was to assess safety and physiological efficiency of industrial exoskeletons application in modeled work activities using up-to-date research techniques.

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a *b*

Figure 1. Workplaces models created in a laboratory:
a) shows a workplace of a logistician; b) shows a workplace of a cashier

Data and methods. Work activities models were developed in laboratories of the Institute basing on labor hardness parameters and characteristics of working postures and movements taken and made by workers with two occupations:

– a logistician working in Sberbank archives and logistics center;

– a cashier working in the precious metals department of Sberbank Main Cash Center.

To model work activities, we created working conditions identical to those existing at workplaces of a logistician working in Sberbank archives and logistics center and a cashier working in the precious metals department of Sberbank Main Cash Center.

Figure 1 shows models of workplaces belonging to workers with the above-mentioned occupations.

We tested the following IE samples: «Exochair» IE produced by «Poleznye roboty» LLC to reduce negative effects produced by static load on the musculoskeletal system of workers dealing with physical labor and having to work standing upright; and «ExoAtlant» («Exoatlant» LLC) made to reduce negative effects produced by dynamic load related to lifting weights and body bending.

Our volunteers were 6 healthy men (aged 27.8±4.8, 183.0±5.8 cm high, with body weight equal to 80.0±11.1 kg and body mass index equal to 23.3±2.8). Prior to the research they were examined by medical experts and were verified to be "healthy" by results of examinations as well as functional and laboratory tests. Each volunteer accomplished modeled work tasks both using an IE and without it.

Safety of IE application was assessed by:

– dynamics of volunteers' overall functional state;

– an extent to which amplitudes of active movements in large joints in the arms and legs and the vertebral column were limited due to IE application.

Physiological efficiency of IE application was assessed by:

– dynamics of energy expenditure borne by volunteers over the total amount of time during which work activities were modeled;

– cardio-respiratory system parameters;

– fatigue of skeletal muscles that participated in maintaining working postures and making movements necessary to accomplish a work task;

– parameters of volunteers' static coordination;

– subjective feelings and psychophysiological state of volunteers;

– labor productivity.

Overall functional state was assessed via an examination by a physician that included external examination, measurement of basic functional parameters, subjective assessment by a volunteer regarding his feelings during making voluntary movements in large joints and vertebral column, interviewing volunteers in order to reveal whether they had unpleasant feelings or pain (assessed with a 10-score scale), subjective assessment by volunteers regarding their functional state and working capacity.

In order to determine to what extent amplitudes of active movements in large joints in

the arms and legs and the vertebral column were limited due to IE application, we used «Biomechanics Trust-M» system for complex objective assessment of movement functions, movement biomechanics registration, and EMG («Neurocor» LLC, Moscow, Russia). Inertial sensors were applied to register amplitudes of active movements in large joints in the arms and legs and the vertebral column.

To determine energy expenditure borne by volunteers, we applied «Metamax 3B» portable complex for ESM testing (Cortex, Germany) and Polar H10 heart rate monitor with elastic belt (Polar Electro, Finland). Gas exchange parameters were registered automatically during work shift modeling.

To assess influence exerted by IE on volunteers' cardio-respiratory system, we applied Ruffier test, Physical Working Capacity 170 test, Stange-Hench test, Serkin's test, as well as active stand test.

Skeletal muscles fatigue was assessed with EMG using «Biomechanics Trust-M» system for complex objective assessment of movement functions, movement biomechanics registration, and EMG (with «Myoton PRO» device («Myoton AS», Estonia)), as well as hand and backbone dynamometry.

When examining physiological efficiency of «Exochair» IE application, we assessed functional state of muscles in the back and legs of a volunteer who was standing still (EMG) or lying (MTM); for «ExoAtlant» IE efficiency, we assessed functional state of muscles in the back and arms beyond modeled work activities (EMG) in two postures taken by a volunteer (standing and holding 31 kg; standing in a working posture with the same weight but using an IE); we also measured muscle tone of erector spine muscle when a volunteer took a working posture carrying some weight (MTM). Besides, we applied hand and backbone dynamometry.

To assess volunteers' static coordination, we applied «Stabilometry Trust-M» platform included into a treatment set for treating and rehabilitating patients with movement pathologies («Neurocor» LLC. Moscow, Russia). We applied Romberg's test with eyes open and closed as a test that allowed assessing functional state of the postural system.

Volunteers' psychophysiological state was determined with UPDK-MK universal psycho-diagnostic complex («Neurocom» LLC, Moscow). We applied an express test for functional state assessment, «Complex motor reaction» test, and «Critical flicker frequency» test, and tapping test. Besides, after all the tests volunteers filled in questionnaires in order to assess exoskeletons' ergonomic properties.

When examining efficiency of «Exochair» IE application, we assessed labor productivity dynamics. As a major task performed by a logistician working in Sberbank archives and logistics center is to find documents kept in boxes that he or she has to move, we took a number of documents found over a certain period of time as a performance indicator. When examining «ExoAtlant» IE efficiency, we modeled work activities in such a way so that loads on one volunteer were the same and constant during the whole working period; therefore, labor productivity was not assessed.

Each IE was examined in two stages. The 1st stage involved work activities modeling without IE (the reference group). At the 2nd stage work activities with IE application were modeled. Tests were accomplished prior to work activities modeling (background testing); during breaks (intermediate testing); after modeling (control testing); the tests were the same at both stages. Examination program for each work activities model is shown in Figures 2.

Test results obtained for different groups were comparatively analyzed both within groups and between them. All the results were statistically processed with Statistica 10.0 and MS Office Excel 2019 software packages.

Results and discussion. Most research procedures applied in this work including functional tests, dynamometry, stabilometry, and psychophysiological testing, yielded such results that in most cases there were no statistically significant differences between parameters registered for volunteers working without IE and with them. It is highly likely

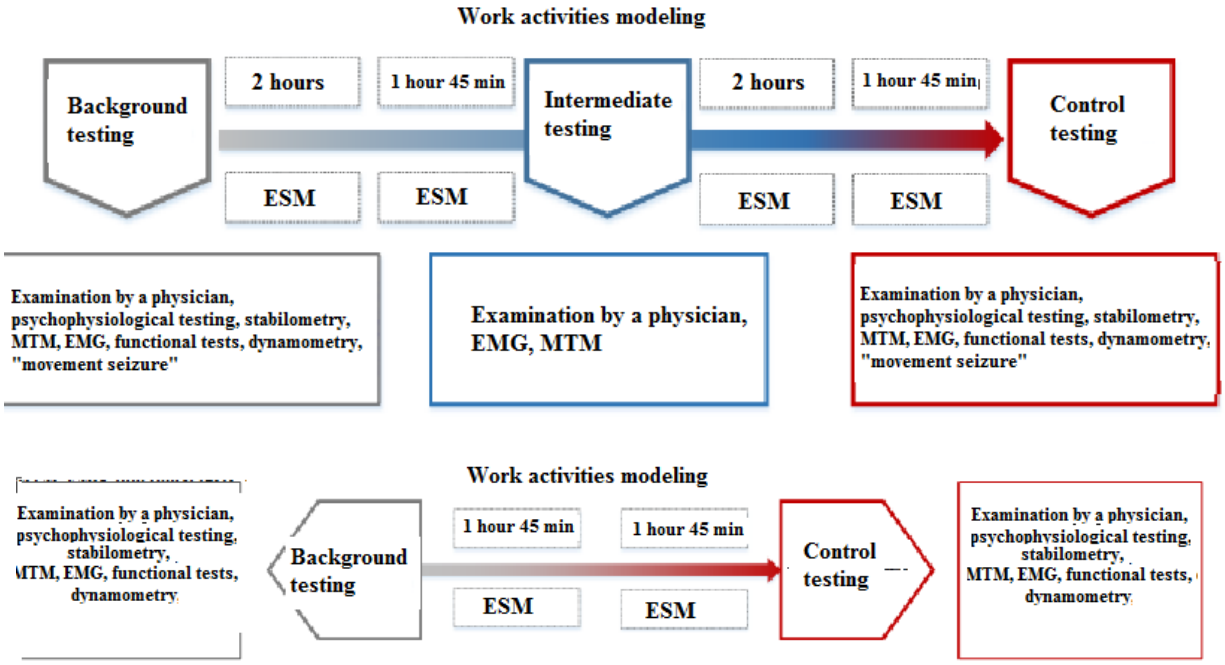

Figure 2. Examination program for a model showing work activities by a logistician working in Sberbank archives and logistics center («Exochair» IE examination) and a cashier working in the precious metals department of Sberbank Main Cash Center («ExoAtlant» IE examination)

that the fact is related to a small sampling, individual peculiarities of volunteers' bodies, and significant influence exerted by the conative component on testing results.

But still, volunteers who applied both examined IE in their work had their heart rate and blood pressure within reference values and being adequate to physical loads (just as in the reference group). Besides, when volunteers estimated movements in their large joints and vertebral column and answered questions during interviewing, their answers and estimations obtained during the whole period of work activities modeling allowed establishing that use of «ExoAtlant» IE didn't result in any pain or impose any limitations on amplitudes of active movements in the lumbar spine that occurred when the same work tasks were performed without IE. The above-mentioned can be considered as facts indicating that use of the examined IE was really safe and physiologically efficient.

We analyzed amplitudes of active movement in the lumbar spine and large joints in the arms and legs using inertial sensors; the analysis revealed a decrease in amplitudes of active movements almost in all the examined joints. Figures 3–5 show amplitudes of active movements in the legs and vertebral column in dynamics in case «Exochair» IE is applied.

As we can see, amplitudes of active movements in the lumbar-thoracic spine of volunteers who worked with «Exochair» IE decreased by 32 % when they bent forward; by 7 %, when they bent to the left; 13 %, to the right; 33 %, when they turned right; 40 %, when they turned left; and 64 % when they squatted.

«Exochair» IE application resulted in a decrease in amplitudes of active movements in the left and right hip joints, by 3 % and 12 % for unbending accordingly; squatting, by 67 % and 64 %; when raising a leg bent at the knee, by 27 % and 28 % accordingly.

We detected that application of this IE led to a decrease in amplitudes of active movements in the left and right knee joints, by 54 % and 56 % accordingly for squatting; by 34 % and 41 % accordingly, for raising a leg bent at the knee; by 47 % and 53 % accordingly for knee joint bending.

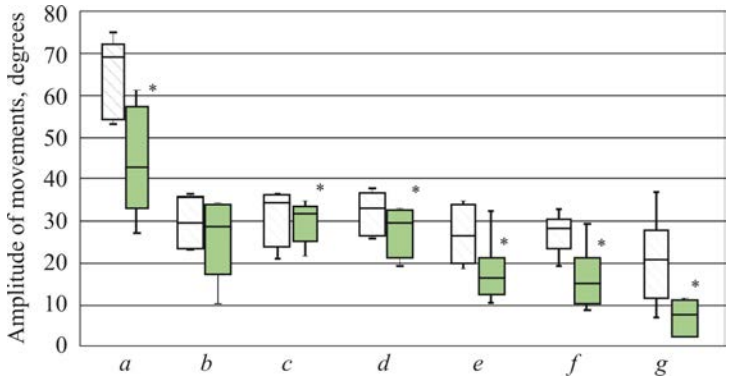

Figure 3. Amplitudes of active movements in the lumbar spine
without «Exochair» IE (□) and with it (■), $n = 6$
Note: a means bending forward; b, backward; c, to the right; d, to the left;
e, turning right; f, turning left; g, squatting;
* means discrepancies in the parameters are statistically significant
in comparison with the reference group ($p \leq 0.05$)

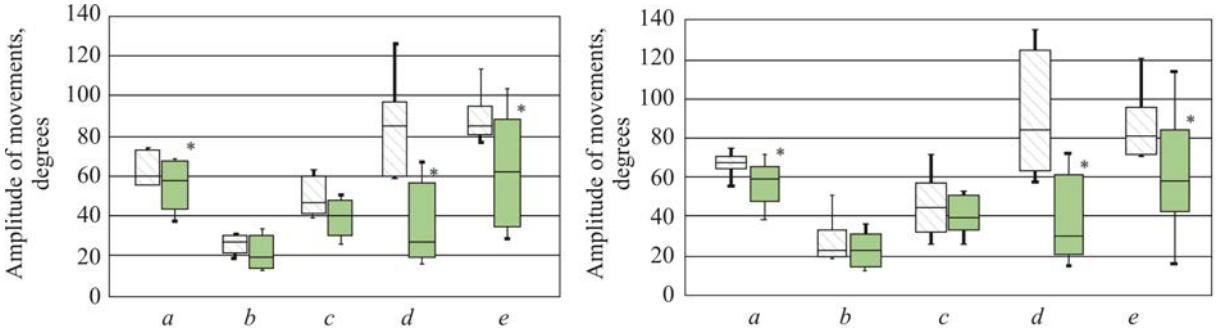

Figure 4. Amplitudes of active movements in the left (left) and right (right)
hip joints without «Exochair» IE (□) and with it (■), $n = 6$
Note: a means bending; b, unbending; c, abduction; d, squatting; e, raising a leg;
* means discrepancies in the parameters are statistically significant in comparison
with the reference group ($p \leq 0.05$)

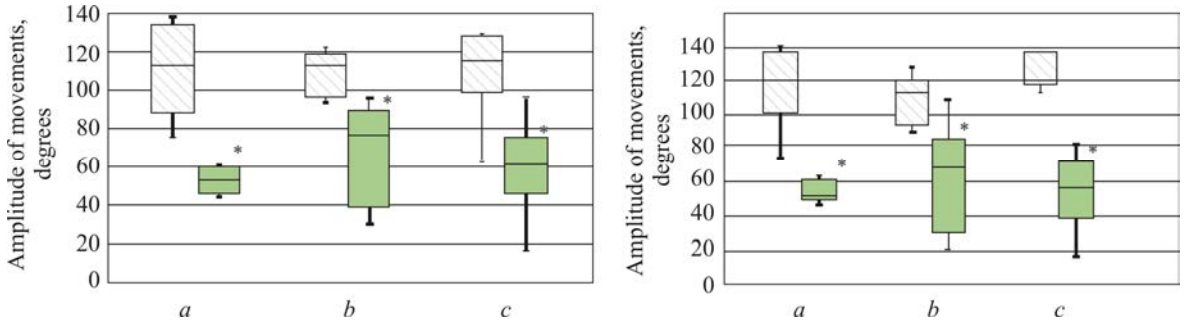

Figure 5. Amplitudes of active movements in the left (left) and right (right)
knee joints without «Exochair» IE (□) and with it (■), $n = 6$
Note: a means squatting; b, raising a leg bent at the knee; c, knee joint bending;
* means discrepancies in the parameters are statistically significant in comparison
with the reference group ($p \leq 0.05$)

Figures 6–8 show data indicating that there are certain limitations imposed on amplitudes of active movements in the lumbar-thoracic spine, hip and knee joints by «ExoAtlant» IE application.

We determined that amplitudes of active movements in the lumbar-thoracic spine went down by 55 % when a volunteer using «ExoAtlant» IE turned right and by 54 % when he turned left.

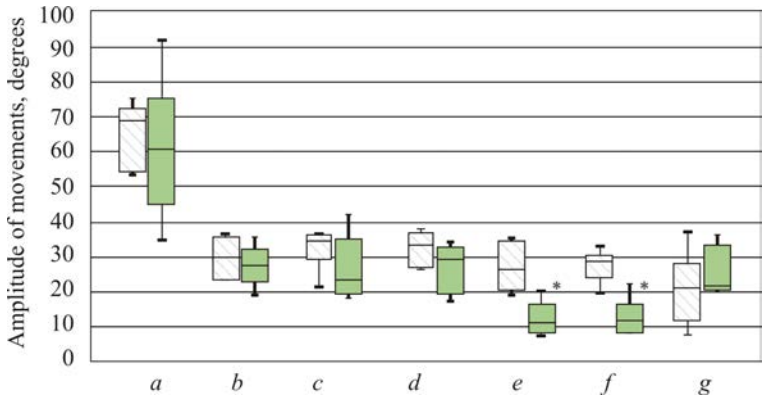

Figure 6. Amplitudes of active movements in the lumbar spine without IE (□) and with it (■), $n = 6$
Note: a means bending forward; b, backward; c, to the right; d, to the left; e, turning right;
f, turning left; g, squatting;
* means discrepancies in the parameters are statistically significant in comparison
with the reference group ($p \leq 0.05$)

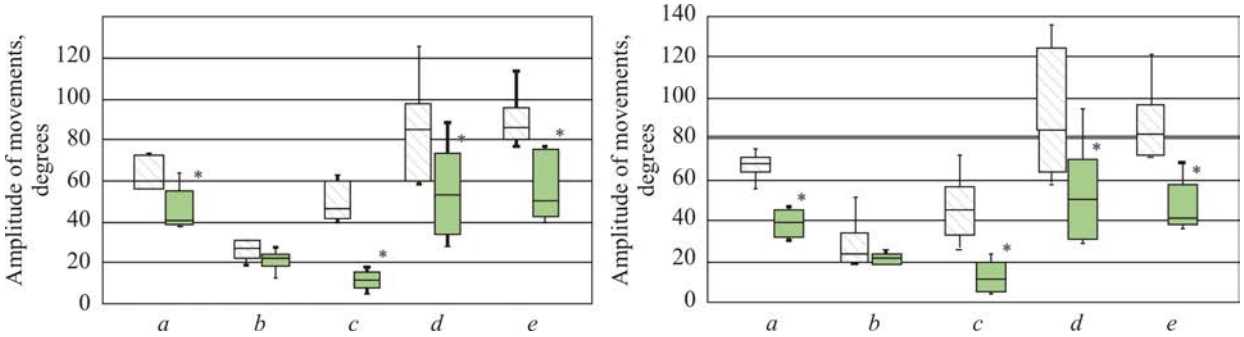

Figure 7. Amplitudes of active movements in the left (left) and right (right) hip joints
without «ExoAtlant» IE (□) and with it (■), $n = 6$
Note: a means bending; b, unbending; c, abduction; d, squatting; e, raising a leg;
* means discrepancies in the parameters are statistically significant in comparison
with the reference group ($p \leq 0.05$)

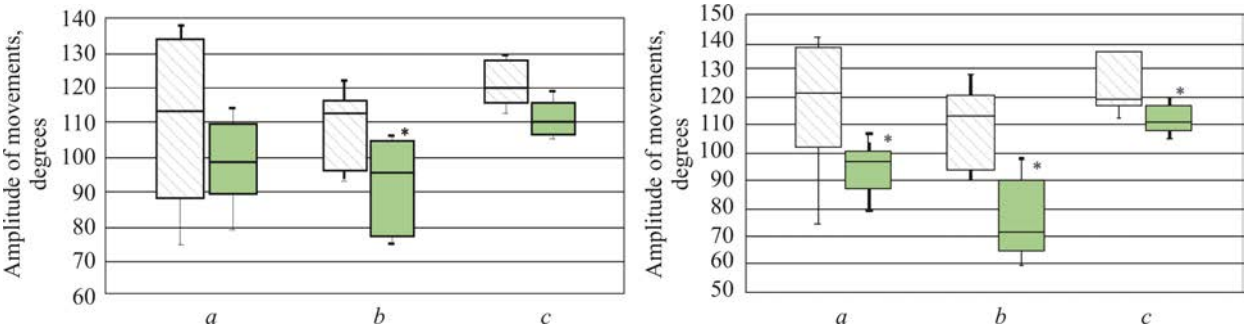

Figure 8. Amplitudes of active movements in the left (left) and right (right) knee joints
without «ExoAtlant» IE (□) and with it (■), $n = 6$
Note: a means squatting; b, raising a leg bent at the knee; c, knee joint bending;
* means discrepancies in the parameters are statistically significant in comparison
with the reference group ($p \leq 0.05$)

Amplitudes of active movements in the left and right hip joints went down due to «ExoAtlant» IE application by 32 % and 41 % accordingly when they were bent; by 74 % and 73 %, when abducted; by 3 % and 39 % when a volunteer squatted; and by 41 % and 49 % accordingly when a volunteer raised a leg bent at the knee.

«ExoAtlant» IE application led to a decrease in amplitudes of active movements: by 20 % in the right knee joint when a volunteer squatted; by 38 %, when he bent the knee; and by 16 % in the left knee joint when a volunteer raised a leg bent at the knee.

The detected limitations on vertebral joints and joints in the legs in volunteers performing their work tasks with IE application allowed us to outline how important it was to be cautious when applying IE at industrial objects, especially when it comes to workers who have to perform work tasks involving a lot of movements with wider amplitudes.

We performed comparative analysis of energy expenditure borne by volunteers with IE and without them; in our opinion, its results are the most important for assessing physiological efficiency of IE application as they revealed a statistically significant decrease in energy expenditure borne by volunteers; it amounted to 5 % and 7 % accordingly for 6 and 8 hours of work activities in a situation when «Exochair» IE was applied (Figure 9 and 10).

We should note that, together with a decrease in energy expenditure borne by volunteers when they performed their work tasks, volunteers' labor productivity had statistically significant growth almost at each hour of work activities modeling (Figure 10). Thus, a number of documents, a volunteer managed to find increased by 13–38 % at 1–7 hours of work.

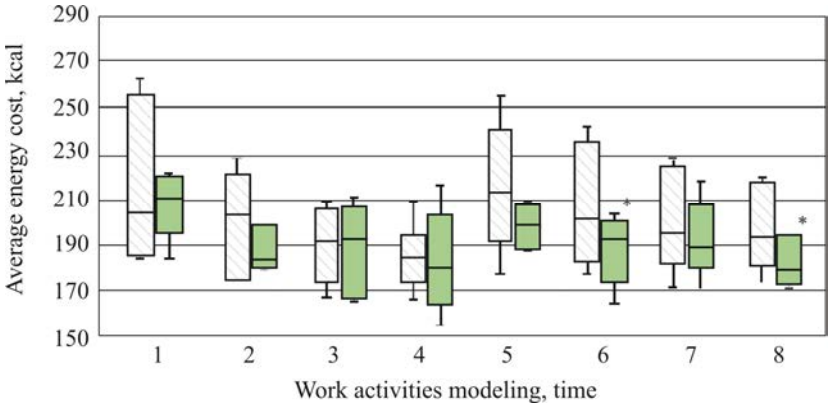

Figure 9. Dynamics of energy expenditure borne by volunteers without «Exochair» IE (□) and with it (■), $n = 6$
Note: * means discrepancies in the parameters are statistically significant in comparison with the reference group ($p \leq 0.05$)

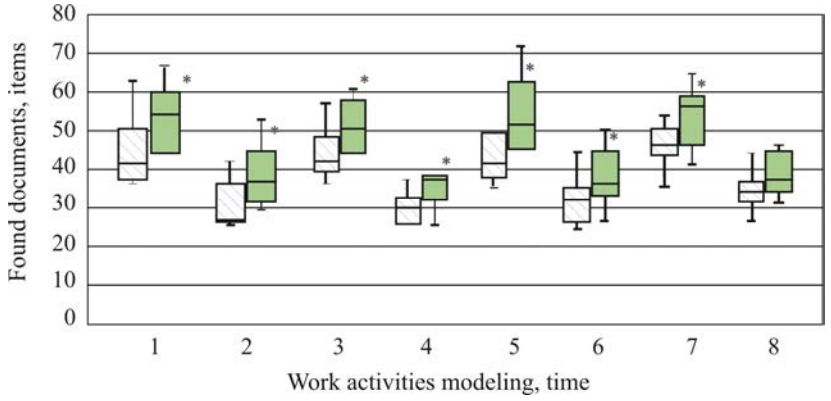

Figure 10. Dynamics of volunteers' labor productivity without «Exochair» IE (□) and with it (■), $n = 6$
Note: * means discrepancies in the parameters are statistically significant in comparison with the reference group ($p \leq 0.05$)

We detected certain changes when assessing fatigue of volunteers' musculoskeletal system. Thus, when examining «ExoAtlant» IE via EMT performed on a volunteer who was standing in a working posture with a load, we revealed a decrease in bioelectrical activity of the erector spine muscle, by 24 % and 36 % on the right and on the left accordingly, during tests with IE against parameters obtained during tests without IE. But at the same time, bioelectrical activity of the left biceps muscle of the arm was by 72 % higher in volunteers who used IE against those from the reference group (Figure 11).

All the above mentioned changes allow us to conclude that there is a decrease in activity of the erector spine muscle as loads on it are reduced due to IE. And an increase in activity of the left biceps of the arm can indicate that loads are possibly redistributed from the spine to the arms.

We also performed MTM on volunteers who were lying at rest on a coach; control tests results revealed a statistically significant decrease in the tone of the lumbar section in the erector spine muscle, by 4 % on the right and 3 % on the left; the semitendinous muscle by 3 % on the right; and the medial vastus thigh muscle on both sides (by 4 % on the right and by 5 % on the left) in volunteers who used «Exochair» IE against the background values (Figure 12). The detected changes can indicate that by the end of the work shift all these muscles were less strained than it was at the beginning of it. As there were no similar changes in the reference group, we can assume that use of «Exochair» IE reduces loads on certain muscles in the spine and thighs that participate in keeping working postures and performing movements required to fulfill work tasks.

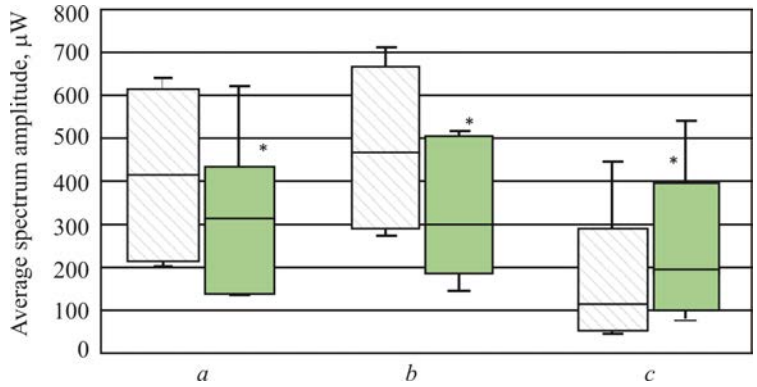

Figure 11. Bioelectrical activity of the electro spine muscle taken in dynamics: on the right (a) and on the left (b), and the left biceps muscle of the arm (c) in volunteers standing in a working posture with a load without «ExoAtlant» IE (□), and with it (■), $n = 6$
Note: * means discrepancies in the parameters are statistically significant in comparison with the reference group ($p \leq 0.05$)

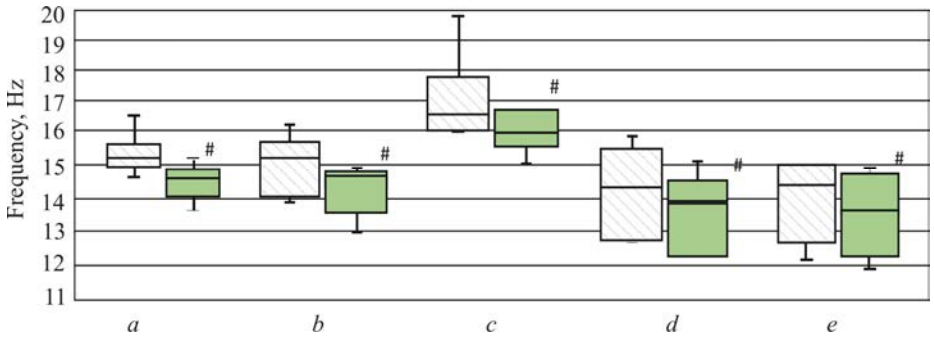

Figure 12. The tone in the illocostal muscle on the right (a) and on the left (b), semitendinous muscle (c), medial vastus thigh muscle on the right (d) and on the left (e) in volunteers who use «Exochair» IE prior to working activities modeling (□) and after it (■), $n = 6$
Note: # means there are statistically significant discrepancies from the background values

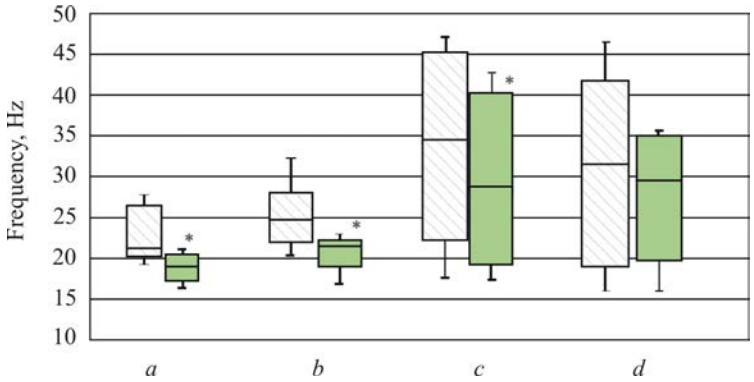

Figure 13. The tone of the longest breast muscle on the right (a) and on the left (b), illocostal muscle on the right (c) and on the left (d) prior to working activities modeling (□) and after it (■) in volunteers who use «ExoAtlant» IE, $n = 6$
Note: # means there are statistically significant discrepancies from the background values

Having performed MTM on the erector spine muscle during its maximum strain, especially when a volunteer was in a working posture and holding 31 kg, we established that the tone of the longest breast muscle on the right and on the left as well as the illocostal muscle in the lumbar spine on the right were by 10 %, 13 % and 17 % lower after work was over than pior to its beginning in volunteers who used «ExoAtlant» IE during work; given that there were no similar changes in the reference group, we can assume that it indirectly indicates there is lower load on these muscles due to IE (Figure 13).

But still, taking into account peculiarities related to myotonometer functioning and caused by difficulties in measuring muscle tones that are either located rather deep or are small in size, absence of unified standards for measured parameters and substantial evidential base, as well as a procedure itself being an experimental one, further investigation is required regarding diagnostics of skeletal muscles fatigue in order to perform physiological and ergonomic assessment of IE using MTM.

Having analyzed questionnaires filled in by volunteers after working with «Exochair» IE, we established that they gave the highest evaluations to the following parameters: IE exterior; overall well-being during work with IE; and IE being quite helpful during work. In volunteers' opinion, there were also some disadvantages such as IE being difficult to put on/off; limited movements in it; a person feeling himself uncomfortable to move in it; IE being too heavy; a volunteer feeling himself uncomfortable when IE was put on.

«ExoAtlant» IE and its ergonomic characteristics got more favorable marks; volunteers mentioned nice exterior, proper size and weight; IE being easy to put on/off; ergonomic design providing comfortable position on a body; IE being easy to handle; overall well-being during work with IE and IE being quite helpful during work; absence of any negative feeling during work in the given IE. However, volunteers gave rather low evaluations to their ability to move in the IE and stated that the IE limited their movements just as it was with «Exochair» IE.

Obviously, all the listed properties of the examined IE can either raise or reduce overall strain during work and they can influence both workers' health and quality of their work. Consequently, further profound examinations and assessment of variable IE properties by workers who are to use them as well as longer periods of IE use during several working shifts will allow eliminating all the revealed drawbacks.

Conclusion. Contemporary approaches to determining a person's functional state including «movement seizure» using inertial sensors, ergospirometry, electromyography, and myotonometry allow performing objective medical and biological assessments whether it is safe and efficient to apply industrial exoskeletons in laboratory conditions.

Results obtained in the present research performed with all the above-mentioned procedures confirmed that it was safe and quite

efficient to apply «Exochair» and «ExoAtlant» industrial exoskeletons at workplaces of a logistician working in Sberbank archives and logistics center and a cashier working in the precious metals department of Sberbank Main Cash Center accordingly. Nevertheless, we concluded that it was advisable to make separate reports on safety and efficiency of these industrial exoskeletons being used at workplaces in field conditions taking into account results of the present research, peculiarities existing at workplaces including harmful, and (or) hazardous factors occurring at them, technological process properties, technological operations peculiarities, equipment being used at different workplaces, etc. First of all, it is due to the fact that use of the examined industrial exoskeletons imposes substantial limitations on amplitudes of certain simplest movements and it can produce negative effects on a worker performing some operations as well as result in substantial inconveniencies in case there is an emergency situation at a workplace.

Several procedures that were used in the present work including functional testing, dynamometry, stabilometry, and psychophysiological testing turned out to be rather unreliable and invalid, and it makes it doubtful that they can be applied in future research.

Procedures that were used in the present work can substantially enrich the existing approaches to examining functional state of workers dealing with physical labor; obtained results can make a substantial contribution into developing a regulatory and technological base for a promising type of personal protective equipment aimed at protecting the musculoskeletal system within the Occupational Safety Standards System.

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Research article

ASSESSING RISKS OF DEVELOPING MYELOPROLIFERATIVE DISEASES COMPLICATIONS WITH LASER DOPPLER FLOWMETRY

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Public healthcare in Russia faces many challenges; meeting them requires non-standard and innovative approaches. The set tasks are being solved within the «Public healthcare development» State program. A sub-program within it is called «Development and implementation of innovative diagnostics, prevention, and treatment procedures as well as basics of personified medicine». This sub-program involves wide use of information and digital technologies. Personified medicine envisages developing such methods that would allow early detection of a probable disease even at a preliminary stage in examining a patient; this detection is to be based on a simple and relatively cheap diagnostic technology and to provide a medical center with reliable data on detected signs of a disease for a further diagnosis. Mass use of such technologies also requires truly reliable mathematic procedures and models for putting a preliminary diagnosis. At present cardiovascular diseases are still the leading cause of death all over the world; they develop due to variable factors including influence exerted by malignant neoplasms and also due to chemotherapy.

The paper contains data collected by contemporary medical experts on case histories and complications of myeloproliferative diseases caused by vascular system pathology that holds the first rank place as per mortality worldwide. It was detected that both pathological cellular mass and medications applied to treat myeloproliferative neoplasms could produce adverse effects on vascular endothelium damage to which plays the leading role in cardiovascular continuum. To assess risks of myeloproliferative diseases complications, we examined patients using Laser Doppler Flowmetry (LDF). The results were processed with a logistic regression model. As per ROC-analysis results the obtained diagnostic criterion has sensitivity ($1 - \beta$) and specificity, ($1 - \alpha$) that are equal to 0.87 and 0.96 accordingly, and it means diagnostics is high-quality. The procedure and the mode can be applied in digital medicine.

Key words: *digital medicine, diagnostics, myeloproliferative diseases, vascular endothelium dysfunctions, Laser Doppler Flowmetry, mathematical model, logistic regression, risk assessment.*

At present the public healthcare system in Russia requires innovative approaches to challenges it has to face. It occurs due to multiple processes such as new diagnostic and treatment techniques being implemented, evolution of infectious agents that cause many diseases, certain socially significant pathologies becoming «younger», issues related to long life span and life quality. Scientific society sees a way out of the existing situation in raising availability of highly specialized innovative medicine via wide-scale practical implementation of new scientific knowledge on what causes a disease, its early diagnostics, treatment techniques as well as due to the very latest information and digital technologies being applied in public healthcare.

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The outlined tasks are being solved in the RF within «The Public healthcare development» State program (hereinafter called The State Program)[1]. A pilot part of the State Program includes «Public healthcare» National project that has been implemented as per 8 sub-programs starting from 2019. There is a subprogram called «Development and implementation of innovative diagnostics, prevention, and treatment procedures as well as basics of personified medicine»; it envisages wide use of innovative procedures for diagnostics and treatment.

A goal set within the State Program is to reduce mortality caused by cardiovascular diseases down to 450 cases per 100 thousand people by 2024. Issues related to preventing and treating various microcirculation disorders are among the most significant ones existing in current medical practices. Difficulties in examining microcirculation occur sue to microvessels being too small and vasculatures inside organs having complicated branching structures. At present in the RF various procedures for examining microcirculation in a human body that involve Laser Doppler Flowmetry (LDF) are being implemented in clinical practices. The procedure has some advantages as it is relatively cheap, suitable for use in digital medicine and mass medical examinations with subsequent data transfer into medical centers via telemetry.

Patients who suffer from oncohematological diseases tend to have complications, primarily cardiovascular events, instead of death and disability due to contemporary achievements in medical practices (timely and qualitative diagnostics, target therapy, and monitoring over a patient's state). Endothelial dysfunction (ED) is a pathology related to progressing damage to vessel endothelium that results in its functional disorders [1]. As a result there is a failure in regulation of systems that are responsible for vessels tonus, homeostasis, adhesive cells properties, and vessels neoproliferation due to imbalance between relaxing and constricting mechanisms and between anti- and pro-coagulant substances production, etc.

Myeloproliferative neoplasms (MPNs) occur due to malignant transformation of pluripotent hemopoietic stem cells in the bone marrow and subsequent clonal proliferation of cells in one or several hemopoiesis branches (erythroid, myeloid, or megakaryocytic one) that are differentiating up to their mature forms [2]. MPNs usually occur in older patients (average age is 55) with their somatic state being significantly burdened with cardiovascular risk factors. Such comorbid states and factors as atherosclerosis, hypertension, metabolic disorders, and unhealthy lifestyle result in much higher risks of cardiovascular disasters among such patients. Research results revealed high frequency of thrombotic complications among people younger than 60 and prevalence of a latent disease at its early stages. Thromboses in arteries prevail regarding localization; they are predominantly acute brain circulation disorders and myocardial infarctions [3]. Mortality due to cerebrovascular diseases is 1.5 times higher among patients with MPNs than among population in general [4].

MPNs include essential thrombocythemia (ET), polycythemia vera (PV), primary myelofibrosis (PMF), and chronic myeloid leukemia (CML).

Polycythemia vera (PV) is an oncohematological myeloproliferative disease that causes a growth in erythrocytes quantity and, consequently, higher blood viscosity which in its turn leads to endothelial dysfunction [5]. Secondary arterial hypertension (AH) occurs in more than half of patients with PV and is also a risk factor that can cause endothelial dysfunction (ED). Arterial hypertension itself is a most significant medical and social issue. AH occupies one of the first rank places as a cause for cardiovascular complications (strokes, myocardial infarctions, etc.) both in Russia and worldwide [6]. According to several research works, patients

[1] The Public healthcare development: the State program of the Russian Federation. The RF Public Healthcare Ministry. Available at: https://www.rosminzdrav.ru/ministry/programms/health/info (20.03.2020) (in Russian).

who suffer from arterial hypertension also have vascular thromboses in 85 % cases and lethal risk is 2–5 times higher among them [7–9].

A problem for patients with chronic myeloid leukemia (CML) is lifelong necessity to take tyrosine kinase inhibitors (TKI) that influence vascular endothelium and it, in its turn, leads to cardiovascular complications [10–12]. Thus, chemotherapy can be a factor that causes endothelial dysfunction.

Microcirculation disorders and vascular endothelium dysfunctions are still a serious problem for patients with oncohematological diseases. Taking absolute (true) polycythemia and chronic myeloid leukemia as an example we can examine a correlation between pathogenesis of a disease itself and endothelial dysfunction (ED) development. Blood hyperviscosity syndrome that develops due to myeloid proliferation in patients with PV leads to an increase in shear stress on vascular endothelium and endothelial cells and basal membrane becomes disorganized. As a result, mechanisms of endotheliocytes apoptosis, adhesion, and blood cells aggregation become active. Disorders in these mechanisms result in endothelial dysfunction. On the contrary, in case of chronic myeloid leukemia the main role belongs to impacts exerted by TKI medications on vascular endothelium; and by-effects occurring notably in the cardiovascular system are explained by non-selective inhibition of multiple tyrosine kinases. Impacts on normal tyrosine kinases responsible for transferring cell signals lead to endothelial cells dysfunctions [13].

Laboratory procedures based on determining concentrations of substances excreted by endotheliocytes are a golden standard for estimating vascular endothelium functions. These substances include endothelin-1, angiotensin-II, von Willebrand factor, nitrogen oxide, NO-synthase, thromboxane, natriuretic peptide, homocysteine, etc. We should also mention some indirect markers showing these damages to vascular endothelium; they are C-reactive protein, fibrinogen, TNF-α, concentrations of high density lipoproteins (HDLP), low density lipoproteins (LDLP), and triglycerides.

Many contemporary authors believe that early diagnostics of endothelial dysfunction has a specific role in selecting a strategy for treating patients with various nosologies aimed at slowing down progression of adverse effects in the cardiovascular system [14]. This aspect is being given a lot of attention in up-to-date scientific research. Experts are looking for and developing new procedures for diagnosing endothelial dysfunction at its earliest stages. LDF, nail bed capillaroscopy and bulbar conjunctiva capillaroscopy are the most frequently mentioned techniques in the latest research works [15, 16].

In order to perform complex assessment of microcirculatory vessels, experts usually apply a combination of several procedures including LDF, optic tissue oxymetry and pulse oxymetry. Use of different tests performed under loads allows estimating not only compensatory abilities but also early changes in hemodynamics and specific aspects in microvessels functioning in case there is some pathology. These approaches can be successfully applied in practical healthcare for dynamic observations over microcirculatory vessels, ED, and assessing efficiency of treatment procedures selected for each specific patient[2].

Our research goal was to determine whether it was possible to apply Laser Doppler Flowmetry (LDF) for early detection and assessing risks of cardiovascular complications in patients with myeloproliferative diseases.

Data and methods. We were the first to examine a possibility to diagnose ED at its early stages basing solely on data obtained via LDF [17]. LDF is based on optical sounding of tissues with laser radiation (wave length is 632.8 nm) and analysis of scattered and reflected radiation from moving erythrocytes. Laser radiation reflection from erythrocytes that move in microvessels results in changes in a signal frequency and it allows determining various microcirculation properties (Figure 1).

[2] Laser Doppler Flowmetry to examine blood microcirculation. Guide for doctors. In: A.I. Krupatkin, V.V. Sidorov eds. Moscow, Meditsina Publ., 2005, 256 p. (in Russian).

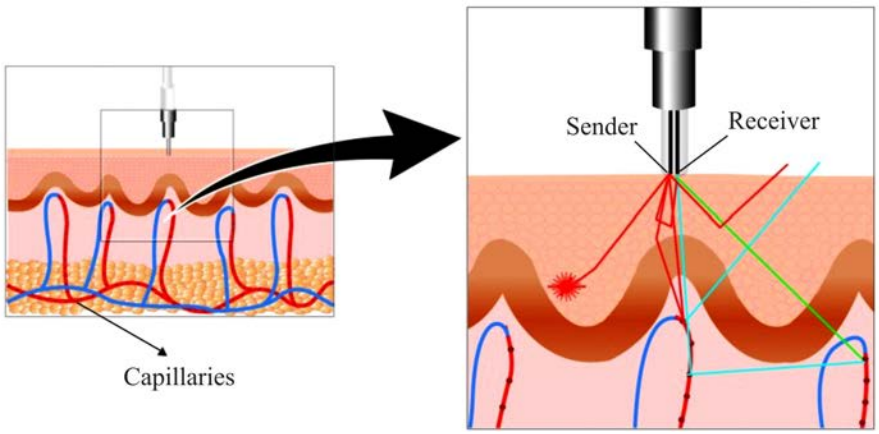

Figure 1. Laser Doppler Flowmetry (LDF) procedure

The procedure has some basic advantages such as simplicity, safety, and cheapness in comparison with expensive invasive ones. Additional motivation to use LDF is a possibility to diagnose ED at its early stage, that is, before any cardiovascular complications have developed. It is possible due to the microcirculatory system being one of the most rapidly reacting to effects produced by pathologic factors [18].

Recently computer technologies and mathematical models have been widely used to put a diagnosis as per results of examinations performed on patients. There is a wide range of mathematical models and computer programs that allow modeling heart and cardiovascular system functioning. For example, there are graph models, difference equations systems, hemodynamics equations, non-linear econometric models, image identification procedures, and artificial intelligence procedures [19–23]. Logistic regression was previously applied in diagnosing ED; however, we haven't been able to find data on its application for predicting complications in patients with myeloproliferative neoplasms in available literature sources[3].

Then we come to examining predictive properties of the regression model that includes 12 parameters (Table 1) measured with LDF procedure performed with Lakk-OP laser microcirculation analyzer.

Overall, 143 patients were examined; 103 out of them had myeloproliferative neoplasms (absolute (true) polycythemia and chronic myeloid leukemia). These nosologies were verified with laboratory-instrumental procedures according to the existing recommendations [24, 25]. In order to determine endothelial dysfunctions, we quantitatively determined endothelin-1 in blood serum and patients with MPNs with endothelin-1 concentration being higher than 1.37 fmol/L were assigned into a group with ED signs.

Our reference group was made up of 40 practically healthy people comparable in terms of age and sex. In order to exclude influence exerted by any concomitant pathology on vessels endothelium, we didn't include patients with chronic heart failure, stages II and III (classified as per Strazhesko-Vasilenko), clinically significant IHD, other symptomatic arterial hypertension, acute cerebral circulation disorders and myocardial infarction during 6 months prior to the research, chronic bronchopulmonary pathology, pancreatic diabetes, inflammatory diseases of the connective tissue, and smoking patients.

Results and discussion. We applied a logistic regression model to estimate probability of ED that could cause cardiovascular complications in the examined patients [26].

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Table 1

Microcirculation parameters

MC parameter	Description	Variable
M	Average perfusion	X_1
Kv	Blood flow variation coefficient	X_2
Am/BFR (blood flow rate)	Standardized amplitude of micro blood flow fluctuations associated with myogenic microvessels regulation	X_3
Sm	Perfusion oxygen saturation index	X_4
RCBF	Reserve capillary blood flow	X_5
An/BFR	Standardized amplitude of micro blood flow fluctuations associated with neurogenic microvessels regulation	X_6
Ae/BFR	Standardized amplitude of micro blood flow fluctuations associated with endothelial microvessels regulation	X_7
I	Index of specific oxygen consumption in tissue	X_8
D2	Correlation dimension	X_9
Ho	Relative entropy	X_{10}
R/S	Hurst parameter	X_{11}
BTI	Breath test index	X_{12}

Our initial sampling was divided into a training one and a test one. 60 % people were randomly selected to be included into the training sampling; overall, there were 86 people in it, 71 out of them with pathology and 15 people being a reference group. The remaining 57 people (32 patients with pathology and 25 being a reference group) were included into the test sampling.

Hereinafter we use the following legend: N is the training sampling volume, $K = 12$ is a number of parameters, vector of parameters that are attributed to a case with the number n

$$\vec{X}_n = \left(X_{1n}, \ldots, X_{Kn}\right), \; n = \overline{1, N}, \qquad (1)$$

ed is an indicator showing there is endothelium dysfunciton (hereinafter pathology) that can be equal to 0 or 1.

We assume that dependence between pathology probability and the vector of parameters can be given with the following equation:

$$P\left\{ed = 1 \mid \vec{X}_n\right\} = f\left(Y_\beta^*\left(\vec{X}_n\right)\right), \qquad (2)$$

where

$$Y_\beta^*\left(\vec{X}_n\right) = \beta_0 + \sum_{k=1}^{K} \beta_k X_{kn} \qquad (3)$$

is a linear combination of microcirculation parameters with beta coefficients,

and

$$f(y) = \frac{1}{1 + e^{-y}} \qquad (4)$$

is a logistic function. A solution to a task of logarithmic likelihood fucntion maximization

$$L(\beta) = \sum_{n=1}^{N} j_n \ln f\left(Y_\beta^*\left(\vec{X}_n\right)\right) + \\ + (1 - j_n)\ln\left(1 - f\left(Y_\beta^*\left(\vec{X}_n\right)\right)\right) \qquad (5)$$

is a vector of regression coefficients

$$\hat{\beta} = \arg\max_{\beta} L(\beta). \qquad (6)$$

ED-index concept was introduced as statistics of classification criterion:

$$ed.index\left(\vec{X}\right) = f\left(\hat{\beta}_0 + \sum_{k=1}^{5} \hat{\beta}_k X_k\right) \qquad (7)$$

Table 2

Significant MC parameters and relevant regression coefficients

MC parameter	Variable	Mean, standard error of the mean (pathology)	Mean, standard error of the mean (reference group)	Regression coefficient	Standard error of coefficient	p-value
M	X_1	$15,73 \pm 0,72$	$18,44 \pm 0,34$	$\hat{\beta}_1 = -0,996$	0.285	0.00065466
Kv	X_2	$6,38 \pm 1,01$	$9,08 \pm 0,73$	$\hat{\beta}_2 = -0,628$	0.153	0.00007332
Am/BFR	X_3	$0,42 \pm 0,02$	$0,51 \pm 0,02$	$\hat{\beta}_3 = -10,014$	3.670	0.00724567
Sm	X_4	$4,29 \pm 0,80$	$5,14 \pm 0,27$	$\hat{\beta}_4 = -1,027$	0.324	0.00190552
RCBF	X_5	$143,81 \pm 7,60$	$129,41 \pm 2,01$	$\hat{\beta}_5 = 0,061$	0.041	0.01402911
				$\hat{\beta}_0 = 25,001$	9.833	0.01218424

At the first stage all the variables were included into analysis; the most significant ones were determined with reverse exclusion. Then, to provide the maximum precise classification, the variables were first excluded in different combinations at the second stage. At the third stage the variables that were excluded at the first stage were included again. Each time a new model was compared with the first one via ROC curve analysis. As a result, the best model included five variables (Table 2).

ROC curves were applied to estimate quality of diagnostics, to select threshold for ED-index, and to make comparisons between different models. The threshold classifier value $c = 0.887$ was obtained basing on a condition of achieving maximum sum of sensitivity and specificity. As per ROC analysis results the obtained diagnostic criterion for the test sampling had sensitivity $(1 - \beta)$ and specificity $(1 - \alpha)$ equal to 0.875 (28 truly positive results out of 32) and 0.96 (24 truly positive results out of 25) accordingly. Square (SUC) under ROC curve (Figure 2) amounted to 0.96 and it was close to the excellent classification quality (significance of the model was the following: p<10E-5).

Therefore, regarding hypothesis testing theory, ED-index was applied as statistics of testing criterion for a zero hypothesis that there was no pathology. A condition for selecting a threshold value was equivalent to selecting Bayesian criterion among criteria with the said statistics that had a value equal to 0.875 at significance level being 0.04.

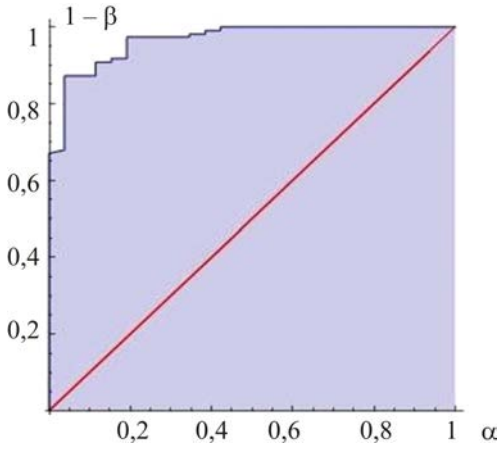

Figure 2. ROC curve

The ultimate probability estimation was determined as piecewise-linear transformation of ED-index in order to reduce a threshold value to an expected one equal to 0.5:

$$P^* = g(\text{ed.index}), \qquad (9)$$

where

$$g(x) = \begin{cases} \dfrac{x}{2c}, & 0 \leqslant x < c \\ \dfrac{x+1-2c}{2(1-c)}, & c \leqslant x \leqslant 1 \end{cases} \qquad (10)$$

Therefore, a certain value $P^* > 0,5$ corresponded to any ED-index value calculated with the model and being higher than the selected threshold value $c = 0,887$.

When considering the most significant parameters in the model separately (with relevant coefficients of significance being lower than 0.005), one should note that a classification

that separately rested on each of the said parameters with the same criterion for selecting a threshold value showed lower results (Table 3) than the model under consideration.

Table 3

Quality of one-dimensional models

MC parameter	Sensitivity	Specificity	SUV
M	0.72	0.68	0.76
Kv	0.875	0.56	0.76
Sm	0.69	0.72	0.69

A software package was developed basing on the obtained research results and a copyright certificate for it was issued.

Conclusion. Procedures for non-invasive differential diagnostics of microcirculatory and main-line vessels pathology based on the latest technologies are given a lot of attention due to multiple reasons. Microcirculatory vessels as a component in the whole circulatory system are rather vulnerable as per their structure and functions to external and/or internal threats. Statistic data collected worldwide clearly indicate that morbidity and mortality caused by cardiovascular pathology hold the first rank place. LDF is an up-to-date non-invasive procedure for assessing microcirculation functioning. The procedure is highly sensitive and manages to grasp subtle changes in microcirculatory blood flow.

The obtained results allow concluding that LDF and the developed regression model have high diagnostic efficiency for early detection and assessment of cardiovascular risks in patients suffering from myeloproliferative diseases.

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

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Review

AIR POLLUTION AS A CONTRIBUTING RISK FACTOR OF RELAPSES AND CASES OF MULTIPLE SCLEROSIS

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The role of air pollution exposure in multiple sclerosis (MS) incidence and relapse worldwide has not yielded a consensus; some studies have reported positive associations, which have failed to reject the null hypothesis. Potential reasons for these contradictory results can in part be explained by differences in study designs and their associated limitations. Of note, rat and canine studies in 2010 and 2013, respectively, have shown that expression of HO-1 enzyme and inflammatory factors increased due to PM_{10} and diesel engine exhaust (DEE) exposure. Of the eight non-null epidemiological studies scrutinized, the majority included a retrospective study design with air pollution monitoring data, which may be an advantage due to large number of study participants and a disadvantage with possible air pollution measurement error for personal exposure. The studies included analyses of PM_{10}, $PM_{2.5}$, SO_2, NO_2, NO_x and/or O_3 with PM_{10} as the common denominator between all of them. Studies from 2003, 2014–2019 from Finland, France, Iran, Italy, and Serbia all provide evidence of an association between PM_{10} and incidence or relapse of MS. Though one 2018 study likewise described associations between exposures to NO_2, O_3, and PM_{10} and MS relapses using a case-crossover design, the multi-pollutant model only associated O_3. Of the epidemiological studies that fail to reject the null hypothesis, there was no evidence of an association between PM_{10} exposure and MS relapse or incidence. Though air pollution has not been conclusively proven to be a cause of MS, evidence from multiple studies have associated incidence and relapse with exposure to pollutants, particularly PM_{10}.

Key words: *air pollution, multiple sclerosis, relapse, particle matter, exposure, pollutants.*

The pathogenesis of multiple sclerosis (MS) is complex and the risk pattern contains both genetic and environmental components, as shown through extensive research over decades [1–3]. Several environmental factors can increase the risk of developing MS, such as Epstein Barr infection (EBV), smoking, low levels of vitamin D/sun exposure, and obesity. Many of these have been investigated in detail by the EnvIMS project (Environmental Risk Factors in MS) [4–9]. In addition, exposure to organic solvents has been investigated as a potential cause of MS [10]. In the EnvIMS studies, interestingly, a negative interaction between the risk of tobacco smoking and EBV infection was identified, indicating that there may be competing pathogenic pathways [5]. Recently, they also found a similar negative interaction regarding exposure to organic solvents versus EBV in-

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fection as well as low vitamin D-level (low outdoor activity). Importantly, there seems to be a synergistic effect between organic solvent exposure and tobacco smoking [10–12]. Subsequently, inhaled chemical agents, like tobacco, obviously can trigger the inflammatory process in MS, and the focus of modern research should now turn to other common inhalations in man. Our interest, in the recent research in this field, has focused on air pollution and risks in MS, and presented as a review.

There have been multiple studies conducted all over the world with regard to the effects of air pollution on MS patients and though no consensus could be reached, there is much to say about the identified patterns. It is first important to note the source of air pollution. Avakian et al. [13] in 2002 noted that combustion processes are major emitters of NOx, SOx and byproducts which include particulate matter (PM) and metals. A 2005 study by Donaldson et al. [14] also noted that in an urban setting diesel engine exhaust emissions (DEE) are a major source of combustion-derived nanoparticles and ambient PM.

Mechanistic studies. Using animal studies in combination with human ones, one can see a pattern emerge. A 2003 study by Calderon-Garciduenas et al. [15] observed that canines exposed to PM had detectable quantities of PM-associated metals like Ni and V in the brain, expression of iNOS and COX2 as well as showed systemic inflammation. Additionally van Berlo et al. [16], like Calderon-Garciduenas et al. [15] noted associations between PM exposure and expression of enzymes like iNOS and COX-2. Van Berlo et al. [16] and Farina et al. [17] both showed through rat and mouse studies, respectively, that expression of Heme Oxygenase 1 (HO-1) enzyme and inflammatory factors increased due to PM_{10} and DEE exposure. In light of this, it is worthy to note that in 2001 Mehindate et al. [18] showed that MS spinal cord astroglia had a HO-1 overexpression, which may promote mitochondrial iron deposition in MS plaques.

With regards to humans, a 2004 study by Rose et al. [19] connected frequent COX-2 expression in association with iNOS in MS patients thereby suggesting the potential contribution to the pathology of MS through the involvement of these enzymes in inflammation. A limitation of this study included patient number.

Studies reporting positive associations. Most prevalent and reported environmental factor associated with MS relapse has been through the exposure to PM_{10}. An Iranian study from 2014 [20] looking at patients living within the area of the city of Tehran, observed significantly ($p < 0.001$) increased levels of PM_{10}, SO_2, NO_2 and NO_x but not NO as compared with controls. There, 2188 patients were geo-referenced and a cluster analysis performed using the average nearest neighbor index. The limitation of this study was that no additional confounder was considered in the analysis. Similarly, a French case-cross over designed study by Jeanjean et al. [21] with 424 MS patients, revealed that for MS relapses, within the scope of significant single-pollution exposures, there were associations due to NO_2, O_3 and PM_{10} levels. In a multi-pollutant model only O_3 remained significantly associated with occurrence of MS relapses. The strength of this study that single-pollutant and multi-pollutant conditional logistic regression models were used, stratified by season («hot» vs. «cold»), and adjusted for meteorological parameters and other factors [21]. A study by Angelici et al. [22] in 2016 that identified 8287 MS-related hospitalizations in the Lombardy region of Italy between 2001 and 2009, showed that hospital admission for MS increased by 42 % on the days preceded by one week with PM_{10} levels in the highest quartile. The limitations of this study were the lack of data on duration and effectiveness of the immunomodulatory therapy and ambient air pollution measurements for personal exposure. Nonetheless, this is in line with the findings of Oikonen et al. [23] (406 patients) and Roux et al. [24] (536 patients) both of which showed a correlation between the levels of PM_{10} and MS relapse. The former study was a retrospective one with data

collected from 1985–1999, while the latter collected from 2000–2009. A 2015 Serbian retrospective study by Vojinovic et al. [25] had results which confirmed the influence of seasonal changes in climate and air pollution on MS relapses. A limitation in this study was lack of blood samples from the MS patients. Bergamaschi et al. [26], using PM_{10} levels in the 5, 10, 15, 20, and 25 days before a brain MRI, also revealed a strong association between elevated PM_{10} levels and the risk of having an inflammatory lesion, independent of immune therapies, smoker status, and season.

Another recent study from 2019 by Tateo et al. [27] that included 1435 patients from the province of Padua, one of the most polluted geographical areas of Italy, revealed that MS prevalence was significantly higher ($p<0.0001$) in urban areas as compared with rural areas and had a strong correlation with the average annual concentrations of $PM_{2.5}$. The study showed that in the period 1998–2015, the annual levels of $PM_{2.5}$ were associated with the number of MS cases in urban areas and that the worst class of air quality was associated with the highest prevalence rate. A 2017 literature review by Mousavi et al. [28] likewise concluded that an association between air pollution and neurodegenerative diseases like MS exists. This was based on the similarity between mechanisms initiated due to MS and PM exposure.

Studies that failed to reject the null hypothesis. Several studies though have come to contradictory conclusions. A study by Palacios et al. [29] in 2017 did not show a significant association between air pollution and MS risk by using 2 large cohorts of US nurses, NHS and NHSII. In the second cohort, an elevation in risk of MS associated with exposure to PM_{10} was found but did not pass the test for trend across quantiles. Limitation wise, the NHS II study had younger participants and therefore showed a greater incidence of MS. Neither cohort showed any significant association between MS and exposure to $PM_{2.5}$. A 2018 study by Bai et al. [30] sought to investigate the association between MS incidence and exposure to $PM_{2.5}$, NO and O_3. 6203 cases were identified between 2001 and 2013 and after various sensitivity analyses as well as annual average temperature, they did not observe any significant associations between incidence and exposure. Some limitations of this study were that the exposure surfaces of $PM_{2.5}$, NO_2, and O_3 were derived at certain periods in time which possibly did not properly represent changes in the long-term in pollutant concentrations. Finally, a 2008 study by Tremlett et al. [31], which included 199 confirmed MS patients, was not able to associate ambient environmental factors such as PM_{10} and O_3 to MS relapses in Tasmania.

Conclusion. Although air pollution has not been directly proven to be a cause of MS, it has been suggested by multiple studies that there are associations between MS and air pollution, particularly PM10. Future in vitro and animal studies should further examine the biological mechanisms of the air pollution-MS relationship. Future human studies should examine the role of sex and epigenetic mechanisms (e.g., DNA methylation) in the air pollution-MS association, as well as study the potential interacting factors such as smoking and vitamin D deficiency. The key to understand the combined role of air pollution emissions is to reconstruct with observational data, hypothetical multi-factorial randomized experiments involving multiple pollutants, as argued by Pashley and Bind [32].

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Review

PRIMARY CNS TUMORS IN ADULTS AND ENVIRONMENTAL FACTORS: AN UPDATE

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The incidence of adult primary brain tumors is increasing in some European countries.

High-dose ionizing irradiation, rare genetic syndromes, and genetic predisposition in 5 % of families are a few established environmental risk factors for brain tumor.

Mobile phone use that causes near brain exposure to radiofrequency electromagnetic waves and thus creates risks of CNS tumors has been the focus of many studies.

Nine meta-analyses were available on this subject. The Interphone multi-center case-control study is the largest one to date; it included 2.708 glioma and 2.409 meningioma cases and matched controls in 13 countries. Studies exploring metals (cadmium, lead), pesticides, outdoor pollution, virus, and risk of glioma created by exposure to them were reviewed.

Interphone study did not show increased risk of glioma or meningioma in mobile-phone users. One recent meta-analysis in 2017 found that prolonged exposure i.e.,> 10 years of all phone types was associated with increased risk of ipsilateral CNS tumor locations. In another meta-analysis, long-term use of mobile-phones was found to be a risk factor for low-grade glioma. In case of all durations regarding mobile phone use and both sides of the head, the results of pooling data were more discordant. A large prospective study in 2014 showed that long term use vs never use increased risks of acoustic neurinoma (10+ years: RR = 2.46, 95 % CI = 1.07–5.64, P = 0.03), but not of glioma or meningioma. Studies of other risk factors showed no/weak/contradictory association with brain tumor risk.

In the absence of robust and consistent evidence, a causal relation between radiofrequency exposure and CNS tumors was not found. Large prospective studies of this kind regarding a disease with low incidence require a high number of participants and a long follow-up period.

Key words: *brain tumor, glioma, meningioma, environmental risk factors.*

Gliomas account for more than 70 % of all adult primary brain tumors. According to the 2016 World Health Organization (WHO) classification of CNS tumors, diffuse gliomas include the WHO grade II and grade III astrocytic tumors, grade II and grade III oligodendrogliomas, and the grade IV glioblastomas [1]. Malignancy ranges from grade I–IV, with grade IV glioblastoma being the most malignant form of gliomas. The prognosis remains dismal for patients with glioblastoma, despite advances in surgery, radiotherapy, and chemotherapy with a median survival time of 9–15 months. Anaplastic grade III WHO gliomas have a median survival time of 1.6 years, and low-grade WHO grade II gliomas that have a more indolent course and grow slowly have a median survival time of 5–10 years [2].

Meningiomas that account for approximately 20 % of all primary brain tumors are the second most common tumors with incidence rates of 3–4 cases per 100,000 males per year and 9–13 cases per 100,000 females per year [3]. Most meningiomas grow slowly, are asymptomatic, and are discovered by accident. According to the 2016 WHO classification of brain tumors, they are regarded as grade I, meaning benign tumors [1]. The presence of brain invasion, necrosis, high cellularity, and prominent nuclei are among the histological features that classify a diagnosis of WHO grade II, atypical meningioma [1].

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Meningiomas larger than 2.5–3 cm usually cause symptoms. Unpredictable and different clinical behavior of meningiomas causes difficulties in assessing mortality and morbidity rates. Estimates of 5-year survival usually range from 73 % to 94 % [4].

The annual incidence of glioma has remained relatively stable since 1983, despite the high prevalence of mobile phone use [5]. However, an increasing trend in the incidence of gliomas has been observed in some European countries. The annual incidence of glioblastoma more than doubled in England between 1995–2015 [6].

Epidemiological studies are of great importance in identifying risks that contribute to the development of CNS neoplasms.

Apart from the well-known risk caused by high-dose ionizing irradiation and classified as a group 1 carcinogen, the genetic predisposition in about 5 % of families, and rare genetic syndromes, there are few established environmental risk factors for glioma [7]. When treating 10,834 Israeli patients with cranial and cervical irradiation with a mean dose of 1–6 Gy for tinea capitis the relative risk for developing a tumor or a glioma after a latency of >30 years increased by 6.9 and 2.6 respectively. This was the first conclusive evidence of an association between ionizing radiation and brain tumors [8]. A 6.5-fold increase in meningioma risk was reported among residents of Hiroshima following the nuclear attack of 1945 [9].

More evidence for Ionizing radiation as an established carcinogen is based on follow-up studies performed on patients who underwent radiotherapy for cancer treatment during childhood, where odds ratios (OR's) equal to 6.78 and 9.94 were reported for glioma and meningioma respectively [10]. Regarding diagnostic head CT scans during childhood, recent follow-up studies of children and adolescents reported an excess RR for brain tumor as large as 23 per Gy [11]. However, to date, no association between CT scans of the head and cancer risk in adults has been established.

Nonionizing radiation in terms of near brain exposure to radiofrequency electromagnetic waves on mobile phones and risks of CNS tumors has been the focus of many studies. By the end of 2018, 67 % of the global population was subscribed to mobile services.

The INTERPHONE study, which was coordinated by the International Agency for Research on Cancer (IARC), was the largest multinational study investigating a possible association between carcinogenic risks of tumors in the head and neck regions and radiofrequency fields emitted by mobile phones [12]. This multi-center case-control study included 2,708 glioma and 2,409 meningioma cases as well as matched controls in 13 countries. The results did not show increased risk of glioma or meningioma in the whole population of mobile-phone users [13].

To date, nine meta-analyses have been published on this subject, mostly based on studies from the INTERPHONE group. The main brain cancer typesincluded in the study were glioma, meningioma, and acoustic neurinoma.

Two recent meta-analyses in 2017 found that prolonged exposure i.e.,> 10 years toall phone types was associated with increased risks of ipsilateral CNS tumor locations, and the long-term use of mobile-phones was found to be a risk factor for low-grade glioma [14–16]. Low-grade gliomas are known to grow slowly and have a long latency period, usually affecting younger patients. Indeed, considering the natural history of low-grade glioma, it is important to keep in mind that this type of tumor may possess different carcinogenic mechanisms as well as different risk factors compared to glioblastoma.

In case of all durations regarding use and both sides of the head, the results of pooling data were more discordant. A large prospective study showed that long term mobile

phone use limited to 10 years vs those who never used a mobile resulted in increased risks of acoustic neurinoma (10+ years: RR = 2.46, 95 % CI = 1.07–5.64, P = 0.03), but not of glioma or meningioma.

In the absence of robust and consistent evidence, a causal relation between radiofrequency exposure and CNS tumors was not found. The only evidence is for an association among long-term users with acoustic neurinoma. Large prospective studies of this kind on a disease with low incidence require a high number of participants and a long follow-up period. Another limitation is how to quantify the level of exposure, depending on a phone type and generation, in addition patterns of mobile phone use change over time. These factors partially explain the limited quality of studies included in meta-analyses. As a result of conflicting scientific evidence, the IARC classified radiofrequency electromagnetic waves in the group 2B, which means possible carcinogens.

N-nitroso compounds (NOCs) are known to be potent carcinogens in animal models. Nitrosamines can form endogenously from foods, and are present in cured meat, tobacco, cosmetics, automobile interiors and drugs such as diuretics, antihistamines, antibiotics, tranquilizers, and narcotics. The observations from animal studies suggested a hypothesis of NOCs as a possible risk factor of brain tumor. The most recent studies are from a decade ago; three prospective studies evaluating consumption of red processed and cured meats did not reveal increased risks of glioma [17–19]. One case-control study investigating transplacental exposure to ethylnitrosurea through maternal diet during pregnancy and risk of brain tumors in childhood showed OR equal to 1.8 for astrocytomas [20]. Studies of this kind do not allow definitive conclusions due to recall and selection bias.

Regarding metals, cadmium as a type 1 carcinogen has been associated with a variety of cancers. However, any evidence for an association with brain tumor risk is weak, and based on only one study [21]. Case-control studies focusing on exposure to lead in the highest quantities revealed slightly increased risks of brain tumor [22].

A possibility of an association between exposure to pesticides and the higher risk of CNS cancers in farmers has been explored in several case-control studies with contradictory results [23]. A cohort study of nearly 200,000 French farmers showed higher risk of CNS tumors in farmers exposed to pesticides, where the greatest increases in risks of meningioma were detected for pig farmers and those growing sunflowers, beets and potatoes. For farmers growing grasslands there were increased risks of gliomas [24].

Outdoor air pollution was classified as a carcinogenic factor by IARC in 2013. Outdoor air pollution has been associated with increased risk of ischemic stroke, Parkinson disease, and has shown a strong causal association with lung cancer. Fine microparticles from pollution such as Particulate matter (PM) and O_3 have been recognized as the most important risk factors to public health [25].

However, the data on brain tumors do not provide evidence for an association with outdoor air pollution, mainly due to small numbers of such studies and conflicting results. Interestingly, a study found a negative association between exposure to air pollution and CNS cancer mortality [26]. The protective effect was suggested to be induced by immune hyperactivity that was characteristic for allergy and asthma. An inverse association between self-reported allergies and gliomas has been confirmed in previous studies [27, 28].

Regarding associations between viruses and risks of glioma, previous studies identified polyomavirus, including JC virus, BK virus, and Simian virus – 40 in human glioma but an association was not confirmed [29]. Human cytomegalovirus (HCMV) being carried by the majority of people world-

wide is the major infectious cause of developmental disorders in the CNS [30].

The presence of CMV genomic expression and protein material in human glioma samples has been well documented [31, 32]. Trials with anti-viral therapy have failed to improve survival in these patients. However, immunotherapy has been used to target CMV antigens in patients with glioblastoma with promising initial results.

In conclusion, identifying the potential risk factors for brain tumors is extremely important due to devastating consequences of the disease. The low incidence of brain tumors, the natural history of slowly growing patterns, difficulties in quantifying exposure to environmental factors, and recall bias remain the main challenges in designing prospective studies.

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Review

VACCINATION AGAINST SWINE FLU CAUSED NARCOLEPSY IN SEVERAL EUROPEAN COUNTRIES

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*Narcolepsy is a rare sleeping disorder that gives sleep onset rapid eye movement periods and excessive daytime sleepiness. It is divided into two subgroups, narcolepsy type 1 where there also is orexin deficiency and cataplexy and narcolepsy type 2 that lack these features. Narcolepsy type 1 is assumed to be an autoimmune disease with destruction of orexin-producing cells. The pathology behind is unclear. There is a strong association to a class II HLA allele, HLADQB1*06:02 and the H1N1-virus and streptococcal infections has also been associated with narcolepsy. The severity of narcolepsy differs between patients from those who can manage their disease without medication to those who has a severe impact on their everyday life. There is a diagnostic delay between the onset of symptoms and time for diagnosis that in some cases can be more than a decade. The global mean prevalence is 30 per 100 000 inhabitants. The incidence in children in northern Europe has risen since 2010. An early study of the 2009 H1N1 influenza A pandemic indicated a high mortality and prompted efforts to rapidly come up with a vaccine. One of these was Pandemrix that was the most widely used in Europe and 61 % of the inhabitants in Sweden was vaccinated. Studies have shown an increased incidence of narcolepsy type 1 in European countries that had used Pandemrix, but no increased risk was seen in countries that had used other vaccines than Pandemrix.*

Key words: *narcolepsy, H1N1-virus, Pandemrix, incidence, prevalence, diagnostic delay.*

Narcolepsy is a rare sleeping disorder giving excessive daytime sleepiness and falling asleep unwillingly during daytime, sleep onset rapid eye movement (REM) periods and might have automatic behaviour, hallucinations when waking up and falling asleep, sleep paralysis, periodic leg movements, psychiatric symptoms and increased weight [1–3]. In narcolepsy type 1 there is also cataplexy (emotions triggering loss of muscle tone) and orexin-deficiency, detectable in cerebrospinal fluid. Cataplexy and orexin-deficiency is not seen in narcolepsy type 2 [4]. In narcolepsy type 1 disrupted sleep with repeated awakenings during night is common [1].

Studies have shown that getting narcolepsy affects life in many domains; for children it affects their education, about half of the children get behavioural problems, the unemployment rates in adults are high and those who work have a lower income [1]. Many patients with narcolepsy complain about working memory problems, but studies have been contradictory and there is little objective evidence for a memory deficit. One study in adolescents found no memory deficits in patients compared

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to controls but suggested that the patients might have a dysregulation in sustained attention [5].

The incidence is 1 per 100.00 inhabitants per year but has risen in children in Northern Europe since 2010 [1, 4]. The global mean prevalence is 30 per 100.000 inhabitants, with the highest prevalence in Japan ($160/10^5$) and the lowest in Israel ($0.23/10^5$) which partly could be explained by genetics but also by the fact that the prevalence is calculated in different age span. Onset of narcolepsy is most common between 10 to 30 years, onset after 40 years of age is rare and before 2010 onset before the age of 10 was seldom reported [1].

There is a delay between onset of symptoms and diagnosis in narcolepsy that can be substantial, but there seems to be a trend towards a shorter delay [5–6]. Different studies report an average diagnostic delay between 8,4 to 16 years [7–13]. A literature review by Lindberger which included previous mentioned studies among others found that most studies show a diagnostic delay over one decade [14].

Diagnostic criteria according to ICSD-3 [1].

Narcolepsy type 1.

Criteria A and B must be fulfilled.

A. The patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least three months.

B. The presence of one or both of the following:

1. Cataplexy and a mean sleep latency of ≤8 minutes and two or more sleep onset REM periods (SOREMPs) on a multiple sleep latency test (MSLT) performed according to standard techniques. A SOREMP within 15 minutes of sleep onset on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.

2. CSF hypocretin-1 concentration, measured by immunoreactivity, is either ≤110 pg/mL or <1/3 of mean values obtained in normal subjects with the same standardized assay.

Narcolepsy type 2.

Criteria A-E must be fulfilled.

A. Daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for at least 3 months.

B. A mean sleep latency of ≤8 minutes and two or more sleep onset REM periods (SOREMPs) are found on a MSLT performed according to standard techniques. A SOREMP within 15 minutes of sleep onset on the preceding nocturnal polysomnogram may replace one of the SOREMPs on the MSLT.

C. No cataplexy.

D. CSF hypocretin-1 concentration has not been measured or CSF hypocretin-1 concentration measured by immunoreactivity is either >110 pg/mL or >1/3 of mean values obtained in normal subjects with the same standardized assay.

E. The hypersomnolence and/or MSLT findings are not better explained by other causes such as insufficient sleep, obstructive sleep apnea, delayed sleep phase disorder, or the effect of medication or substances or their withdrawal.

Treatment in Sweden.

In an expert meeting summoned by Swedish medical products agency in Sweden in February 2013 directions for the symptomatic treatment of narcolepsy was drawn. It is important that the patient has regular sleeping habits, avoid sleep deprivation, plans regular naps during the day and avoid meals rich in easily digestible carbohydrates. Support and advice from a treatment team with good knowledge of narcolepsy and treatment of comorbidity was also stressed as important [15].

Medical treatment of hypersomnia for adults consists of modafinil, methylphenidate or amphetamine. Methylphenidate can be combined with modafinil. Cataplexy in adults can be treated with natriumoxybate or antidepressants. Natriumoxybate can also reduce the frequency of nocturnal awakenings and reduce subjective daytime sleepiness. Antidepressants might have an effect on hallucinations and sleep paralysis associated to falling asleep and awakening [15]. Pitolisant belongs to a new class of drugs and has been showed to have an effect on cataplexy, daytime sleepiness, hallucinations and sleep paralysis in some patients [16, 17].

Hypersomnia in children and adolescents can be treated with modafinil or methylpheni-

date. Antidepressants (mainly SSRI or SNRI) is used to treat cataplexy. Sleep disturbance is often treated with melatonin and sometimes with natriumoxybate [15].

It is assumed that narcolepsy type 1 is an autoimmune disease that results in orexin-deficiency by destructions of neurons in the lateral hypothalamus that produce orexin but the pathology behind this is unknown. Cell-mediated autoimmunity, autoantibodies or cytotoxicity has been proposed as possible mechanisms. Infection with the H1N1 virus and streptococcal infections has been associated with onset of narcolepsy [1, 4]. Another support for the autoimmune hypothesis is the presence of the class II HLA-allele HLADQB1·06:02 in 98 % of patients with narcolepsy type 1. HLADQB1·06:02 is common in Western countries were 20–30 % of the population has this allele, but still it has been estimated that it increases the risk of narcolepsy with about 250 times compared with non-carriers. Other genes have also been associated with narcolepsy and most of them are involved in the regulation of the immune system [4, 18].

Pandemrix and the risk of narcolepsy. An early observational study of the H1N1 influenza A pandemic in 2009 indicated that infection with the virus had a high mortality, especially in young people and pregnant women. This led to efforts to rapidly come up with an effective vaccine against the H1N1-type influenza A virus [4].

Pandemrix was the most widely used vaccine in Europe [4]. It was approved in line with European regulations for accelerated assessment. In Sweden about 61 % of the inhabitants were vaccinated with Pandemrix between October 2009 and March 2010 but the vaccination coverage was higher in some groups, for instance in children, health workers and vulnerable patient groups [19]. In total there were eight different vaccines used in Europe [4]. Three of the them, including Pandemrix, had adjuvants which increase the effect of vaccines. Two vaccines had the adjuvant MF59 and Pandemrix had the adjuvant AS03 which was also used in Arepranrix, a vaccine used in Canada [20]. Two differences between Pandemrix and Arenpanrix was the amount of antigen that was higher in Pandemrix and differences in protein modifications and protein compositions between the two vaccines [4].

An increased incidence of narcolepsy type 1 was seen after Pandemrix-vaccination campaign in several European countries [1, 4]. In Sweden the first signals about an increased risk of narcolepsy in children vaccinated with Pandemrix came in June 2010 [19] and in Finland there was similar observations during the summer of 2010 [1]. An increased risk of narcolepsy after Pandemrix vaccination was seen in mainly children and young adults during a follow up period to 2011 with about a three to fourfold increased risk in people under 21 years of age at vaccination and an increased but lower risk for individuals of age 21–30 [19]. On the contrary no increased incidence of narcolepsy was seen in Saudi Arabia after vaccination with Pandemrix in November 2009, but the vaccination coverage is unknown [21].

In a cohort study Persson et al investigated if there were an increased risk of a number of autoimmune and neurologic diseases after vaccination with Pandemrix, for instance multiple sclerosis, polyneuropathy, epilepsy, rheumatoid arthritis, thyroid disease, myasthenia gravis and Addison's disease. The study showed an increased risk of narcolepsy after vaccination with Pandemrix but not for any other neurologic or autoimmune disease [22].

A meta-analysis and systematic review showed an increased incidence of narcolepsy in Finland, France, Ireland, Norway, the Netherlands, Norway, Sweden and United Kingdom where Pandemrix was used but no increased risk in countries that had used other vaccines including Arepanrix. For children and adolescents, the incidence was 5–14 times higher and for adults 3–7 times higher [20]. In China there was an increased incidence of narcolepsy after the 2009 H1N1-pandemic without vaccination [1, 4], but this has not been shown in other countries [4]. However, Trog-

stad et al report a synergistic effect of infection with the H1N1-influenza virus and vaccination with Pandemrix on the risk of developing narcolepsy in Norwegians [23]. It is possible that a genetic susceptibility in combination with several environmental triggers, where Pandemrix acts as one of them, contributes to the onset of narcolepsy [1].

It has been suggested that individuals who has autoimmunity themselves or in their families might be at risk of getting auto-immune reactions after vaccination as well as people with genetic susceptibility and Sarkanen et al. suggest that, for instance, streptococcal infection could reduce self-tolerance temporarily in addition to vaccination [4].

The severity of post Pandemrix narcolepsy spans from individuals who don´t need medication to manage their disease to very handicapped individuals and some people also get serious psychiatric symptoms [4]. Studies that has compared Pandemrix vaccinated and unvaccinated patients, mainly children, with narcolepsy type 1 has found a more rapid onset in vaccinated patients, that facial hypotonia and tongue protrusion was more common as a sign of cataplexy in vaccinated children [4] and that it was more common to have cataplexy as one of the initial symptoms in the vaccinated group as well as more than two initial symptoms [19]. A more disturbed nocturnal sleep was seen in Finnish children with post Pandemrix narcolepsy type 1 compared to unvaccinated Italian children with narcolepsy type 1 [3]. One study found that patients with post Pandemrix narcolepsy typ1 had more frequent cataplexy and that 10 % of patients with onset of narcolepsy before Pandemrix vaccination had worsening of cataplexy after vaccination with Pandemrix [3]. The clinical course of narcolepsy type 1 is wide and overall the clinical course seems to be similar between vaccinated and unvaccinated patients [3].

In countries where Pandemrix was used narcolepsy is considered an adverse event of the vaccination and patients who has developed narcolepsy after Pandemrix vaccination are compensated, but rules for compensation varies among the countries [3]. The time window for an increased risk of narcolepsy after Pandemrix vaccination has been estimated to two years after vaccination in studies in Sweden and Finland, but it is still unclear [4].

At our neurology clinic in Uppsala we frequently encountered narcolepsy patients who had diagnostic delays. For example, we found seven patients with Pandemrix related narcolepsy with diagnostic delays of nearly a decade. Previous misdiagnoses had been anaemia, asthma, psychosocial problems, depression and unspecified tiredness.

Conclusion. Pandemrix has been showed to increase the risk of narcolepsy in several studies with an estimated time window of two years. Narcolepsy can have a huge impact on everyday life and onset is primarily in young people. There is also a diagnostic delay which means that some individuals might be without necessary treatment for years before diagnosis. Since onset of narcolepsy can have a huge impact on a young individual's life and also give rise to comorbidity it is important to get a proper diagnosis as soon as possible. The notion that a vaccination might be a trigger for an autoimmune disease rises the importance of identifying possible risk factors in individuals to be considered in future vaccination campaigns.

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