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SANITARY-EPIDEMIOLOGICAL SURVEILLANCE: A NEW STAGE IN DEVELOPMENT STIMULATED BY DIGITALIZATION AND CHANGES IN LEGISLATION

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The paper dwells on methodical approaches that provide implementation of provisions fixed by the Federal Law No. 248 «On state control (surveillance) and municipal control on the Russian Federation» that comes into force on July 01, 2021. The Law has strengthened the significance of a risk-oriented model for control and stressed the necessity to assess surveillance efficiency as per criteria related to minimizing risks for protected values and to enhance digitalization and electronic communication between all the concerned parties in the sphere.

Taking into account more specific list of objects that are subject to control fixed in the Law, we suggest a procedure for determining categories of health risks caused by specific industrial objects combined with determining a risk category for an economic activity performed by an economic entity. Risk is assessed as a combination of a probability that obligatory requirements are violated and severity of outcomes that result from such violations. The procedure allows optimal planning of control and surveillance activities regarding enterprises and organizations that perform their activities on multiple industrial sites (network companies, large holdings, etc.). We also considered an approach to creating dynamic risk-oriented checklists and suggested specific ranking for sanitary-epidemiologic requirements that were included into such checklists basing on frequency and history of violations that were committed by an object under surveillance regarding legislative requirements and risks that damage to health might occur due to such violations. The paper contains a description of methodical approaches to creating a statistic risk profile for an object under control. Creating a risk profile with mathematical procedures for data processing (including neural network modeling) allows achieving more qualitative risk detection, drawing up a maximum targeted program for a control activity, and operative reacting to types of violations that have not occurred previously.

The paper describes a principle way for introducing forms and procedures for distance control into the sanitary-epidemiologic surveillance system. It is shown that efficient distance control should be based on digitalized documents required during control and surveillance activities; maximum possible use of data taken from state, municipal, and other data sources; intensified practices of remote hardware control; as well as development and scientific and methodical support provided for an intellectual information system within control and surveillance activities.

***Key words:** sanitary-epidemiologic surveillance, risk-oriented model, distance control, risk profile, information system.*

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In 2009 the Federal Law No. 294-FZ "On protecting rights of juridical persons and private entrepreneurs when accomplishing state control (surveillance) and municipal control" came into force; at that time it brought about significant changes in the legal regulation in the sphere of state and municipal control[1]. For more than 10 years this law was a central document in the state regulation and determined public interactions between control and surveillance authorities and economic entities. There were numerous alterations made into the law that reflected actual needs of the society and business[1]: a concept of risk-oriented control (surveillance) was fixed; risk indicators of obligatory requirements being violated were listed; there was also an alteration on organizing and accomplishing control activities without any interactions with juridical persons / private entrepreneurs, etc.

But still, economic and social processes in the country called for further development in the legal sphere of control and surveillance activities (CSA). Annually 4 or 5 new types of state control activities were introduced, new forms of control were implemented, new instruments for control were applied, etc. But the basic principle remained valid and it stated that "lowering administrative barriers for business should not occur at the expense of neglecting safety issues" [1, 2].

All the above mentioned resulted in issuing the Federal Law No. 248 "On state control (surveillance) and municipal control in the Russian Federation"[2] with its provisions being aimed at creating a new system for regulation over control and surveillance activities which can fully satisfy all the present demands.

This new model for state control (surveillance) involves the following:

– strengthening the role played by the risk oriented-approach and its further development;

– putting greater emphasis in control and surveillance on stimulating economic entities to be conscientious and law-abiding in their activities and preventing risks that damage would be done to values protected by the law;

– assessing efficiency and productivity of control and surveillance activities as per achieved risk minimization regarding damage prevention; it is not allowed to assess efficiency of activities as per direct results such as a number of accomplished control inspections, detected violations, and a number of economic entities / people made accountable for these violations;

– reducing intensity of control and surveillance activities due to developing a system of prevention activities, wider implementation of independent assessments (audit, self-assessment, risk insurance, certification procedures, etc.) etc.

It should also be mentioned that this new law stipulates the necessity to rely on electronic interactions between a control and surveillance authority and an object under surveillance.

Partially, the law has fixed the trends and approaches that have already become an integral part of control and surveillance practices performed by several federal executive authorities including the Federal Service for Surveillance over Consumer Rights Protection and Human Well-being. Thus, since 2015 Rospotrebnadzor has been basing all its sanitary-hygienic control and surveillance activities on the risk-oriented model[3]. CSA productivity and efficiency is assessed basing on population

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[1] On protecting rights of juridical persons and private entrepreneurs when accomplishing state control 9surveillance) and municipal control (with alterations and supplements): The Federal Law issued on December 26, 2008 No. 294-FZ. *Garant. Informational and legal support*. Available at: https://base.garant.ru/12164247/ (May 20, 2021).

[2] On state control (surveillance) and municipal control in the Russian Federation: The Federal Law issued on July 31, 2020 No. 248-FZ. *Garant. Informational and legal support*. Available at: https://www.garant.ru/products/ipo/prime/doc/74349814/ (May 20, 2021).

[3] MR 5.1.0116-17. Risk-oriented model for control and surveillance activities in the sphere of providing sanitaryepidemiologic well-being. Ranking economic entities, types of activities, and objects under surveillance as per potential risks of damage to health for organizing scheduled control and surveillance activities: Methodical guidelines (approved by the Federal Service for Surveillance over Consumer Rights Protection and Human Well-being. On August 11, 2017). *Garant. Informational and legal support*. Available at: https://www.garant.ru/products/ipo/prime/doc/71681784 / (May 20, 2021).

health analysis and assessments are usually performed using reliable mathematical models for relations within "violations of obligatory requirements by objects under surveillance – population mortality and morbidity" system on a territory under surveillance[4].

At the same time it is obvious that the risk-oriented model has a lot of potential that has not been used to the full. At present risks that might be caused by effects produced by an object on protected values are assessed within sanitary-epidemiologic surveillance only for determining periodicity of scheduled inspections. Meanwhile, the risk-oriented model provides an opportunity to take risks into account both when an inspection plan is drawn up and when decisions are made as per its results together with substantiating prevention activities[2].

Sanitary-epidemiologic surveillance can be made more mature[5] and control and surveillance activities can be made more efficient due to, among other things, developing regulatory and methodical support and implementing innovative approaches into activities performed by Rospotrebnadzor. It is even more vital since the law fixes several types of objects under surveillance such as activities, industrial objects, and results of activities (products and services), and each such type requires testing new control and surveillance procedures and risk assessment practices.

Digitalization may be and should be a vital trend in developing CSA performed by Rospotrebnadzor regarding both specific procedures and the overall system of control and surveillance activities. Many researchers have stressed that digitalization of control and surveillance activities is truly vital and it can be seen in many domestic and international projects[6] [3, 4].

According to data provided by the Higher School of Economics [1, p. 89], initially the law fixed orientation at wide-scale and profound digitalization of state control and surveillance. It was assumed that in case there were no data on a certain control and surveillance activity in an information system, such an activity should not become legally significant. Moreover, it was fixed that information technologies would automate such procedures as ranking objects under surveillance into specific risk categories, creating plans of control and surveillance activities, detecting risk indicators, selecting types of control and surveillance activities relevant for a specific situation, making a list of obligatory requirements and checklists relevant for a specific economic entity etc.

The Federal Law No. 248-FZ stipulates orientation at considerable expansion of prevention activities performed by surveillance authorities; it requires analyzing substantial amounts of information that could describe variable properties of an object under surveillance and its relations with other economic entities and provide an insight into probable effects this object could produce on the environment, both static ones and taken in dynamics over time and space. Obviously, there is a demand for Big Data processing. Digitalization provides wider opportunities for applying a result-oriented managerial model. Owing to big data public management authorities get more prompt access to data on risk sources and types and achievable (or non-achievable) results [5–7].

Undoubtedly, use of big data and science-intensive procedures for processing formalized and digitally transformed data will secure more objective assessments obtained during

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[4] MR 5.1.0095-14. Calculation of actual economic losses and those prevented due to control and surveillance activities caused by mortality, morbidity and disability among population associated with negative effects produced by environmental factors: Methodical guidelines. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200129398 (May 22, 2021).

[5] The standard for maturity of managing productivity and efficiency of control and surveillance. Approved by the Meeting Report of the Project Committee on basic trends in the strategic development of the Russian Federation "The Reform of control and surveillance activities" issued on February 13, 2018 No. 1. *Garant. Informational and legal support*. Available at: https://base.garant.ru/71930516/ (May 15, 2021).

[6] PREKOP-RF. *The joint project by the European Union and European Council "Protection of entrepreneurs' rights from corruption in the Russian Federation"*. Regulatory and surveillance authorities of the European Council member-states responsible for accomplishing inspections and control activities in economy – structure, practices, and examples: a regulatory document, 2015, 39 p.

control procedures [8]. Besides, automation and digitalization result in a substantial reduction in required routine and the most labor-consuming procedures, both for a surveillance authority and for an object under control. The latter allows concentrating on developing and implementing preventive activities.

The state should make a demand for relevant big data and make a decision on inspections and responsibility for violations basing on them. In other words, the state relies on distance control and it is only in exceptional cases when control procedures are to be performed directly at a place where an object under surveillance performs its activities.

At present distance control and distance monitoring as a specific type of state risk-oriented control are widely used in banking and financial sphere [9–11].

Over the last 10 years distance control has been performed via wide use of hardware and instrumental monitoring means and means for recording events. Instrumental control techniques including those for uninterrupted observation are widely used in traffic control [12–14], industrial and ecological safety provision [15, 16], forest protection [17, 18], communal services [19, 20] etc. Distance control and monitoring seem to have a lot of potential in the sphere of providing hygienic-epidemiological safety and sanitary-epidemiologic well-being. Photo- and video-recording can be used in assessing conformity with obligatory requirements to activities performed by educational establishments, social objects, catering, retailing, etc. Audio-recording can be applied to assess conformity with communal hygiene requirements in places where potentially “noisy” objects are located close to residential areas. Tools used to distantly measure parameters of environmental objects can be efficient for assessing ambient air quality, chemical structure of water from the first and second intake from drinking water supply systems, temperature of hot water in a distribution network etc. Tools used in distance control over environmental objects can be successfully introduced within systemic control over risk indicators when social and hygienic monitoring is performed etc.

Undoubtedly, Rospotrebnadzor aims to digitalize and automate its activities[7]. At present the Unified Information-Analytical System (UIAS) of the Service is being implemented. UIAS is aimed at automating work processes in the basic activities performed by Rospotrebnadzor bodies and institutions as well as at external electronic interactions with state authorities, economic entities, civil society and other participants in public management in the sphere of population preservation, providing population safety and consumer right protection. Electronic data are being collected promptly in real time mode; these data are necessary for performing control and surveillance functions in the sphere of providing sanitary-epidemiologic well-being of population, protecting consumer rights and consumer markets (emergency messages about communicable diseases, complaints from citizens about sanitary-epidemiologic welfare or consumer rights being violated and some others).

In order to provide interdepartmental electronic interaction, Rospotrebnadzor and the Federal Customs Service have concluded an agreement on working out technical conditions for informational interactions between these two federal services. Rospotrebnadzor is included into development of the Interdepartmental integrated automated information system that covers all federal authorities responsible for control at entry points on the state border of the Russian Federation (IIAIS).

The state information system for consumer rights protection is active and available at Rospotrebnadzor’s official web-site (http://zpp.rospotrebnadzor.ru).

There are several interdepartmental and common public information sources that are kept operational. They include “The Register of certificates on products registration (unified form used on the Customs Union territory)”; “The Register of sanitary-epidemiologic certificates issued for products that underwent sanitary-epidemiologic examination”; “The register of licenses

[7] On approval of the informatization plan for this year (2020) and future 2021 and 2022: The Order by Rospotrebnadzor dated March 11, 2020 No. 148. The Federal Service for Surveillance over Consumer Rights Protection and Human Well-being. Available at: https://www.rospotrebnadzor.ru/documents/details.php?ELEMENT_ID=14590 (May 22, 2021).

granted for activities involving use of communicable diseases agents and licenses for activities involving use of (generating) sources of ionizing radiation) "; "The Register of notifications about specific entrepreneurial activities now being performed"; The Federal Register of potentially hazardous chemicals and biological substances and "Hazardous substances" automated distributed information retrieval system (ADIRS), etc.

But at the same time, new legal provisions and new procedures and organization types of control and surveillance activities require concrete approaches, methodical support, precise algorithms, implementation programs, efficiency assessment criteria, etc.

Our research goal was to develop certain methodical approaches to improving sanitary-epidemiologic control (surveillance) taking into account requirements fixed in new federal legislation and digital transformation of activities performed by Rospotrebnadzor.

Data and methods. When developing new approaches, we took into account already existing documents on risk-oriented surveillance that were already implemented into routine practices by Rospotrebnadzor; valid and already invalid regulatory documents and instructions; as well as materials taken from the Technical specification on UIAS design.

Results and discussion. ***Developing approaches to ranking both activity types and industrial objects as per risks of potential damage to health.*** Clause No. 16 in the Federal Law 248-FZ stipulates that objects under surveillance include the following:

– activity (inactivity) of citizens and organizations that should comply with obligatory requirements;

– results of activities performed by citizens or organizations, including products (goods), works, or services that should comply with obligatory requirements;

– buildings, constructions, or linear objects… that belong to citizens and organizations and (or) are used by them and that should comply with obligatory requirements (hereinafter called "industrial objects")".

Objects under surveillance should be assigned into a certain risk category as per potential risks of damage to protected values (as regards Rospotrebnadzor activities, these are risks of damage to health or health risks).

Prior to 248-FZ coming into force risk categories were assigned to types of economic activities performed by economic entities within sanitary-epidemiologic surveillance activities according to Clause 8.1 in the Federal Law 294-FZ and The RF Government Order No. 806[8].

The task was to assign a category as per a health risk not only for a type of activity but also specific industrial objects (buildings, constructions, etc.). And here it was assumed that industrial objects were material resources where a specific activity was performed and it was inadvisable and hardly correct to consider them separately.

Potential health risk caused by a specific activity performed by a specific juridical person (JP) or a private entrepreneur (PE) at one or several industrial objects was calculated as per the following formula (1):

$$R^l = \sum_{i=0}^{n} R_i\,(l), \qquad (1)$$

where R^l is potential health risk caused by l-th activity performed by JP or PE; $R_i\,(l)$ is potential health risk occurring at i-th industrial object when l-th activity is performed there.

Potential health risk caused by l-th activity performed by JP or PE at a specific industrial object is calculated as per the formula (2):

$$R_i\,(l) = p(l)\cdot u(l)\cdot M_i\,, \qquad (2)$$

where $R_i\,(l)$ is potential health risk occurring at i-th industrial object due to l-th activity being performed there; $p\,(l)$ is a probability that sanitary legislation would be violated by JP or PE at a specific object when l-th activity is performed there. As data on frequency of violations at different objects are accumulated, $p\,(l)$ should be replaced with $p_i\,(l)$ or a probability that sanitary legislation would be violated at an i-th-type object when l-th activity is per-

[8] On applying risk-oriented approach when organizing specific state control (surveillance) activities and making alterations into certain acts issued by the RF Government: The RF Government Order issued on August 17, 2016 No. 806. *Garant. Informational and legal support*. Available at: https://base.garant.ru/71473944/ (May 20, 2021).

formed; *u* (*l*) is a parameter that characterizes damage to health due to obligatory requirements being violated. As data on severe consequences for health due to violations at different objects are accumulated, *u (l)* may be replaced with u_i *(l)*. M_i is a parameter showing a number of people exposed to effects produced by *i*-industrial object (exposure scale), million people.

Probability that sanitary legislation would be violated is characterized with frequency of violations detected due to control and surveillance accomplished at objects belonging to JP and PE that perform a specific activity (*p (l))*. Value of *p (l)* is determined as 95%-th percentile in distribution of regional relative frequency revealed for violations detected during one inspection at objects under surveillance performing *l*-th activity over a 3-year period.

The parameter that characterizes damage to health caused by sanitary legislation being violated (*u (l))* is determined basing on systemic, including expert, analysis of cause-and-effect relations between frequency of specific clauses in the sanitary legislation being violated and health disorders prevalence becoming apparent via population mortality and primary morbidity taking their severity into account.

The parameter that shows relative frequency of violations detected during one inspection at an *i*-th object under surveillance that performs *l*-th activity is determined as per the following formula:

$$p_i^l = \frac{m_i^l}{n_i^l}, \tag{3}$$

where p^l_i is a parameter that shows relative frequency of violations detected during one inspection at an *i*-th object under surveillance that performs *l*-th activity and is determined taking into account data collected in all regions in the RF; m^l_i shows how many violations of sanitary legislation were detected during one year at *i*-th objects under surveillance that performed *l*-th activity, units; n^l_i is a total number of inspections during one year at an *i*-th object that performs *l*-th activity, units.

Frequency of violations and 95 % -th percentile that is taken into account in ranking are to be revised not rarer than every three years.

Both industrial objects and activity types are to be ranked using the unified scale showing potential health risk:

a) higher than 10^{-3} means extremely high risk;

b) from higher than 10^{-4} to 10^{-3}, high risk;

c) from higher than 10^{-5} to 10^{-4}, considerable risk;

d) from higher than 10^{-6} to 10^{-5}, average risk;

e) from higher than 10^{-7} to 10^{-6}, moderate risk;

f) lower than $1 \cdot 10^{-7}$, low risk.

Risk category is given to both an activity and to each specific industrial object. Periodicity of control is determined basing on a risk category (extremely high risk means scheduled inspections are accomplished annually; high risk, every two years; etc.).

This unified ranking that covers both activity type and industrial objects provides quite a flexible mechanism for control over JP / PE that perform their activities at multiple industrial sites and/or industrial objects (retail networks, catering networks, and networks that render services to population; large industrial holdings, etc). An overall high risk category as per an activity (see Formula 1) gives an opportunity to a surveillance authority to accomplish control over an object that, as a rule, exerts its influence on a considerable number of people (those who consume products or services, workers employed at it, or people who live in a zone exposed to it); consequently, negative outcomes caused by sanitary requirements being violated by this object are likely to be wide-scale. And lower risks detected for specific industrial objects give surveillance authorities more freedom in planning annual scheduled inspections (an example is given in Table 1).

When this or that industrial object is included into a plane of scheduled inspections, additional criteria can be taken into account; for example, environmental quality on a territory where the object is located, population density, overall sanitary-epidemiologic situation, etc. And if inspections are based on analyzing more extensive data, it can provide permanent control over activities performed by a large JP / PE without violating requirements to frequency of control procedures fixed for industrial objects.

Table 1

A draft procedure for planning inspections at an economic entity that performs its activities at multiple industrial objects belonging to different risk categories

An activity is retail trade in food products, drinks, and tobacco goods.
Overall number of industry objects (IO) is 31.
Risk category for the activity is extremely high risk ($2.03 \cdot 10^{-3}$).
A surveillance authority is entitled by the law to accomplish annual scheduled inspections

No.	Risk	Any grounds for change of a risk category[9]	Risk category determined for an industrial object	Periodicity of scheduled inspections according to the law	Future planning (in years starting from a year after the year of account)					
					1	2	3	4	5	6
1	$9.6 \cdot 10^{-4}$	no	high	Every two years	1		1		1	
2	$8.7 \cdot 10^{-5}$	no	considerable	Every three years	1			1		
3	$8.6 \cdot 10^{-5}$	no	considerable	Every three years		1			1	
4	$7.3 \cdot 10^{-5}$	no	considerable	Every three years	1			1		
5	$6.7 \cdot 10^{-5}$	no	considerable	Every three years		1			1	
6	$6.6 \cdot 10^{-5}$	no	considerable	Every three years	1			1		
7	$8.5 \cdot 10^{-6}$	no	average	Not more than every 4 years	1				1	
8	$6.7 \cdot 10^{-6}$	no	average	Not more than every 4 years		1				1
…			…							
12	**$5.4 \cdot 10^{-6}$**	**yes**	**considerable**	**Every three years**			1			1
13	$4.4 \cdot 10^{-6}$	no	average	Not more than every 4 years		1				1
14	$4.3 \cdot 10^{-6}$	no	average	Not more than every 4 years	1				1	
15	**$5.1 \cdot 10^{-7}$**	**yes**	**considerable**	**Not more than every 4 years**		1				1
16	$5.1 \cdot 10^{-7}$	no	average	Not more than every 6 years	1					
17	$5.0 \cdot 10^{-7}$	no	average	Not more than every 6 years			1			
18	$4.9 \cdot 10^{-7}$	no	moderate	Not more than every 6 years			1			
…										
30	$6.4 \cdot 10^{-7}$	no	moderate	Not more than every 6 years				1		
31	$2.0 \cdot 10^{-7}$	no	moderate	Not more than every 6 years						1

Methodical approaches to creating dynamic checklists. Periodicity of scheduled control procedures that is determined with risk categories taken into account is a most essential element in risk-oriented control. But at the same time, it is only one component in the model. It is often the case that a rather wide range of obligatory requirements is fixed for a specific activity, industrial object, a product, or a service. The risk-oriented model implies that primarily surveillance authorities are to control those requirements violation of which creates the greatest risks for protected values.

The task can be solved via creating and implementing dynamic risk-oriented checklists. Obligatory requirements that are included into checklists are ranked taking into account priority of requirements determined as per risk criteria.

I value is a product obtained via multiplying functions of a probability that a requirement would be violated and severity of consequences this violation would cause; this value is a criterion for determining priority of requirements (4):

$$I = f(p_k) \cdot f(g), \qquad (4)$$

where $f(p_k)$ is a function of a probability that requirements would be violated by an object under surveillance at *k*-th level: at an object itself (*k*=1), municipal (*k*=2), regional (*k*=3), and federal level (*k*=4). $f(g)$ is a function of consequences severity[10].

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[9] Grounds for changing a risk category are fixed in the Order on types of control.
[10] According to the Methodical guidelines MR 5.1.0116-17.

A variant for the function (4) to be used is use of weighted averaging:

$$f(p_k) = \\ = \frac{a_1 \cdot f(p_1) + a_2 \cdot f(p_2) + a_3 \cdot f(p_3) + a_4 \cdot f(p_4)}{a_1 + a_2 + a_3 + a_4}. \quad (5)$$

In case there are no representative statistic data on a probability that requirements would be violated at any level, then a_k is considered to be equal to zero. Weight coefficients in the function are set for different *k* levels by experts; it is advisable to assume that $a_1 > a_2 > a_3 > a_4$.

Therefore, this formula takes into account peculiarities related to violations of obligatory requirements by objects under surveillance not only in the country in general but also in a specific region or a city / town / settlement.

Checklists can be created individually for each specific object under surveillance. Priority given to controlling requirements that are violated the most frequently or with the gravest consequences of their violation aims at making economic entities always remember that this requirement will necessarily be checked. On one hand, it is a motive for JP / PE to perform proactive preventive activities (and it is exactly what should be achieved via state control); on the other hand, it provides a surveillance authority with firm assurance that the main risks are given special attention.

Making checklists in formats that can be "read" by machine and having automated procedures for analyzing results obtained via filling in these checklists give an opportunity to perform logic analysis and cross-verification of data submitted by an economic entity itself (including laboratory research data obtained via industrial control) in filled checklists and data provided by other information system. It is important to analyze whether data provided by JP / PE corresponded to data obtained from external sources.

Overall, checklists are potentially considered to be dynamic systems that can change according to changes in statistic data accumulated due to inspections and analysis of their results. The latter makes them even more effective and productive for protecting citizens' life and health (regarding consumers, workers, etc.)

Methodical approaches to creating a statistic risk profile of an object under surveillance. When objects under surveillance are ranked as per results obtained via generalizing the whole set of control and surveillance activities, this ranking in its essence is based on determining specific types of objects under surveillance. But at the same time each JP / PE has its peculiarities, specific internal organization, and specific quality of the environment on a territory where it performs its activities (quality of ambient air, water objects, soils; population density on nearby territories, etc.). Given that, any additional data on an object allow more precise assessment of it bearing in mind potential risks that can be caused by its activities. In this situation it seems advisable to create a "statistic risk profile of an object under surveillance". Risk profile here is seen as a multidimensional statistic model of an object under surveillance; it is a set of frequency-probabilistic properties of this object that show probable (possible) violations of sanitary legislation as well as their consequences for health and other values protected by law.

Statistic risk profiles are created using the whole set of accumulated data over the longest available period including data taken from external sources (so called information traces left by an object under surveillance). Their creation requires algorithms that can provide an opportunity to process results obtained via control and surveillance activities by machine and procedures for applying artificial intellect based on machine training of artificial neural networks. A neural network model analyzes all detected violations on typical objects basing on data that are input in real time mode; it determines risk indicators, selects significant violations of obligatory requirements and adjusts statistic risk profiles of all registered objects under surveillance. While iterative determination of significant risk indicators flows uninterruptedly, the system automatically determines a set of rules for risk assessment as per a set of type-determining properties (an activity, a type of an industrial object, a territory where this object is located, etc.). A risk profile for a specific object can be adjusted taking into account historical results obtained due to accomplished inspections.

Analyzing statistic profiles of objects under surveillance allows finding solutions to tasks that are generally aimed at optimizing control and surveillance activities:

– revealing non-typical objects via searching for statistical anomalies in multidimensional space of objects' properties. Such objects can potentially be the most 'risky" and require special attention from a control and surveillance authority;

– determining correlations and regressions between various digital parameters that allow assessing whether obligatory sanitary requirements are met or not;

– detecting negative influence exerted by violations of sanitary legislation on population health basing on cross-correlation analysis;

– assessing risk levels of the environment around objects and subjects due to automated building up and analyzing graphs that show their interrelations;

– structuring checklists and making them more targeted;

– organizing selective control procedures due to searching for statistically significant trends and permissible ranges of risk indicators values;

– predicting and assessing risks related to an economic entity meeting (or not meeting) obligatory requirements and standards basing on time series analysis, including, for example, use of autoregressive models with moving average, exponential smoothing, and their modifications [21, 22].

Statistic risk profiles have certain advantages:

– they allow multidimensional and precise estimates due to using big data;

– there is feedback with results of control and surveillance activities;

– infringing objects are profiled in the most optimal way due to using the most advanced mathematical procedures for data processing;

– prompt reaction since the whole set of profiles is renewed automatically and simultaneously;

– there is an opportunity to prevent risks due to reacting to new violations that have not occurred before;

– new risk indicators: use of additional automatically calculated risk indicators in all the other modules in the system;

– better quality achieved in risk detection due to additional data (spotting out closely connected unities out of a common graph and analyzing dynamics of a risk spreading as per a graph; assessing risk significance and risk levels for specific nodes and relations; revealing pathways between objects and subjects);

– interpretation is simple and obvious since all the obtained data are given graphically and can be easily used in any activity aimed at risk minimization.

Risk profiles should be renewed constantly; it requires feeding data on results obtained via accomplished inspections into the risk management system. "Feedback" allows maintaining precision of risk assessments via increasing or reducing significance of a subject's initial parameters depending on inspection results. Data used for building up a risk profile for a specific object are analyzed basing on the whole set of results obtained via control and surveillance activities regardless of a surveillance procedure that was applied in this or that case.

Approaches to implementing distance control basing on digitalization and automation of control and surveillance activities. If we wish to develop control and surveillance activities given new alterations into the existing legislation, to provide dynamic ranking of objects under surveillance and to build up correct statistic risk profiles for them, to optimize checklists contents, and to plan efficient control and surveillance procedures, we need to constantly improve organization of information flows and big data processing. And this requirement is common for all public management systems, both in Russia and abroad [23–30].

There is an official document entitled "The National action plan aimed at providing recovery of employment and population incomes, economic growth, and long-term structural changes in the economy". The document envisages developing a concept of distance control /

monitoring[11] and it is well in line with striving to digitalize and automate activities performed by Rospotrebnadzor. This concept includes creating and using information technologies and technical tools aimed at making control and surveillance activities automated so that they do not require direct (contact) interaction with economic entities. It is assumed that control and surveillance activities (both scheduled and off-scheduled ones) can be accomplished via distant interaction between experts from Rospotrebnadzor's bodies and institutions and those who represent economic entities. Basic surveillance procedures are automated due to using functional capabilities offered by an intellectual information system that operates relying on analytical algorithms for data processing including artificial intellect. In future the system will allow a significant increase in a share of distance control over activities performed by JP / PE as well as over quality and condition of buildings, constructions, products, and services.

A principle scheme showing how distance control procedures can be included into the overall system for automation of control and surveillance procedures performed by Rospotrebnadzor is given in Figure.

The system includes the following key elements:

– databases included into the Rospotrebnadzor's Unified information and analytical system;

– databases that belong to external sources (open access DB and DB that are open for information exchange with Rospotrebnadzor basing on bilateral agreements);

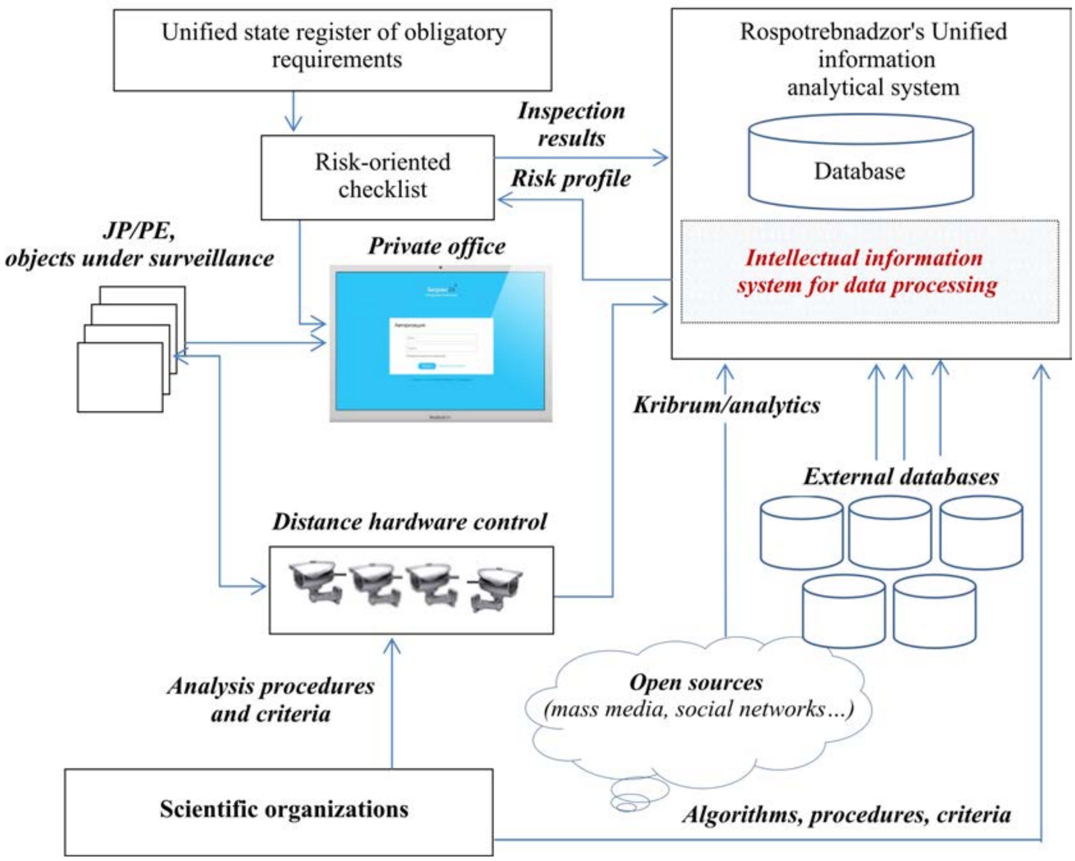

Figure. A principle scheme showing how distance control procedures can be included into the overall system for automation of control and surveillance procedures performed by Rospotrebnadzor

[11] The National action plan aimed at providing recovery of employment and population incomes, economic growth, and long-term structural changes in the economy (approved by the RF Government on September 23, 2020. (The meeting report No. 36, section VII) No. P13-60855 dated October 2, 2020). *Informational and legal support*. Available at: https://www.garant.ru/products/ipo/prime/doc/74678576/ (May 20, 2021)..

– a private office of an object under surveillance that allows communication with a surveillance authority;

– communication means;

– intellectual information system that provides science-intensive processing of all incoming data including those coming from distance hardware control.

An intellectual information system can become a powerful tool in providing information and analytical support for control and surveillance procedures including distance ones; its development and implementation requires wide-scale and comprehensive formalization of all processes, procedures, and specific actions performed by inspecting authorities and their transfer into electronic form.

It provides the following:

– unified interaction between all participants in control and surveillance activities;

– connection and possibility to exchange data with external information sources (both state-owned and private ones), optimized and automated preparation of all documentation necessary for a control procedure; data transfer, storage and further analytical processing as regards results obtained via control and surveillance activities.

This intellectual information system is a set of software-hardware and information-analytical solutions that provide an opportunity for all participants in control and surveillance activities and other concerned parties to fulfill their responsibilities, exercise their rights, and interact electronically.

The intellectual information system, together with data provided by UIAS belonging to departmental information systems (Rospotrebnadzor's UIAS) should provide complex analysis of results obtained via control and surveillance activities as per all control and surveillance procedures. This analysis allows the following:

– revealing the most common problems related to meeting (failing to meet) safety requirements as per a specific activity, territory, economic entity, its production capacity and specific technological processes, types and volumes of manufactured products, a period of time during which production facilities have been in operation, etc. (as per any parameter that is included into a relevant profile in a surveillance register);

– dynamic adjustment of checklists taking revealed priorities into account;

– analyzing legal practices existing in different regions when the same violations are detected there;

– analyzing productivity of administrative measures taken as a response to a violation including analysis as per a specific activity, economic entity, etc. (no repeated violations, all instructions fulfilled timely etc.);

–assessing and predicting risks that obligatory requirements would not be met by economic entities performing specific activities, belonging to a specific category, located in a specific region etc.;

– detecting and analyzing a relation between violation of obligatory requirements and condition of protected values (environmental quality, occupational morbidity, morbidity and mortality among population including products and services consumers etc.) taking into account results obtained via a specific surveillance activity; combined with data on conditions of protected values (via a connection with SHM module, data obtained from other information systems);

– creating a system of targeted preventive activities aimed at preventing violation of obligatory requirements including raising awareness among economic entities about risks that obligatory requirements would be violated occurring at similar objects and best available practices for minimizing such risks.

The most important task here is to analyze the greatest available information volume and, basing on it, to reveal logic in sanitary requirements violations; to parameterize relations between violations of sanitary requirements and other parameters of activities performed by economic entities or conditions of buildings and constructions; to reveal a wide range of risk indicators showing that sanitary requirements might be violated. The latter allows taking proactive decisions in case there are data in any external system indicating that criteria parameters of risk indicators were exceeded.

In future analysis might also include data taken from mass media and social networks. There is experience in using such data, including consumer rights protection; and kribrum techniques (a service that allows examining and monitoring interests, opinions, and demands of networks users) are widely used in marketing, business organization, public opinion studies and studies on people's confidence in public authorities [31].

Therefore, risk-oriented model of control and surveillance activities is combined with risk management elements (hedging). The latter fully corresponds to goals and tasks of sanitary-epidemiologic service since its primary mission is to minimize and prevent risks, dangers, and threats for life and health of country citizens.

Successful functioning of the system to a great extent depends on scientific and methodical support provided for solving each set task.

Conclusions. Taking into account changes in legislative basis of control and surveillance activities and digitalization of functions performed by public authorities in the Russian Federation, we suggest several methodical approaches aimed at developing the existing base of risk-oriented sanitary-epidemiologic surveillance. These approaches provide the following:

– ranking specific industrial objects (as objects under surveillance) as per risks that might cause damage;

– developing statistic risk profiles for objects under surveillance;

– creating dynamic risk-oriented checklists;

– implementing distance control basing on digitalization and automation of control and surveillance activities.

It appears that recommended methodical approaches supplemented with other procedures (non-numeric data statistics, fuzzy theory; neural networks, genetic algorithms, etc.) can provide new prospects in sanitary-epidemiologic control (surveillance) organization and make for the following:

– correctly determined priority risk sources and factors and the strictest control over them together with minimized control over objects and factors with low or insignificant risks of any damage to protected values;

– maximum precise prediction on changes in a situation and iterative development of control and surveillance activities that involves making them more targeted taking into account a constantly renewed data base on results obtained via control activities;

– gradual transformation of scheduled control and monitoring over objects under surveillance with wide use of distance hardware monitoring and science-intensive analysis of all the available data on an object under surveillance and on potential recipients who might be exposed to its influence.

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Research article

GROUP HEALTH RISK PARAMETERS IN A HETEROGENEOUS COHORT. INDIRECT ASSESSMENT AS PER EVENTS TAKEN IN DYNAMICS

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The present work focuses on describing a procedure for assessing intensive and cumulative parameters of specific risk when observing cohorts under combined exposure to several external or internal factors.

The research goal was to reveal how to use well-known heuristic-descriptive parameters accepted in remote consequences epidemiology for analyzing dynamics of countable events in a cohort; analysis should be performed on quite strict statistic-probabilistic grounds based on Bayesian approach to explaining conditional probabilities that such countable events might occur. The work doesn't contain any new or previously unknown epidemiologic concept or parameters; despite that, it is not a simple literature review. It is the suggested procedure itself that is comparatively new as it combines techniques used to process conventional epidemiologic information and a correct metrological approach based on process description.

The basic result is providing a reader with understanding that all basic descriptive epidemiologic parameters within cohort description framework turn out to be quantitatively interlinked in case they are considered as conditional group processes. It allows simultaneous inter-consistent assessment of annual risk parameters and Kaplan – Meier (Fleming – Harrington) and Nelson – Aalen cumulative parameters as well as other conditional risk parameters or their analogues. It is shown that when a basic descriptive characteristic of cumulative parameters is chosen as a measure for measurable long-term external exposure, it is only natural to apply such a concept as a dose of this risk factor which is surrogate in its essence. Operability of the procedure was confirmed with an example. The suggested procedure was proven to differ from its prototype that previously allowed achieving only substantially shifted estimates, up to ~100 % even in case an operation mode was normal. Application requires creating specific but quite available PC software.

Key words: *risk, parameter, epidemiology, risk factor, competition, indirect estimate, mortality, process, cohort, strata, model.*

There is a well-established opinion on a health risk being an objective probability that this or that undesirable event will occur in future [1–3] due to certain conditions/factors including a period of observation. Such examined undesirable events are usually death, a disease or, a bit less frequently, sub-clinical irreversible changes in a person's health that are reliably diagnosed. Accordingly, a risk can be given quantitatively as a certain numeric or functional indicator. In prediction practices it can characterize an event that hasn't yet occurred; however, it is rather difficult to reach a stage at which risks can be managed if experience gained via observing similar events in similar conditions hasn't been generalized, that is, risks have not been assessed a posteriori as per previously collected data. In that respect a task related to risk measuring is similar to a metrological procedure used for determining a certain unknown (but objectively existing) value or to an establishing a correlation between a risk indicator and conditions for its potential realization. This logical scheme contains a seeming internal contradiction related to the fact that a concept of probability implies "randomness" category being active and this category contradicts "link" category since the latter is a determined one. Yes, randomness is present here and it produces its effects but still there is no contradiction. It makes sense to apply "risk" category only if there is a probable

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alternative course of events. However, risk factor can be present here as this or that determined combination thus creating "factors – risk" link which is quite real; this dependence should be examined thoroughly prior to a stage at which risks are managed.

Let us note that "risk" as a concept has certain properties that are purely mathematical and make risk assessment procedures rather complicated. A link or a potential link with risk factors indicates that we deal with a conditional probability. Further complications arise due to time or age being usually taken as a risk factor when specific health risks are analyzed; therefore, we can conclude that health risk is not only an indicator (a number) but also a dynamic random process. And finally, if there is a task aimed at eliminating influences exerted on a metrological procedure by random or uncontrollable factors, this risk can never be assessed individually since assessment is possible only for a homogenous group of individuals as a certain biological property which is common for them.

Intensive risk rate[1] of common or specific mortality or morbidity, which is also known as "force of mortality", "hazard rate", or "instantaneous incidence rate", is a typical and widely spread rate used in descriptive occupational epidemiology, clinical epidemiology, medical-ecological and demographic research [4, 5]. When remote consequences are described using this value, it is usually attributed to a year on an age scale or calendar scale as the most commonly used time unit. A series of risk rates is usually used as a measurement due to its dynamics being quite reproducible when describing remote consequences of a wide range of effects, for example, non-communicable diseases for a great number of isolated sub-cohorts or sub-populations that live in similar socioeconomic conditions. It allows considering an intensive risk rate taken in its overall dynamics practically as a species-specific property. This circumstance, for example, is a reason for regular regional screening of all oncologic morbidity and mortality exactly as per the above mentioned rate [4]. As a rule, it is exactly this parameter with its excessive values being equal to 0.001–1 ‰ per year serving as permissible risk limits[2] which is taken by regulatory authorities as a sign that it is time to make relevant decisions. Intensive group risk rate is also known as "individual risk", however, this name is incorrect since it contradicts its group essence.

An insight into the given rate and its direct link with risk value and other objective parameters can be easily derived from a simple example published in the work [5] and given in Table 1.

Table 1

An example of a 5-year cohort study

	Exposed	No exposed
Died due to the cause	30	10
Didn't die due to the cause	70	90
Total	100	100

In this example, two population groups (strata) with practically the same structure were observed over a relatively short period of time $T = 5$; the only difference between them was that one group was exposed to a certain risk factor while the other was not, and it is influence exerted by this factor that we are trying to assess. If a risk is a probability that a person will die due to the examined cause, than its assessment amounts to obvious 30 out of 100 cases in the exposed group or $R_e = 0.30$; similarly, in the non-exposed group $R_n = 10/100 = 0.10$. Then excess risk of death due to the examined cause amounts to $0.3–0.1 = 0.2$; it is quite natural to relate it to effects produced by exposure to a risk factor. Relative risk for these effects is calculated as $RR = R_e / R_n = 3.0$.

These given values are cumulative death cases over the observed 5-year period. They give

[1] Epidemiologic glossary. In: D.M. Last for the International epidemiologic association, eds. 4th edition, 316 p.

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

an opportunity to assess intensive rates relaying on the following ratios $M_e = N_e \cdot (1-\exp(-h_e T))$ and $M_n = N_n \cdot (1-\exp(-h_n T))$ as well as on an assumption that intensive rates are constant in both exposed and non-exposed group. Here M_e, M_n are a number of "cases" in the exposed and non-exposed strata; N_e, N_n is an initial number of people in the strata; h_e, h_n are "hazards" or annual risk rates. Exponents occurring in these formulas indicate that h_e, h_n values are sliding, that is, related to a condition that a person reaches the current age within the observed period; whereas cumulative rates R_e, R_n refer to the whole observation period in comparison with the initial state of sub-strata. Due to it, h_e, h_n values are similar to continuous rate of discounting in economic theory as per their mathematical properties thus creating a link with exponential ratios. Their calculation brings the following results: $h_e \approx 71$ ‰ per year and $h_e \approx 21$ ‰ per year accordingly. Hazard ratio is $HR = h_e/h_n = 3.38 \neq RR = 3.0$ under effects produced by a factor.

If we neglect this ambiguous interpretation of a relative risk and return to the heading of our work, it is quite relevant to ask – why is it a problem to assess rates in a heterogeneous cohort? It seems so simple if we look at the example given in Table 1. But at the same time, methodological issues here are multiple.

1) $h = h(t)$ rate is not actually a number but a function of an age or time, that is, a process; whereas assessments given in Table 1 were reduced to simple scalar (numeric) values;

2) Table 1 is based on only one factor that influences the risk whereas when it comes down to a real sampling or a cohort, it is almost always a multi-factor study. It requires a specific procedure for statistical assessing that involves stratifying a heterogeneous cohort into more than two strata taking into account all relevant combinations of risk factors;

3) as we can see, neither h intensity nor its cumulative analogue $h \cdot T$ are not directly observed values. Contradicting (and outdated) beliefs are still alive due to a known approximated property of the value h that allows calculating it as a "ratio of a number of specific cases to a number of person-years under risk"[1]. But it is a mistake to believe that this approximated property is an exact definition. In fact, it is dynamics of countings given in Table 1, both in cumulative and individual forms, that is initial empirically observed data. This circumstance leads to a task to accomplish an ***indirect assessment*** of $h(t)$ process or its cumulative analogue as per observing countings accumulation in each homogenous stratum in the cohort;

4) countings in a homogenous stratum which is a part of a random sampling, are also random. It is necessary to assess a parameter of a certain homogenous and almost general aggregate. Due to it parameters can be assessed with certain relative uncertainty which tends to be the greater, the fewer is a number of cases in examined cohort/strata. For example, interval assessments of cumulative risks for the examined exposed and non-exposed strata (with 95 % confidence probability) amount to $R_e = 0.219\ldots0.396$ and $R_n = 0.056\ldots0.175$, and we can clearly see that uncertainty range is wider than the central assessment for the non-exposed group. It practically forbids us to work with small strata with a number of "cases" in them being lower than 4 since extended relative risk uncertainty will certainly exceed 100 %. It is completely impossible to reliably identify any process relaying on fewer than 4 points although statistically significant differences between strata may occur even with a smaller number of cases [6]. Therefore, it is necessary to create such an assessment algorithm that could preserve all advantages gained due to factor space stratification together with an opportunity to indentify ***optimal model dependence*** for risks that takes into account relations with all risk factors for the whole set of strata simultaneously.

Therefore, it is vital and natural to make an attempt to create an algorithm for assessing intensive and cumulative specific risk rates in a heterogeneous cohort basing on data obtained via a long-term observation period.

Description of the assessment procedure and its prototype. Let us note that an issue related to heterogeneity of actual observations has long been of interest when it comes down both to cohort samplings and population studies on medical and demographic problems [7]. There are a lot of established various reasons for heterogeneity that are observed while sampling representatives are still alive or revealed after their death including non-observable hidden factors [8].

Without claiming to cover everything, we are going to concentrate on examining influence exerted by only a priori known risk factors and to assume that latent variables are absent. We can only rely on a researcher-physician's intuition when he or she keeps registers and collects initial epidemiologic data. It allows grouping individual by strata even before mathematical data analysis starts with the possibility to permanently bind them to their predefined strata during the entire observation period. It is implicitly assumed that all people in a specific stratum have the same chance to fall sick or die to any examined disease coded in the ICD-9 or ICD-10. It is especially easily achieved regarding risk factors that can be described via binary attributes, for example, sex, or smoking status (smokes / doesn't smoke). Even an interfering disease in case history in a period of observation can be a binary attribute. Such factors can be considered almost immutable over a long period of time. Certain quantitative factors that exert their impacts on health can also turn out to be useful for the chosen stratification scheme in case intensity of their influence is the same for all cohort members. It is obvious for acute single exposure or chronic even exposure with the same individual intensity. In this case, it is possible to introduce such a (surrogate) cumulative factor as a dose accumulated by the end of observation period. In this case it seems only natural to analyze conditional dependence for "cumulative risk – cumulative dose" pair.

This approach has its functional prototype in epidemiology, AMFIT module in Epicure software package[3]. This software has been successfully applied in epidemiologic research all over the world [9, 10]. In particular, it was approved on as the software standard for radiation and epidemiologic studies: "… Epicure is the de-facto standard for modeling radiation health effects …" [11]. Practically all national standards for radiation safety in countries where radiation-hazardous objects are located, including Russia[4], are based on results obtained with AMFIT (Poisson regression). And it is considered to be established that an equivalent radiation exposure dose is a commonly recognized risk factor of remote radiation-oncologic consequences.

The approach which we suggest in this work is a bit different from AMFIT in spite of common goals. There are three basic differences:

a) if we stick to strictly probabilistic approach, then observations can't be described and composed function of their aggregate assessment can't be built via applying Poisson distribution for countings of "cases" in strata since Poisson statistics is suitable only for describing rare events in an unlimited sampling. Actual cohorts cease to be unlimited even in the rough sooner or later as their members die. It is necessary to describe deviations from a basic trend (process) more correctly basing on binomial statistics which is suitable for limited samplings and is not bound to a condition that events should be rare;

b) AMFIT algorithm is based on assessing intensity of specific events at the expense of assessing related cumulative parameters. Meanwhile, intensity is not a directly observed descriptive characteristic; however, the Kaplan – Meier cumulative estimator can be successfully used instead of it since it is directly linked to individual countings of "cases" and random binomial deviations. Application of this rate would allow achieving more sustainable

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[3] EPICURE User's Guide. In: D. Preston, J. Lubin, D. Pierce, M. McConney eds. Seattle, Hirosoft, 1988–1993, 334 p.

[4] SER 2.6.1.2523-09. Radiation safety standards (NRB-99/2009). Moscow, The Federal Center for Hygiene and Epidemiology of Rospotrebnadzor, 2009, 100 p.

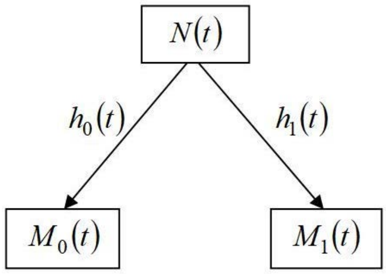

Figure 1. Markov structure scheme for dropping out from observation for two competing causes of death. There is an initial state compartment and two compartments for two registered causes of death

assessments and simultaneously preserving an opportunity to calculate intensity of events;

c) AMFIT algorithm is based on maximum likelihood as it was interpreted by Ronald Fischer which, strictly speaking, is not probabilistic and has purely heuristic basis just as its prototype, Karl Gauss' maximum likelihood [12].

Although any algorithm used for statistical processing yields biased estimates, we can still hope that measuring precision can be improved significantly due to eliminating drawbacks of AMFIT algorithm which has already been applied successfully and therefore can easily be taken as a prototype.

A relation between intensive and cumulative conditional statistical parameters and epidemiology of long-term effects. A desire to assess epidemiologic rates objectively requires applying a bit more profound mathematical apparatus than that used to process data given in Table 1. However, this mathematics shouldn't mislead anybody regarding an intention to move to analytical epidemiology sphere. Our described procedure still corresponds to common descriptive statistics which is not related to an essence of cause-and-effect relations when health is described should we refer to events in a conditionally homogenous stratum included into a heterogeneous cohort. A descriptive approach involves obvious formalism: in cases when a simple Markov scheme can be used to describe a flow of events with specific causes of deaths or diseases in a homogenous group, and this Markov scheme has three states and two competing reasons for a person to be dropped out from observation, a speed of change in a number of people in a compartment responsible for the initial state is proportionate to a number of people in it (Figure 1, Formula (1)). Regardless of how such a model is close to reality, a coefficient of proportionality between a speed of dropping out and a number of people in a basic state can also be calculated and given as a sum of two intensities of events, under study and competing.

This scheme given in Figure 1 can be roughly described with a system of common differential equations

$$\frac{dN}{dt} \approx -\left(h_0(t) + h_1(t)\right) \cdot N, \qquad \frac{dM_1}{dt} \approx h_1(t) \cdot N, \qquad (1, 2)$$

where t is time (age); $h_0(t), h_1(t)$ are intensities of events related to the examined and competing causes of death; $N(t)$ is a number of people in the initial state; $M_1(t)$ is cumulative (accumulated) number of deaths due to the examined cause. Equations (1, 2) are only approximate due to inability to calculate any derivatives from discrete-valued functions that are also susceptible to random fluctuations. However, it doesn't prevent us from moving to expected conditional fractions calculated from an initial number of people in a homogenous sub-group at a certain initial observation point t_0, and hence to conditional probabilities or prevalence in a stratum. In this case our ratios can become continuous and precise (3, 4):

$$\frac{dS}{dt} = -\left(h_0(t) + h_1(t)\right) \cdot S, \qquad \frac{dR}{dt} = h_1(t) \cdot S, \qquad (3, 4)$$

if we conditionally take $S(t_0) = 1$ at a point where observation starts. Due to its linearity the system (3, 4) has a simple analytical solution:

$$S(t) = S(t|t_0) = S(t_0) \cdot P_0(t|t_0) \cdot P_1(t|t_0), \quad (5)$$

$$\Delta R\left(t|t_0\right)=\int_{t_0}^{t}h_1\left(\tau\right)\cdot S\left(\tau\right)d\tau, \qquad (6)$$

where $P_0\left(t|t_0\right)=\exp\left(-H_0\left(t|t_0\right)\right)$; $P_1\left(t|t_0\right)=$ $=\exp\left(-H_1\left(t|t_0\right)\right)$; $H\left(t|t_0\right)=\int_{t_0}^{t}h\left(\tau\right)d\tau$; ΔR is a growth in a risk of death due to the examined cause over a period $[t_0,t]$. As it logically comes from solutions to (5, 6) and according to experience gained by a wide circles of epidemiologists [13–23] these expressions provide an opportunity not only to know intensity of examined specific events $h_1\left(t\right)$ but also an exact survival function $S\left(t|t_0\right)$, additional conditional lifetime risk of death due to the examined cause $\Delta R\left(t|t_0\right)$, cumulative probability that a person will not die to the examined cause provided that he or she reaches an age t_0 and conditional absence of any competing causes of death – $P_1\left(t|t_0\right)$, as well as an analogue of Nelson – Aalen estimator $H_1\left(t|\ t_0\right)$ which is also known as cumulative intensity of specific mortality provided there are no other causes of death (cumulative hazard) [19, 20]. It may seem that interrelated values $P_1\left(t|t_0\right)$ и $H_1\left(t|t_0\right)$ are non-observable; however, it is not true. Epidemiologic applications of martingales theory [19] stipulate that a conditional but still quite measurable Kaplan – Meier survival function [22] corresponds to the value $P_1\left(t|t_0\right)$; and measurable and already mentioned martingale Nelson – Aalen estimator corresponds to the value $H_1\left(t|t_0\right)$. Recall that the value $H_1\left(t|t_0\right)$ which in its essence is an area below the curve showing the process $h_1\left(t\right)$ has been successfully and efficiently controlled for more than 2 decades within oncologic monitoring [4] in the Russian Federation. This parameter is convenient not only for measurements within a cohort, but also within a population.

Therefore, 6 descriptive epidemiologic parameters, 4 cumulative and 2 intensive, turn out to be related within a simple dynamic scheme shown in Figure 1. It should be noted that values of relative parameters are bound to different bases. For example, a conditional lifetime risk is calculated against a point where observation starts; but intensive parameters and their cumulative attributes $P_1\left(t|t_0\right)$ and $H_1\left(t|t_0\right)$ are sliding, that is, they are calculated against an achieved share of survived people since they are related to a condition that a person reaches a moment of observation. Besides, a true survival function turns out to be stronger related to competing causes of death and uncontrollable history of a stratum prior to a moment when observation starts in comparison with parameters that are responsible for the examined cause of death. Due to it the parameters $H_1\left(t|t_0\right)$ and $P_1\left(t|t_0\right)$ are interesting as such. Given the relation $P_1\left(t|t_0\right)=\exp\left(-H_1\left(t|t_0\right)\right)$ the parameter $P_1\left(t|t_0\right)$ can be viewed as a certain conditional analogue of a “survival function”; its peculiarity is that its limit value can fail to reach zero at $t\to\infty$ as opposed to a true survival function. This situation is quite possible in case the examined cause of death is not a leading one as opposed to a set of competing causes of death. It will also occur in such cases when fatal potential of the examined cause of death is finite due to a share of people who are potentially prone to the examined diseases being also finite. These properties allow interpreting the parameters $1-\exp\left(-H_1\left(t|\ t_0\right)\right)$ and $H_1\left(t|t_0\right)$ in a way similar to a specific risk value and almost equate them numerically but only if the limit value of Nelson – Aalen estimator doesn’t exceed approximately ~ 0.1. Population cumulative mortality related to a specific localization of an oncologic disease practically always meets this condition [4]. However, for example, mortality due to all diseases of the circulatory system in a population usually overlaps this limitation and in that case $H_1\left(t|\ t_0\right)$ is not a risk assessment. $H_1\left(t|\ t_0\right)$ can also reach relatively high values among people treated in specialized clinics or departments since they are specifically admitted there for treatment. For example, the work [24] contains assessments obtained for a group risk of death caused by prostate cancer being up to $1-P_1 \approx 24\,\%$ and it corresponds to the limit value $H_1 \approx 0.27$ over a period of time exceeding 3,000 days. For comparison, cumulative risk of prostate cancer among men in Russia doesn't exceed 5.7 % over 75 years of life [4]. Risk rate $1-\exp\left(-H_1\left(t \mid t_0\right)\right)$ is usually abbreviated as RADS in radiation epidemiology [15, 16].

Construction principles and model parameterization. Bayesian interval statistic estimates. As was shown, estimation of cumulative rates for specific countries doesn't involve considerable technical difficulties; however, any detailed stratification of observations within factor space results in a decrease in a number of "cases" in each stratum and, accordingly, to a risk assessment becoming more and more uncertain. The only way to make assessment more exact and simultaneously preserve detailed description is to apply a unified approximating mathematical model for all strata simultaneously. Thus all the observed "cases" are included into calculations and it, provided there is relevant optimization, will allow achieving more steady risk assessments. It is exactly the role that should be played by a unified model for all strata. It should be dynamic, that is, suitable for all observations distributed as per time (age). Strictly speaking, this model should correspond to an essence of correlations between factors and risk rates; however, usually it is a research object by itself, that is, there is usually no such model until analysis is completed. In this case we can rely on expected similarity in dynamics of risk realization over time for different strata $h = h\left(t \mid \mathbf{z}, \boldsymbol{\beta}, Data\right)$ basing on already examined trends for parameters in a certain reference group. Here $\mathbf{z}$ is a risk factors vector; $\boldsymbol{\beta}$ is a relevant vector of adjustable model parameters. When examining oncologic effects, it seems advisable to use population parameters [4] and, basing on perturbation technique, to introduce a relation with risk factors and relevant parameterization into the description. For example, we can use the fact that most intensive parameters showing a risk of death due to analogue oncologic diseases are unimodal functions if they are taken in time dynamics; these functions are characterized with approximately power-law growth within a range of ages being 60–65 years with a drastic fall at an age exceeding 75 years.

If a continuous model $h\left(t \mid \mathbf{z}, \boldsymbol{\beta}, Data\right)$ to a certain extent is adequate to examined multiplicity of discrete empirical $Data$ countings, it is an attempt to dually describe the same events either directly via countings or within a space of parameters $\boldsymbol{\beta}$. Certain continuous conditional distribution of parameters over space will correspond to natural dispersion of observations over space. It will be interesting for interval estimation of multiple suitable parametric hypotheses if estimation procedures are given a probabilistic form.

Bayes' theorem is a suitable instrument for it since it allows linking these two above-mentioned types of conditional distributions:

$$\psi\left(\boldsymbol{\beta} \mid Data\right) = \frac{L\left(Data \mid \boldsymbol{\beta}\right) \cdot prior\left(\boldsymbol{\beta}\right)}{\int L\left(Data \mid \boldsymbol{\beta}\right) \cdot prior\left(\boldsymbol{\beta}\right) d\boldsymbol{\beta}} \qquad (7, 8)$$

или $\psi\left(\boldsymbol{\beta} \mid Data\right) \propto L\left(Data \mid \boldsymbol{\beta}\right) \cdot prior\left(\boldsymbol{\beta}\right)$.

Although Bayesian approach is considered to be a direct statistical competitor for a well-known maximum likelihood procedure, both approaches are organically related to each other. Here $L\left(Data \mid \boldsymbol{\beta}\right)$ is density of observations distribution for a fixed parametric model; $\psi\left(\boldsymbol{\beta} \mid Data\right)$ is density of model parameters distribution for collected observations; $prior\left(\boldsymbol{\beta}\right)$ is a priori distribution of parameters in a presumably relevant "hazard" model. In a sense of conditional distributions ψ is Bayes' likelihood; L is Fischer's likelihood, and an expected area of the most probable parameters lies close to a maximum likelihood point in the function L, at least in such studies where a result is unknown until experimental data have been analyzed. The relations (7, 8) would be quite strict if the a priori distribution $prior(\boldsymbol{\beta})$ were known; due to this an opinion is valid[5] that the concept of parametrically dependent likelihood is not identical to the concept of conditional probability density [25]. However, let us speak for Bayesian approach via mentioning that each new study, and especially a single one, is characterized with almost complete absence of pre-experimental knowledge due to which the function $prior(\boldsymbol{\beta})$ certainly has a significantly greater width than c $L(Data \mid \boldsymbol{\beta})$ as a function of parameters $\boldsymbol{\beta}$ in a certain significant area. Therefore it will not be a mistake to assume there is certain non-informative a priori distribution or even $prior(\boldsymbol{\beta}) \propto 1$ in a significant area. Then formally $\psi(\boldsymbol{\beta} \mid Data) \approx L(Data \mid \boldsymbol{\beta})$ and it is exactly what Ronald Fischer used and it still didn't prevent him from rejecting Bayesian approach completely in his publications [25]. This similarity of concepts developed within Bayesian and Fischer's likelihoods justifies considering constant parameters of likelihood function $L(Data \mid \boldsymbol{\beta})$ as adjustable model variables. What is considered a constant vector in frequentist concepts by Fischer and Pearson turns out to be a continuous random variable as per Laplas / Bayes under stricter consideration.

Let us point out the main thing here: likelihood for a set of strata due to their independence is simply equal to a product obtained via multiplying likelihoods for each homogenous stratum. Therefore, let us build likelihood for a separate homogenous stratum. To do that, we introduce our grid of time moments t_i within its limits and each node in this grid is bound to a specific event on a numerical axis showing age. The point t_0 corresponds to a beginning of observations. It is rather rare, that 2 or 3 such events occur in the same node simultaneously, therefore each semi-open interval $(t_{i-1}, t_i]$ between two neighboring nodes is related to its own quantity of accumulated specific cases m_i. Usually $m_i = 1$. Overall number of accumulated cases amounts to $M_i = \sum_{j=1}^{i} m_j$ by the examined moment of t_i.

Combined likelihood of observations over the whole sequence of specific events in the j-th stratum with a factor vector $\mathbf{z}_j$ as a chain of sequential transitions is

$$L_j = L(M_{i\max}, M_{i\max-1}, \dots, M_1 \mid \mathbf{z}_j, \boldsymbol{\beta}) = = 1 \cdot \prod_{i=1}^{i\max} p\left(M_i \mid M_{i-1}\right), \quad (9)$$

where

$$p(M_i \mid M_{i-1}) = = \frac{N_{i-1}!}{m_i!\ (N_{i-1} - m_i)!} (\pi_i)^{N_{i-1}-m_i} (1-\pi_i))^{m_i}. \quad (10)$$

Here we also introduce $\pi_i = \exp(-H_i)$ and $H_i = H(t_i \mid t_{i-1}, \mathbf{z}, \boldsymbol{\beta})$ where increases in cumulative risk intensity are integrals of model intensity function

$$H_i = H_i\left(t_i \mid t_{i-1}, \mathbf{z}, \boldsymbol{\beta}\right) = \int_{t_{i-1}}^{t_i} h\left(\tau \mid \mathbf{z}, \boldsymbol{\beta}\right) d\tau. \quad (11)$$

The likelihood (9, 10) is differential in its structure just as Fischer's conventional likelihood for independent events; however, it is not quite true. If we analyze partial likelihoods $L_i \sim \pi_i^{N_{i-1}-m_i} (1-\pi_i)^{m_i}$, we can easily note that they reach their maximum value at $\pi_i^{opt} = (N_{i-1} - m_i)/N_{i-1}$, that is, they satisfy to Kaplan – Meier procedure locally [22] at each i-th time step for a homogenous stratum. Therefore, using functional (9, 10) to its maximum can potentially result in interpolation of a cumulative parameter if we consider estimates $\hat{\pi}_i = \pi_i^{opt}$ to be interpolating model parameters. Naturally, the same property holds approximately in case there are fewer parameters within a considered vector $\boldsymbol{\beta}$ but with added filtrating property of likelihood as estimating functional. Therefore, this constructed

[5] Reference book on applied statistics. In: E. Lloyd, U. Lederman, eds. Moscow, Finance and statistics Publ., 1989, 510 p.

likelihood can simultaneously provide both differential and cumulative approximation (regression). Intensive rates are estimated analogically to numerical differentiation of a changing noisy function. Empirical data differentiation is a poorly grounded (incorrect) numerical operation. On the contrary, derivatives from a smoothed cumulative function are going to be more stable.

It is technically more convenient not to use drastically changing likelihood function $L(Data\,|\,\boldsymbol{\beta})$ or density function $\psi(\boldsymbol{\beta}\,|\,Data)$ but to operate with their doubled natural logarithm that is shifted against the ultimate saturation point (interpolation). Then, instead of searches near to a maximum in the expression (9) for one stratum, we should analyze the function

$$\Omega(\boldsymbol{\beta}|\,Data)= = 2\cdot\sum_i \left[\begin{array}{l} \left(N_{i-1}-m_i\right)\ln\left(\dfrac{N_{i-1}-m_i}{N_{i-1}\,\pi_i(\boldsymbol{\beta})}\right)+ \\ +m_i\,\ln\left(\dfrac{m_i}{N_{i-1}\left(1-\pi_i(\boldsymbol{\beta})\right)}\right) \end{array} \right] \quad (12)$$

close to its minimum. Contributions (12) are to be summed for the whole set of strata that are not empty. Ultimately in this case we can speak about achieved deviation (estimation functional)

$$\Omega_\Sigma(\boldsymbol{\beta})=\sum_j \Omega_j(\boldsymbol{\beta}|\,Data); \qquad \Omega_j(\boldsymbol{\beta}|\,Data)\geq 0. \quad (13)$$

According to well-known concepts [26, 27] that are typical for Fischer's approach, a value at which $\Omega_\Sigma(\boldsymbol{\beta})$ deviates from zero gives grounds for making judgments on quality and statistical significance of completed approximation; and models are to be selected basing on difference in achieved optimal values. If parametric deviation (13) is close to a quadratic one as per small offset from the center (that is, $\psi(\boldsymbol{\beta}\,|\,Data)$ is almost normal multidimensional distribution), then random scattering of $\Omega_\Sigma(\boldsymbol{\beta})$ near to the minimum is close to "chi-square" distribution with a number of degrees of freedom equal to difference between a number of grouped summands in (13) and a number of dimensions in the vector $\boldsymbol{\beta}$.

Bearing in mind that in practice parametric dependence of $L(Data\,|\,\boldsymbol{\beta})$ and $\psi(\boldsymbol{\beta}\,|\,Data)$ likelihoods can turn out to be far from multidimensional normal distribution, it seems advisable to complete an estimation algorithm as per a logic following the sequential continuation within Bayesian approach. It means transition to interval estimates based on multidimensional joint distributions (7, 8). However, together with sufficient strictness, Bayesian approach is highly labor-consuming and prone to accumulating computational errors related to direct calculation of multidimensional integrals with participating probability density $\psi(\boldsymbol{\beta}\,|\,Data)$ within the space of parameters $\boldsymbol{\beta}$. Given that, in practice it seems more realistic to apply multiple probability simulation (Monte–Carlo method) since it allows us to average functions or parameters that are being considered, together with assessing their marginal statistic properties, as per a great number of point pseudo-observations (~1 million or more) that comply with the distribution $\psi(\boldsymbol{\beta}\,|\,Data)$. This algorithm is also labor-consuming, but still, the most realistic one. It is implemented in practice via several ways and one of them, Gibbs' algorithm, is based on well-known theoretical grounds [28]. Herewith estimates of a distribution center as per maximum likelihood method in case density $\psi(\boldsymbol{\beta}\,|\,Data)$ is unimodal can be relevant initial approximation for building up a stochastic sequence of pseudo-observations.

Results obtained via assessing risk rates in a heterogeneous cohort with previously known properties. Let us consider an artificially created epidemiologic register that describes a certain "etalon" cohort with events not being random in it and complying with a previously known model. Choice on imitation data instead of actual ones is preferable in this case since there is no actual register with risk research results obtained for it certainly coinciding with exact and previously known rates. Since only determinate imitation of stochastic behavior by participants may occur in an artificial cohort, we should expect that zero or almost zero deviation (13) would probably be reached numerically. In other words, we are to give a practical answer to a question whether the examined estimation algorithm has asymptotic convergence. This question concerns not only the examined algorithm but also its prototype, AMFIT algorithm within Epicure software package, although it has never been checked before.

Let us consider a radiation-epidemiologic study with the following underlying characteristics as an example. We construct an imitation sampling made up of distinctly limited homogenous strata that differ as per a gamma-irradiation dose (from 0 to 2 Sv), sex, and age. We consider a cumulative radiation dose to be a risk factor and this dose is a result of single acute even irradiation of the lungs that occurred at an age of 19. Our basic reasons for changes in oncologic mortality are a) conditionally linear growth in such cumulative rate as intensity of a risk of death caused by lung cancer with a growth in a dose that is known and limited as per its value; b) a certain decrease in life expectancy for all irradiated members in the cohort; c) sex as a heterogeneity factor that results in both background risk parameters being different for men and women and differences in sensitivity to radiation. Such cause-and-effect relations are well known due to a series of studies on an actual cohort made of people who survived atomic bombing in Hiroshima and Nagasaki [29, 30]. Figure 2 shows a fragment of a diagram (men) with rough estimates of annual risks as per a typical scheme for a three-factor "etalon cohort" (sex, dose, and age). Overall there were 25,000 individual entries in the database (15,000 men and 10,000 women). Overall number of death cases caused by specific cancer providing the cohort totally died out amounted to 1,118 (995 cases among men and 123 cases among women). Overall period of observation over the cohort amounted to 1,031,414 person-years. If we group the participants as per 14 age intervals, 2 sexes, and 5 dose levels, we obtain $14 \cdot 2 \cdot 5 = 140$ homogenous strata. Only 91 out of them turned out to contain non-zero number of specific cancer cases. Non-empty strata corresponded to 754,106 person-years of observation.

It seems obvious that in case there are no random fluctuations in sampling parameters in this "etalon cohort", dose- and age-trends in Figure 2 are to be visible to the naked eye. Simultaneously quantitative regularities for background risk rates fully correspond to population ones [4]. An expert who studies risks should "see" all the preset detailing. So what results can be yielded due to the suggested algorithm and its closest prototype?

The suggested procedure for estimating changes in cumulative and intensive rates turns out to be quite efficient for solving the task; we can see it in Figures 3 and 4, both for women sub-cohort and men sub-cohort within the unified parametric model ($\boldsymbol{\beta} \in R^8$).

Calculated minimum deviation $\Omega_{\min}$ for the computed extreme solution amounted to only 0.40 units in this case given a significant increase in component "observations" as per Kaplan – Meier and a growth in a number of degrees of freedom in comparison with traditional preliminary grouping with applying 5-year age intervals (Figure 2). It, if recalculated

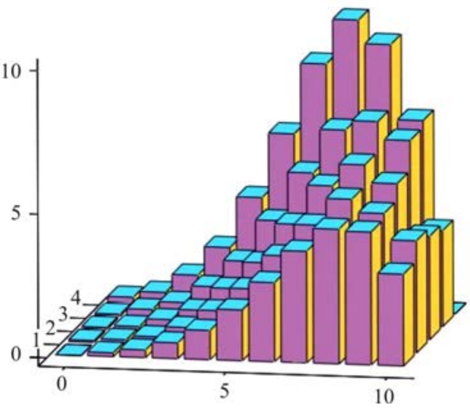

Figure 2. Three-dimensional diagram "age-dose-rate" for men in the "etalon cohort". Horizontal axes show age strata (14) and dose strata (5). Vertical axis shows rough estimates of specific mortality rate within a stratum (‰ per year)

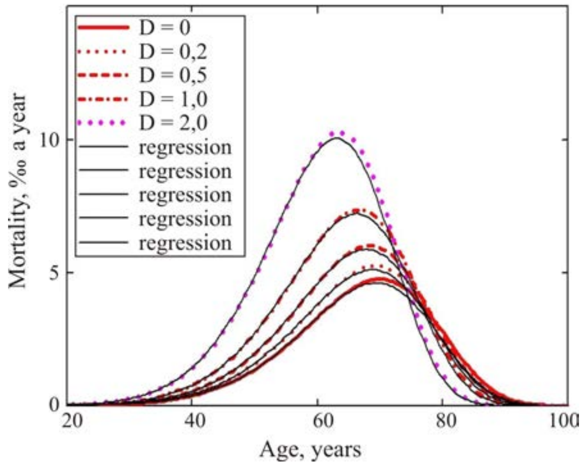

Figure 3. Dynamic dependences for specific mortality rates among men in "etalon cohort" preset and estimated as per binomial regression algorithm

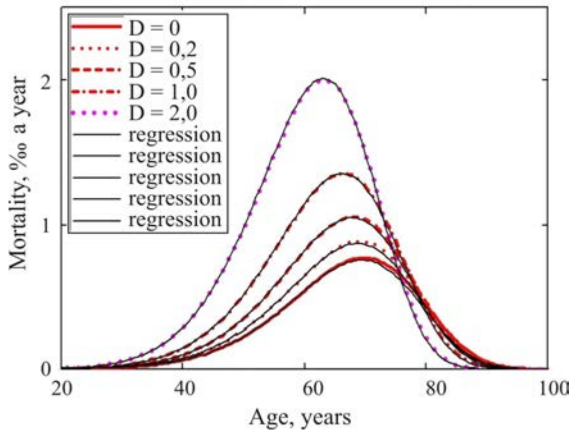

Figure 4. Dynamic dependences for specific mortality rates among women in "etalon cohort" preset and estimated as per binomial regression algorithm

per 1 case out of 1,118, approximately corresponds to visually observable standard mean-root square deviation in estimated "hazard" rates being about $\sqrt{0.40/1118} = 0.019 = 1.9\,\%$. Residual deviation $\Omega_{\min}$ didn't reach exact zero and it indicates that it is impossible to overcome discrete nature of entries in the sampling database in comparison with continuous nature of parameters in an actual general population. However it is hardly possible to further reduce this deviation. Coefficients for a dose trend in cumulative value of the accumulation intensity of the excess lifetime risk and its uncertainty assessed as per Fischer's information matrix

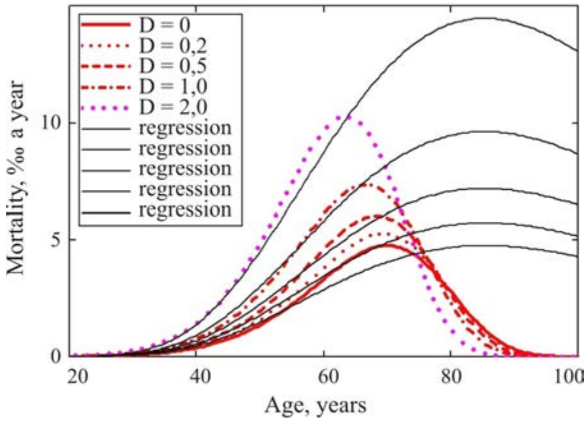

Figure 5. Results obtained via AMFIT-estimates of does and age trends in specific risk compared to its actual behavior for men sub-cohort. Obviously, a typical model [9, 10, 31–33] showing background and examined risks behavior is a source of systemic deviations in all estimates

amounted to $0.49\,Gy^{-1}$ $(95\%\,\text{CI}: 0.24 \ldots 0.99)$ for men and $0.68\,\text{Gy}^{-1}$ $(95\%\,\text{CI}: 0.33 \ldots 1.35)$ for women. We should pay attention to significant uncertainty that still occurs although achieved deviation is extremely low. It occurs due to dimensions of uncertainty area being extremely dependent on function (13) curving close to the extremum and not on its reached minimum value since confidence intervals are estimated in such ways so that countings in the "etalon cohort" were still prone to random fluctuations to the same extent as if they were real ones. It is the basic difference between binomial regression and regression as per least-squares procedures.

Unlike the obtained results, AMFIT procedure, when applied within its typical group of models [9, 10, 31–33], showed significant systemic deviation in annual risks in older ages areas (Figure 5, men sub-cohort). Only ascending parts in the curves can be approximated properly. Also models within this algorithm turned out to fail "to see" probable intersections between group of "hazard" curves related to a certain decrease in life expectancy of irradiated people.

Observed minimum deviation (the formula 13) amounted to 24.3 units for computed extreme solution with a number of degrees of freedom being 85 (a number of strata minus a number of parameters). Given this number of degrees of freedom, 90 % -interval of expected random minimum deviation occurrence that is seemingly [26] distributed as per "chi-square law" should amount to 64.7 … 107.5. Therefore, the observed value 24.3 is less statistically significant than a typical random value. This observable overfitting practically assuredly indicates that this "etalon cohort" is an artificial one. However, it is rather surprising that Ω_{min} deviated from zero significantly; it is obviously due to absurd systemic bias of $h(t|\ D, sex, \mathbf{\beta})$ in an area with ages exceeding 75 years and even 100 years for all dose exposures. Actually reached significance p ~ 10^{-11} formally indicates there is extremely low probability that a model will deviate from data, but it corresponds to an actual situation only in an area where risk intensity grows rapidly (Figure 5) but not in a wide range of ages. Since all curves showing annual risks have been biased, the same has happened to dose trends. For example, annual parameter $h(t|\ D, sex, \mathbf{\beta})$ for men aged 60 years moved at a rate of changes in a dose being $\approx 82\,\%\ \text{per}\ 1\,\text{S}v$, and it is almost 3 times higher than a dose trend parameter for cumulative lifetime value determined via the previously examined algorithm under the same conditions. Discrepancy between these two types of relative trends and, consequently, the necessity to distinguish between them has also been mentioned by other authors [34]. Therefore, AMFIT can be prone to overestimating effects produced by irradiation. In some cases use of annual parameters may also result in actual (cumulative) risks being underestimated [31]. Potential basis for such errors is obvious in Figures 3 and 4.

Algorithm for assessing risks in a heterogeneous cohort: discussing advantages and drawbacks. Let us mention the basic aspects in which our algorithm for risk measuring differs from its analogues and primarily from its prototype, AMFIT algorithm. First of all, countings of all examined specific events are considered to be binomial processes in the suggested algorithm, and cumulative and intensive rates are determined on probabilistic basis and not as heuristic values. It allows using risk assessment as a procedure for indirect measurements of continuously-distributed parameter estimates basing on Bayesian approach. As opposed to that, both AMFIT algorithm, and some other algorithms that are not so frequently applied [35–38] are based on point estimate of the whole set of events and smooth approximation of obtained non-smooth empiric distributions within Pearson and Fischer's frequency-discrete statistic paradigm.

These mentioned alternative approaches to risk assessment have obvious but frequently neglected drawbacks together with mathematical simplicity in comparison with process assessment. For example, an actual intensive risk is not either constant or a set of constants as it would be stated within Poisson's statistics. Owing to it, a role played by inaccuracy related to stratification of a heterogeneous cohort as per age is not clear. Too small age intervals can results in cases disappearing in them for cohorts that are small in volume and Poisson's regression functional can lose its extreme properties in that case. Too large intervals, on the contrary, will result in groundless averaging of risk accumulation intensities within an interval. It is difficult to set an optimal width for intervals in advance when performing stratification as per age. A similar drawback of Poisson's regression becomes obvious as a cohort dies out and a number of specific cases tends to zero. What boundary in age distribution should we stop at? Binomial law for event distribution would be more relevant here since Poisson's law arises from it asymptotically as a partial statistical model for rare events.

We should also note that a quality of approximation $h(t|\ D, sex, \mathbf{\beta})$ for describing exposure to radiation depends on how well this function operates in case there is no external influence ($D = 0$). Here we speak about this exact reference group which is an integral component in any comparative study. This nuance is often neglected by researchers [32, 33] since they rely on simple models for power-level growth or models with saturation. Formally it means that background life-long cumulative intensity can reach very high values or approach infinity and a specific risk of death due to the examined cause reaches 1. However, there are no such diseases in reality as it can obviously be seen already at a stage when data are being grouped preliminarily (Figure 2). Such data have already been successfully taken into account in models showing intensive risk parameters in dynamics within Bayesian studies on limited samplings with an incomplete period of observation and data losses, for example as per such procedures as "right censored spell models" [39], "cure rate models" [40], "bounded cumulative hazard models" [41]. Moreover, we can justly assume that a shift in estimates in Figure 5 is predominantly related to improper background risk model and not only to the nature of the process being neglected and a statistic law being selected incorrectly. We should also note that such a parameter as *p-value* that is determined via testing likelihoods is not always a reliable reference point when approximation quality is assessed in a multidimensional case.

All the above mentioned doesn't mean that the newly suggested procedure for risk assessment is an ideal researcher's tool. Recall that it is based on such cohort stratification that doesn't provide for cohort members going from one stratum into another during an observation period. Should such transition appear, strata can't be considered independent and it means that functional of probabilistic estimation should be built on other grounds. Another vulnerability is that factor space is not completely covered with available observations; this vulnerability is typical for any empiric sampling. CONSORT standards [42] cover any sampling studies. Even if there is a strong correlation in one pair of factors, effects produced by one of them can be disguised by seeming effects produced by another. Due to that, if we want to assess processes successfully, we should either work with sufficiently large and diverse samplings, or we should examine correlations between risks and factors via a controlled experiment.

It is important to note that this paper doesn't promote any theory in the sphere of analytical epidemiology. We merely suggest one instrument for practical analysis within a "dose – time – risk" mental scheme instead of a conventional limited approach "dose – risk" since the latter imposes interpreting harm caused by external influences only as simple one-dimension dependence in a plain two-axis graph. Indeed, a simplifying "dose – risk" concept can create artifacts in a form of false trends that are hard to explain. Interpretation of a radiation-oncologic trend which we took form the document [43] is a good example.

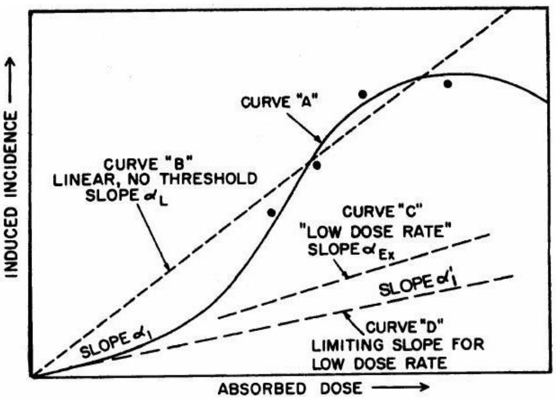

Figure 6. Schematic behavior of excessive risk depending on a radiation exposure dose as expected by BEIR VII experts. Taken from the report [43]

This graph obviously shows a non-linear response in excessive intensity of specific events with a clear non-monotonous drop in an area of large doses. This trend can't be plausibly explained either within a well-known liner non-threshold model or within well-grounded linear models. However, it should be noted that if "intensity" is used instead of "risk", this graph can be linked to only one age group in the cohort. In this case it is easy to reveal that a dose trend shown in Figures 3 and 4 looks exactly like this within age range from 60 to 65 years with a typical drop and even a change in a sign of "excessive" effects in older age groups. And here cumulative risk grows only monotonously with a growth in a cumulative dose. Here we should also remember that a well-known linear-non-threshold "dose – effect" model by N.V. Timofeev-Ressovskiy and K.G. Zimmer [44, 45] was developed exactly for a pair of cumulative values, an analogue of the Nelson – Aalen estimator being one of them long before this estimator was invented. An author who developed a well-known "effective dose" concept [46] had similar opinions about a sphere where cumulative parameters could be successfully applied.

Conclusion. Therefore, it seems quite promising to analyze dynamics of specific events occurrence in a heterogeneous cohort combined with Bayesian methodology for risk assessment provided that researchers have detailed information about cohort members collected during a sufficiently long period of time or even in a life-long observation and complete and comprehensive description of individual risk factors. Applied computation technique is within conventional epidemiologic procedures for health risk assessment since it combines application of annual group risk rates together with cumulative ones. It has been shown that when experts try to predict damage caused by external influence on people's health within conventional "dose – effect" mental schemes, they should preferably rely on a combination of cumulative doses and cumulative risks or their descriptive analogues (effects).

But at the same time we can't fail to mention that using the described parametric version of Bayesian procedures is rather labor-consuming. This drawback can be partially overcome only via creating relevant software[6] that is able to provide automatic tools for grouping data, selecting models, searching for extreme solutions, and modeling statistic uncertainty of Bayesian estimates.

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Research article

ASSESSING HEALTH RISKS ASSOCIATED WITH DRINKING WATER QUALITY (ON THE EXAMPLE OF REGIONS IN BASHKORTOSTAN WHERE OIL FIELDS ARE LOCATED)

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Providing population with drinking water conforming to all hygienic standards is a pressing issue on territories where oil fields are located. In our research we focus on assessing water supply sources located in areas with oil fields and health risks for people who consume water from centralized water supply systems aimed at providing drinking water and water for communal use.

Our research goal was to hygienically assess health risks for people living in areas where oil fields were located in Bashkortostan; these health risks were caused by people consuming water from centralized water supply systems.

Our analysis was based on data obtained via laboratory research performed by «Bashkommunvodokanal» water supply facility and Bashkortostan Center for Hygiene and Epidemiology; the data were collected in 2016–2018 in Chishminskiy and Dablekanovskiy districts. Risks associated with drinking water quality were assessed taking into account all the requirements fixed in the Guide R 2.1.10.1920-04. Organoleptic risks related to water olfactory-reflex properties were assessed according to procedures fixed in the Methodical Guidelines MR 2.1.4.0032-11.

Overall carcinogenic health risk assessed in Chishminskiy and Davlekanovskiy districts was higher than maximum permissible level due to chromium^{6+}, DDT, lindane and arsenic detected in drinking water. Population carcinogenic risks amounted to 7 additional cases for people who consumed water supplied via water intake in Alkino-2 settlement; 69 additional cases, Isaakovskiy water intake; 76 additional cases, Kirzavodskoy water intake.

Results obtained via non-carcinogenic risk assessment performed for all examined territories indicate that diseases might occur in the hormonal system (HQ =3.04–4.56), liver (HQ =2.3–3.83), and kidneys (HQ =1.47–2.45). The highest non-carcinogenic risks were detected for people who took water from Kirzavodskoy water intake in Davlekanovskiy district.

We also detected unacceptable organoleptic risk (higher than 0.1) caused by excessive water hardness in Chishminskiy district.

All the obtained results call for developing and implementing a set of activities aimed at reducing health risks for population.

Key words: *health risk assessment; carcinogenic risk, non-carcinogenic risk, organoleptic risk, oil extracting industry, water supply, «Clean Water » Federal project, health risk, industrial enterprises, population health, drinking water.*

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Providing population with drinking water that meets all hygienic requirements is of vital importance in areas with oil extraction, treatment and transportation [1, 2]. This is due to the fact that in these areas water intended for communal use and drinking does not meet hygienic standards [2, 3] as per a number of factors, such as hardness, manganese, iron, copper, chromium, lead, cadmium concentrations, etc.

When oil fields are exploited, aquifers are known to be adversely affected and many toxicants penetrate into ground and surface water objects. Thus, the quality of the water used for communal needs and drinking deteriorates [1–4]. For example, in the Khanty-Mansiysk Autonomous Okrug – Yugra [5], in areas with oil fields, drinking water does not meet the established hygienic requirements. Water in certain districts contains certain compounds in concentrations exceeding maximum permissible ones (MPC) including oil products (up to 2.4 times), chlorides (up to 3.9 times), bromides (up to 2.2 times), lead (up to 2 times), and cadmium (up to 3 times). In surface springs located in Perm region (Kokuyskoye oil field) [3], such compounds as xylene (up to 14 times), oil products (up to 13 times), and toluene (up to 3 times) are detected in concentrations exceeding MPC. In Saratov and Orenburg regions, underground water sources deviated from hygienic standards as per oil products, manganese, iron, total hardness, oxidability, mineralization, nitrogen and bromine compounds [6, 7].

Environmental risk assessment allows identifying primary pollutants and making decisions concerning public health. Thus, studies carried out in various regions in the Russian Federation [8–13], as well as in foreign countries [14–18], indicate that there are existing population health risks associated with drinking water quality.

People's right to have access to high-quality drinking water that meets current requirements fixed in hygienic standards is envisaged in the Federal project "Clean Water" of the national project "Ecology"[1]. Implementation of the project involves considering issues related to water treatment and problems with maintaining quality of drinking water in distribution networks in the existing systems. In case people live settlements that are not equipped with modern piped water supply systems[2], the project envisages developing a water supply network using advanced water treatment technologies including those developed by military-industrial complex.

The purpose of the study was to perform hygienic assessment of health risk levels associated with the use of water from centralized water supply sources for population living in oil extraction areas located in the Republic of Bashkortostan (RB).

Data and methods. The study comprised two largest oil extraction districts in the Republic of Bashkortostan, Chishminsky and Davlekanovsky. The analysis was based on research materials collected in 2016–2018 and obtained from the laboratories of "Bashkommunvodokanal" and the Center for Hygiene and Epidemiology in the Republic of Bashkortostan in Chishminsky and Davlekanovsky districts. Totally, we analyzed twenty indicators for territories with developed oil industry, including 16 sanitary and chemical (Table 1) and 4 microbiological ones (total coliform bacteria, thermotolerant coliform bacteria, coliphages and total microbial count).

At present, there are 3 main water intakes in Chishminsky district: Isakovsky, Kuchumovsky and Nizhnehozyatovsky. The study was performed at the largest one, Isakovsky, which supplies water to an urban-type settlement of Chishmy and adjacent rural settlements (Ignatovka village). There are 30 operating

[1] Official site of the Ministry of Construction, Housing and Utilities of the Russian Federation. Profile of the Federal Project "Clean Water". Available at: https://minstroyrf.gov.ru/upload/iblock/9a0/88020e9ed93742b78845763a395cd20e.pdf (December 01, 2020).

[2] Official website of the Government of the Republic of Bashkortostan. Profile Of the Federal Project "Clean Water". Available at: https://pravitelstvorb.ru/ru/natsionalnoe-razvitie/natsionalnye-proekty/g5.pdf (December 01, 2020).

Table 1

Findings on hazard rates for non-carcinogenic and carcinogenic effects development

Substance	RFD	Organs and systems	SFO
Anionic surfactants	–	–	–
Oil products	0.03	Kidneys	–
Ammonia	0.98	–	–
Total iron	0.3	Mucous membranes, skin, blood system, immune system	–
DDT	0.0005	Liver, hormonal system	0.34
Lindane	0.0003	Liver, kidneys, hormonal system	1.3
Arsenic	0.0003	Skin, central nervous system, cardiovascular system, immune, hormonal system, gastrointestinal tract	1.5
Chrome $^{6+}$	0.005	–	0.42
Copper	0.019	Gastrointestinal tract, liver	–
Manganese	0.14	Central nervous system, blood system	–
Lead	0.0035	Central nervous system, blood system, biochemistry, development processes, reproductive system, hormonal system	0.047
Mercury	0.0003	Immune system, kidneys, central nervous system, reproductive system, hormonal system	–
Cadmium	0.0005	Kidneys, hormonal system	0.38
Cyanides	0.02	Nervous system, hormonal system	–
Chlorines	–	–	–
Hardness	–	–	–

Note: compounds with carcinogenic properties are highlighted in bold.

wells in the Isakovsky water intake. Alkino-2 is a village in Chishminsky district, where 1 water intake with 5 wells is currently operating. Bactericidal lamps are installed for water disinfection.

Communal and drinking water is supplied in Davlekanovsky district from underground via 3 water intakes, Kirzavodsky, Kurmankeyevsky and Yuzhny. The study was performed at Kirzavodsky water intake, which consists of 7 wells. Water is disinfected with bleach.

Carcinogenic, non-carcinogenic and population risks were assessed taking into account the conditions and requirements stipulated in the Guide R 2.1.10.1920-04[3]. To calculate carcinogenic and population risks, we made up a list of 6 compounds from groups 1, 2A, 2B according to the classification by the International Agency for Research on Cancer (IARC) (Table 1). In order to predict risks in case there were no concentrations of certain chemical compounds, we used a 1/2 of the quantitative determination limit for a chemical compound. This technique is allowed by the risk assessment methodology. Risk acceptability was determined to be within $1\cdot10^{-6}$–$1\cdot10^{-4}$.

Organoleptic properties of drinking water were hygienically assessed basing on the MR 2.1.4.0032-11[4], and the list of indicators (Table 2) was selected given the limiting hazardous indicators according to SanPiN 1.2.3685-21[5]. According to MR 2.1.4.0032-11, the acceptable risk was equal to 0.1.

Risks related to olfactory-reflex properties of drinking water are calculated according to equations (1 and 2) taken from MP 2.1.4.0032-11:

$$\text{Risk} = \left(\frac{1}{\sqrt{2\pi}}\right)\cdot\int_{-\infty}^{\text{Prob}} e^{\frac{-t^2}{2}}\cdot dt \qquad (1)$$

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[3] R 2.1.10.1920-04. Guidelines for assessing health risks caused by exposure to chemicals that pollute the environment. Moscow, 2004. 143 p.

[4] MR 2.1.4.0032-11. Integral assessment of drinking water in centralized water supply systems as per chemical safety indicators. Moscow, Federal Service for Supervision of Consumer Rights Protection and Human Welfare Publ., 2011, 32 p.

[5] SanPiN 1.2.3685-21. Hygienic standards and requirements for ensuring safety and (or) harmlessness of environmental factors to humans. *KODEX: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573500115 (December 03, 2020).

where π = 3,14 ……..; *e* is the base of the natural logarithm; *d* is differential sign; *t* is the confidence factor.

$$\text{Prob} = -2 + 3{,}32 \cdot \lg (\text{Concentration / standard}) \qquad (2)$$

Results and discussion. Having analyzed data obtained via monitoring observations over drinking water quality (Table 3), we have revealed that water supplied to population on certain territories doesn't meet hygienic requirements. There is evidence that hygienic standards are violated regarding sanitary and chemical indicators (water hardness), as well as detected salts of heavy metals and compounds from the pesticide group. However, there are no deviations in other indicators, including microbiological ones, in the drinking water in the examined areas.

An assessment of individual carcinogenic risks (Table 4) has identified four compounds with their contents being higher than maximum permissible risks: chromium^{6+}, DDT, lindane and arsenic. They are classified as being within the third risk range. Lead and cadmium concentrations correspond to the second risk range (maximum permissible risk).

Table 2

Primary indicators for organoleptic assessment

Indicator	MPC	Criterion
Manganese	0.10	Organoleptic
Copper	1.0	Organoleptic
Total iron	0.3	Organoleptic
Chlorines	350.0	Organoleptic
Total hardness	7.0	Total indicator

Table 3

Percentage of unsatisfactory water samples by main indicators in oil extraction areas in the Republic of Bashkortostan over 2016–2018 (according to "Bashkommunvodokanal")

Territories	Fraction of samples that do not meet the established requirements (%)			
	Before entering the distribution network		Water supply network	
	1*	2**	1*	2**
Davlekanovsky	17.25	0	16.56	0
Chishminsky	21.43	0	16.67	0

Note: 1 * means sanitary and chemical indicators; 2 **, microbiological indiactors.

Total carcinogenic risk rates for population health associated with drinking water in Chishminsky and Davlekanovsky districts are equal to 1.3E-03 and 1.9E-03, which corresponds to the fourth risk range and is unacceptable for all population groups. The analysis of the obtained results has shown that the greatest contribution to total carcinogenic risk rates is made by the following compounds: lindane (43.64–47.5 %), arsenic (16.21–24.16 %), chromium^{6+} (17.53–23.7 %) and DDT (11.7–12.4 %). We should also note that the leading contribution to carcinogenic risks is made by such priority compounds as those from the pesticides group (DDT and lindane).

Population carcinogenic risk rates were equal to 7 additional cases for people using the water intake in Alkino-2; 69 additional cases, Isakovsky water intake; and 76 additional cases, Kirzavodsky water intake. These population carcinogenic risks rates reflect the additional (to the baseline) number of cases of malignant neoplasms that can occur throughout life (70 years) due to exposure to carcinogenic compounds containing in drinking water. Carcinogenic risk rates show only a tendency towards a change in the oncologic background which is possible under certain conditions.

The results obtained via assessing non-carcinogenic risks in chronic oral exposure to priority chemical compounds contained in drinking water are presented in Table 5. The first rank place belongs to the hazard index for the hormonal system (HQ = 3.04–4.56) due to lead, DDT, lindane, arsenic and cadmium; the second place, changes in the liver (HQ = 2.3–3.83), associated with DDT and lindane. Changes in the kidneys (HQ = 1.47–2.45) caused by oral exposure to toxicants occur due to presence of lindane and cadmium in drinking water. The highest non-carcinogenic risks have been identified at Kirzavodsky water intake in Davlekanovsky district.

Table 4

Carcinogenic risks for population associated with concentrations of carcinogenic hazardous compounds in drinking water

№	Indicator	Carcinogenic risk (CR)		
		CWR*, Isakovsky water intake	CWR, Alkino-2	CWR, Kirzavodsky water intake
1	Lead	3.02E-05	3.02E-05	1.8E-06
	Contribution (%)	2.35	2.35	0.1
2	Chrome $^{6+}$	2.25E-04	2.25E-04	4.6E-04
	Contribution (%)	17.53	17.53	23.7
3	DDT	1.5E-04	1.5E-04	2.41E-04
	Contribution (%)	11.7	11.7	12.4
4	Lindane	5.6E-04	5.6E-04	9.23E-04
	Contribution (%)	43.64	43.64	47.5
5	Arsenic	3.1E-04	3.1E-04	3.15E-04
	Contribution (%)	24.16	24.16	16.21
6	Cadmium	8.0E-06	8.0E-06	1.5E-06
	Contribution (%)	0.62	0.62	0.08
Total carcinogenic risk		1.3E-03	1.3E-03	1.9E-03
Population carcinogenic risk (PCR)		69.0 (per 53037 people)	7.0 (per 5424 people)	75.6 (per 39812 people)

N o t e : * means here and further CWR is clean water reservoir.

Table 5

Non-carcinogenic risks (hazardous indices) related to drinking water quality

№	Organs and systems	(HQ) Non-carcinogenic risk		
		CWR, Isakovsky water intake	CWR, Alkino-2	CWR, Kirzavodsky water intake
1	Central nervous system	0.7	0.7	0.72
2	Liver	2.3	2.3	3.83
3	Kidneys	1.47	1.47	2.45
4	Gastrointestinal tract	0.7	0.7	0.71
5	Cardiovascular system	0.7	0.7	0.71
6	Skin	0.7	0.7	0.71
7	Hormonal system	3.04	3.04	4.56
8	Reproductive system	<0.1	<0.1	<0.1
9	Immune system	0.7	0.7	0.71
10	Blood system	<0.1	<0.1	<0.1
11	Biochemical changes	<0.1	<0.1	<0.1

Given numerous complaints from people about drinking water having bitter taste, an organoleptic risk analysis was carried out (Table 6). The results obtained revealed an unacceptable level of organoleptic risk (more than 0.1) associated with increased hardness of drinking water at Isakovsky water intake in Chishminsky district. In all areas, hardness exceeded hygienic standards by 1.14–2.11 times.

Basing on all obtained data, total carcinogenic risk for people using water from Isakovsky and Alkino-2 water intakes was 1.3E-03 and it was within the fourth risk range (unacceptable for all population groups). We also revealed an unacceptable level of organoleptic risk associated with elevated hardness of drinking water at Isakovsky water intake.

According to data provided by the Bashkortostan Rospotrebnadzor Office in 2018, population health in Chishminsky and Davlekanovsky districts is characterized with morbidity with certain diseases being higher than on average in the Republic: urolithiasis among the adult population, up to 2 times higher and

Table 6

Assessment of organoleptic risk related to drinking water quality

Indicator	Value	Prob.	Risk
CWR, Isakovsky water intake			
Manganese	0.052	-2.91	0.0018
Copper	0.01	-8.64	2.81E-18
Total iron	0.05	-4.656	1.61E-06
Chlorides	33.8	-5.35	4.4E-08
Total hardness	11.76	-1.253	0.105
Maximal values	–	-1.253	0.105
CWR, Alkino-2			
Manganese	0.05	-2.996	0.0014
Copper	0.01	-8.64	2.81E-18
Total iron	0.05	-4.656	1.61E-06
Chlorides	31.7	-5.47	2.25E-08
Total hardness	11.45	-1.3	0.097
Maximal value	–	-1.3	0.097
CWR, Kirzavodsky water intake			
Manganese	0.085	-2.234	0.013
Copper	0.025	-7.318	1.26E-13
Total iron	0.05	-4.59	2.22E-06
Chlorides	40	-5.127	1.5E-07
Total hardness	21.14	-0.4064	0.34222
Maximal value	–	-0.4064	0.34222

Table 7

A set of measures within the "Clean water" Project implementation

№	Measures	Measures within the "Clean water" project, recommended and being implemented at the moment
1	Technological and technical	– Reconstruction of a water supply network in Chishmy settlement
2	Sanitatary and technical	– Construction of a drinking water purification system in the town of Davlekanovo – Improving sewage treatment and avoiding the discharge of untreated sewage – Application of additional methods for water softening – Industrial control over water quality in water intake and before it enters distribution networks
3	Administrative	– Industrial control over technical conditions of water intake facilities – Clinical examination and medical check-ups of population among risk groups (children, pregnant women and the elderly) as per the detected diseases.

for children, more than 2.5 times higher; there was also a high growth rate for this nosology between 2014 and 2018. Also, there was a 19.7 % increase in mortality rate caused by neoplasms within the analyzed period.

The results obtained are very similar to other studies published by several authors [21–25]. However, it is necessary to take into account natural peculiarities and priority contaminants typical for each area.

Given all the obtained data, we have developed a set of measures (Table 7) aimed at minimizing risks associated with the quality of drinking water in the Republic of Bashkortostan within the framework of the "Clean water" Project implementation.

When these works are completed, it is advisable to re-conduct research in order to determine whether the accomplished activities have been truly effective.

Conclusions:

1. The total carcinogenic risks for both Chishminsky and Davlekanovsky districts have been assessed as unacceptable due to the presence of chromium^{6+}, DDT, lindane and arsenic compounds in water.

2. High non-carcinogenic risks have been identified at Kirzavodsky water intake in Davlekanovsky district. The presence of basic compounds in water can lead to chronic diseases of the hormonal system, liver and kidneys.

3. The organoleptic risk at Isakovsky water intake in Chishminsky district is characterized as unacceptable due to elevated hardness of drinking water.

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Research article

ANALYZING HEALTH RISKS CAUSED BY CONTAMINATED DRINKING WATER (EXPERIENCE GAINED IN SAMARA REGION)

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Environmental contamination is still a pressing issue, in particular, contaminated drinking water sources and contaminated drinking water from centralized communal water supply systems, since it produces negative effects on human health.

Our research goal was to estimate probable impacts exerted on overall morbidity in Samara by quality of drinking water taken from centralized communal water supply systems as a most significant environmental factor. Our research tasks included taking and analyzing drinking water samples from centralized communal water supply systems; calculating carcinogenic and non-carcinogenic health risks caused by analyzed chemicals.

To fulfill the tasks and achieve the goals, in 2018–2019 we performed sanitary-chemical analysis of drinking water quality as per 20 sanitary-chemical parameters; our research object was drinking water taken from centralized communal water supply systems in 7 districts in Samara. Obtained actual data on contamination of water taken from centralized water supply networks in Samara were used as primary basis for calculating hazard indexes and carcinogenic risk coefficients using conventional exposure scenarios.

In our research we revealed that maximum total non-carcinogenic hazard quotient was determined by arsenic and petroleum products introduction. Assessment of carcinogenic risks caused by contaminants in drinking water revealed that total health risk for children younger than 18 was within the second range as per its median; total carcinogenic risks for adults, within the third range. At the same time, arsenic contents did not exceed hygienic standards in all examined samples.

So, we assessed carcinogenic and non-carcinogenic risks, basing on actual data on quality of drinking water taken from centralized communal water supply systems. It seems vital to perform a wider-scale controlled study in several regions in order to assess significance of revealed factors for morbidity among population.

Key words: *centralized communal water supply, carcinogenic risks, non-carcinogenic risks, sanitary-chemical analysis, ecological monitoring, petroleum products, heavy metals, drinking water.*

The environment produces variable effects on a human body. As per data obtained via epidemiologic observations, environmental contamination influences prevalence of various diseases as well as their severity [1]. Considerable share of overall disease burden is environmentally induced since practically the whole range of technogenic emissions is made up of toxicants that are able to produce acute or chronic effects on a body depending on a dose. Sub-threshold and thresholds impacts exerted by chemical factors occurring due to anthropogenic contamina-

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tion are of special concern since they may cause non-specific pathological processes [1].

Most part of population living on urban territories is to a certain extent exposed to anthropogenic factors. Ecologic and hygienic conditions existing in different republics, regions, and autonomous areas are, on the one hand, determined by specific local natural and climatic conditions and, on the other hand, by essence and scale of impacts exerted by industry, transport, agriculture, and communal activities on the environment [1, 2].

At the same time, impacts exerted by most chemicals on health when various occupational activities are performed have been studied quite profoundly; but as for scales and gravity of consequences caused by chronic exposure to anthropogenic (and natural) contaminants occurring in the environment in insignificant (trace) quantities, they are being actively examined at the moment [2].

As per data provided by the WHO European Regional Office, ambient air contamination with chemicals is a priority risk factor that causes mortality and overall morbidity; this contamination can cause untimely death due to ischemic heart disease, stroke, chronic obstructive lung disease, oncologic diseases, etc. [1]

However, world ecological priorities also include studies on sanitary-chemical conditions of water sources and drinking water which is an integral part of any proper life activity. Chemical contamination of drinking water can contribute into chronic diseases occurrence and development including neoplasms, gastrointestinal disorders, disorders of the nervous system etc. [2–5].

There were epidemiologic examinations performed with participating children who lived in settlements where chlorinated organic compounds occurred in excessive quantities in drinking water; these examinations revealed that almost in 100 % children's biological media contained chloroform and it was detected practically on each examined territory; also, 1,2-dichloroethane was detected in some settlements (12.5 % cases). Both these substances are carcinogenic.

Diseases caused by poor quality of drinking water can also occur in a body due to disturbed balance between its internal and external environment which is typical for endemic diseases. For example, it has been detected that fluorosis that occurs in many regions in the world is caused by excessive intake of fluorides with dirking water; endemic goiter develops due to insufficient iodine concentration in drinking water and food products and besides this disease can be related to effects produced by certain chemicals that disturb balance in the hormonal system [5, 6].

In the Russian Federation the Volga River is the primary water source for drinking water supply in most regions located in the European part of the country. Its total flow accounts for practically one quarter of the overall river flow in this part of Russia (260 km^3)[2]. Surface waters in Volga basin are exposed to anthropogenic burdens that differ in scale and danger. Volga basin is contaminated due to industrial and communal sewage being introduced into it. Sewage is discharged into the river in the greatest amounts in such cities as Moscow, Samara, Nizhniy Novgorod, Yaroslavl, Saratov, Ufa, Volgograd, Balakhna, Tolyatti, Ulyanovsk, Cherepovets, Naberezhnye Chelny, etc. There is no positive long-term dynamics of water contamination detected for most watercources in Volga basin that is among water objects in the Russian Federation with maximum burden and contamination varying from high (HC) to extremely high (EHC) (905 out of 2,743 HC and EHC cases registered in 2018). More than 10 cases were registered in Astrakhan, Kirov, Moscow, Nizhniy Novgorod, Ryazan, Samara, Sverdlovsk, Tver, Tula, Chelyabinsk, and Perm regions and Udmurtia[2].

Substantial contamination of surface waters in Volga basin can't fail to influence

[1] The guide on complex prevention of environmentally induced diseases basing on risk assessment. Moscow, 2017, 68 p.

[2] On the conditions and use of water sources in the Russian Federation in 2018: The State Report. Moscow, NIA-Priroda, 2019, 290 p.

drinking water supply and population health. Samara region and Samara city in particular are among RF regions that are exposed to great anthropogenic burdens; the Saratov water reservoir is the primary source for drinking water supply on these territories. In 2018 experts detected that surface waters quality in the reservoir deteriorated; there was a growth from 0 to 38 % in a number of cases of contamination with petroleum products in concentrations equal to 1–2 MPC detected in 2018 against 2008–2017; a number of cases when contamination with copper compounds was detected grew to 47 %. Besides, there were cases when water turned out to be contaminated with ammonium nitrogen, concentration being up to 2 MPC; nitrite nitrogen, 1–3 MPC; cadmium compounds, from 1 to 2 MPC[4]. Underground waters in Samara Zarechye are another source for drinking water supply in some districts in Samara city.

Our research goal was to assess probable impacts exerted on overall morbidity in Samara by quality of drinking water taken from centralized water supply systems as a most significant environmental factor.

Our research tasks included the following:

– to analyze overall morbidity in Samara region in comparison with average morbidity in the country and average data on the Privolzhskiy Federal District since Samara region is included into it;

– to take and analyze samples of drinking water from centralized communal water supply systems;

– to calculate carcinogenic and non-carcinogenic risks caused by chemicals included into the analysis;

– to assess a probable relation between increased morbidity and calculated risk values.

Data and methods. To achieve our goals and solve the tasks, in 2018–2019 we performed sanitary-chemical analysis of drinking water quality taken from centralized dirking water supply networks in 7 districts within Samara city. Samples were taken in apartments belonging to water consumers according to GOST R 56237-2014[3]. Water samples were examined as per 20 sanitary-chemical parameters (Table 1). Drinking water quality was assessed according to requirements fixed in the SER 2.1.4.1074-01[4].

Obtained actual data on drinking water contamination in Samara city districts were primary data for calculating hazard indexes and carcinogenic risk coefficients basing on standard exposure scenarios. Health risks were assessed according to the Guide R 2.1.10.1920-04[5]. An algorithm used to analyze health risks included 4 basic stages: hazard identification, analysis of "dose – response" dependence, exposure calculation, and health risk calculation. Standard exposure factors were applied in all calculations performed in the present work. Carcinogenic risk was calculated via multiplying a daily dose (I) by carcinogenic potential factor (SFo): $CR = I \cdot SFo$ (1). Hazard quotient value (HQ) was determined via dividing annual average concentration (C) by reference concentration (RfC) (2): $HQ = C/RfC$ (2). In case there were several contaminants, hazard index (*HI*) was calculated for their simultaneous introduction into a body as per the following formula: $HI = \sum HQ$.

Results were statistically processed with Statistica for Windows (Release 6.0, StatSoft Inc.) and MS Excel for Windows. We applied Kolmogorov – Smirnov test to check whether values were distributed normally in a sampling. In case a sampling deviated from normal distribution, data were presented as median and range (minimum and maximum values and 10-th and 90-th percentiles). Differences between districts with surface and underground water supply were estimated with Student's *t*-test and were considered valid in case probability degree was higher than 95 % ($p < 0.05$).

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[3] GOST R 56237-2014. Drinking water. Taking samples at water treatment facilities and from distribution systems. Moscow, Standartinform Publ., 2019, 27 p.

[4] SER 2.1.4.1074-01. Drinking water and water supply in settlements. Drinking water. Hygienic requirements to quality of water in centralized drinking water supply systems. Quality control. Hygienic requirements to providing safety of hot water supply systems. Sanitary-epidemiologic rules and standards. Moscow, The RF Public Healthcare Ministry Publ., 2002, 103 p.

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

Table 1

Assessed sanitary-chemical parameters and regulatory documents that stipulate rules and procedures for examining and assessing water quality

No.	Examined parameter	Measuring unit	MPC	A document that stipulates rules and procedures for examinations (tests) and measurements
1	Smell	scores	Not higher than 2	GOST R 57164-2016
2	Turbidity	mg/dm³	1.5	GOST R 57164-2016
3	Color	degrees	20	GOST 31868-2012
4	pH	pH	6-9	FR 1.31.2018.30110
5	Hardness	° H	7.0	GOST 31954-2012
6	Solid residue	mg/dm³	1.000	GOST 18164-72
7	Permanganate oxidation (PO)	mg/dm³	5.0	GOST R 55684-2013
8	Petroleum products	mg/dm³	0.1	GOST R 51797-2001
9	Sulfates	mg/dm³	500	GOST 31940-2012
10	Chlorides	mg/dm³	350	GOST 4245-72
11	Ammonium and ammonium ions	mg/dm³	2.0	GOST 33045-2014
12	Nitrites	mg/dm³	3.0	GOST 33045-2014
13	Nitrates	mg/dm³	45	GOST 33045-2014
14	Cadmium	mg/dm³	0.001	PND F 14.1: 2: 4.69-96 PND F 14.1: 2: 4.149-99
15	Lead	mg/dm³	0.03	PND F 14.1: 2: 4.69-96 PND F 14.1: 2: 4.149-99
16	Zinc	mg/dm³	5.0	PND F 14.1: 2: 4.69-96 PND F 14.1: 2: 4.149-99
17	Copper	mg/dm³	1.0	PND F 14.1: 2: 4.69-96 PND F 14.1: 2: 4.149-99
18	Arsenic	mg/dm³	0.05	FR.1.31.2002.00589
19	Iron (total)	mg/dm³	0.3	GOST 4011-72
20	AASSA (Anion-active synthetic surface-active agents)	mg/dm³	0.5	GOST 31857-2012

Note: MPC means maximum permissible concentration

Results and discussion. According to results obtained via sanitary-chemical analysis, analyzed drinking water samples conformed to obligatory requirements as per many sanitary-chemical parameters[2]. There were sporadic samples of drinking water supplied from the Saratov water reservoir that deviated from hygienic standards as per such parameters as color, iron contents, permanganate oxidation; some samples of drinking water taken from underground water sources (Kyibyshevskiy district and Krasnaya Glinka settlement in Krasnoglinskiy district) deviated from hygienic standards as per water hardness and solid residue. We also detected petroleum products contents that were higher than hygienic standards (0.1 mg/dm^3) and it can indicate that water treatment was not efficient as well as that pipes in distribution networks were in poor condition. We also detected iron in contents being higher than maximum permissible concentration (MPC) in certain samples if drinking water taken in Kyibyshevskiy, Zheleznodorozhniy, and Krasnoglinskiy districts; it might be due to engineering infrastructure being worn out. All the other metals were detected in water samples in quantities that did not exceed hygienic standards.

Table 2 contains the results obtained via drinking water analysis as per several sanitary-chemical parameters.

Actual data on drinking water quality obtained in city districts in Samara were used for calculating hazard indexes and carcinogenic risk coefficients.

In 2018 total carcinogenic risks caused by drinking water varied from $1.5 \cdot 10^{-6}$ to $6.0 \cdot 10^{-4}$ (the median was $4.9 \cdot 10^{-5}$; 10-th and

Table 2

Quality of drinking water supply to population in Samara ($M \pm m$)

District		Chlorides, mg/dm^3	Sulfates, mg/dm^3	Iron, mg/dm^3	Ammonium ions, mg/dm^3	Nitrites, mg/dm^3	Nitrates, mg/dm^3	Petr. products, mg/dm^3	As*, mg/dm^3	Pb, mg/dm^3	Cd, mg/dm^3
MPC		350	500	0.3	2.0	3.0	45	0.1	0.05	0.03	0.001
1	2018	29.1 ± 2.0	76.6 ± 8.36	0.10 ± 0.02	0.32 ± 0.06	<0.003	2.05 ± 0.30	0.34 ± 0.17	0.006 ± 0.002	<0.001	<0.001
	2019	38.4 ± 2.0	63.4 ± 7.0	0.55 ± 0.13	0.10 ± 0.03	<0.003	4.95 ± 0.74	0.15 ± 0.08	0.008 ± 0.002	<0.001	<0.001
2	2018	26.3 ± 2.0	350.6 ± 38.6	0.52 ± 0.0	0.83 ± 0.17	0.11 ± 0.04	7.14 ± 1.07	0.50 ± 0.25	0.004 ± 0.001	<0.001	<0.001
	2019	20.2 ± 2.0	234.1 ± 25.8	0.49 ± 0.11	0.20 ± 0.04	0.05 ± 0.03	7.75 ± 1.16	0.76 ± 0.19	0.008 ± 0.002	<0.001	<0.001
3	2018	169.0 ± 2.0	448.0 ± 49.0	0.12 ± 0.02	0.83 ± 0.17	0.30 ± 0.08	6.04 ± 0.91	0.17 ± 0.08	0.008 ± 0.002	<0.001	<0.001
	2019	163.2 ± 14.0	98.5 ± 10.0	0.25 ± 0.06	0.36 ± 0.07	0.08 ± 0.04	6.27 ± 0.94	0.17 ± 0.08	0.008 ± 0.002	<0.001	<0.001
4	2018	26.3 ± 2.0	48.1 ± 5.3	0.13 ± 0.02	0.34 ± 0.07	<0.003	1.68 ± 0.33	0.43 ± 0.21	0.006 ± 0.001	<0.001	<0.001
	2019	20.2 ± 2.2	52.0 ± 5.7	0.28 ± 0.07	0.40 ± 0.08	<0.003	3.85 ± 0.58	0.22 ± 0.11	0.012 ± 0.002	<0.001	<0.001
5	2018	22.6 ± 2.0	53.3 ± 5.8	0.13 ± 0.03	0.39 ± 0.08	<0.003	1.62 ± 0.32	0.43 ± 0.21	0.004 ± 0.001	<0.001	<0.001
	2019	42.2 ± 4.6	61.8 ± 6.8	0.22 ± 0.05	0.34 ± 0.07	<0.003	5.00 ± 0.75	0.15 ± 0.08	0.004 ± 0.001	<0.001	<0.001
6	2018	75.2 ± 6.5	201.2 ± 22.1	2.91 ± 0.62	0.96 ± 0.19	<0.003	7.70 ± 1.15	0.21 ± 0.10	0.026 ± 0.006	0.0023 ± 0.0003	<0.001
	2019	73.0 ± 6.3	136.0 ± 15.0	0.06 ± 0.01	< 0.10	< 0.003	15.87 ± 2.40	0.20 ± 0.10	0.005 ± 0.001	0.004 ± 0.001	0.0010 ± 0.0002
7	2018	27.3 ± 2.5	43.4 ± 4.7	<0.05	0.69 ± 0.14	0.19 ± 0.07	0.18 ± 0.03	0.41 ± 0.20	0.005 ± 0.001	<0.001	<0.001
	2019	42.2 ± 4.6	83.1 ± 9.1	0.23 ± 0.06	0.19 ± 0.04	<0.003	4.97 ± 0.75	0.40 ± 0.20	0.003 ± 0.001		<0.001
8	2018	25.4 ± 2.0	46.4 ± 5.1	0.15	0.42 ± 0.08	<0.003	1.94 ± 0.38	0.57 ± 0.14	0.006 ± 0.001	<0.001	<0.001
	2019	38.4 ± 4.1	79.4 ± 8.7	0.15 ± 0.04	0.16 ± 0.03	<0.003	5.26 ± 0.79	0.24 ± 0.12	0.008 ± 0.002	<0.001	<0.001
9	2018	23.5 ± 2.0	44.9 ± 4.9	<0.05	0.30 ± 0.05	<0.003	1.79 ± 0.35	0.68 ± 0.17	0.008 ± 0.002	0.0022 ± 0.0003	<0.001
	2019	40.0 ± 4.3	58.1 ± 6.4	0.16 ± 0.04	0.19 ± 0.04	<0.003	4.57 ± 0.68	0.37 ± 0.18	0.004 ± 0.001	<0.001	<0.001
10	2018	22.6 ± 2.0	40.5 ± 4.4	0.11	0.21 ± 0.04	<0.003	1.78 ± 0.35	0.22 ± 0.11	<0.002	0.004 ± 0.003	<0.001
	2019	41.3 ± 4.5	50.0 ± 5.5	0.26 ± 0.06	0.34 ± 0.07	<0.003	4.56 ± 0.68	0.17 ± 0.08	0.0020 ± 0.0004	<0.001	<0.001
11	2018	25.4 ± 2.1	71.3 ± 7.8	0.15	0.28 ± 0.05	<0.003	2.16 ± 0.32	0.21 ± 0.10	0.006 ± 0.002	<0.001	<0.001
	2019	41.3 ± 4..5	54.1 ± 6.0	0.31 ± 0.07	0.10 ± 0.03	<0.003	4.71 ± 0.70	0.27 ± 0.13	0.021 ± 0.004	0.0012 ± 0.0001	<0.001
12	2018	94.0 ± 8.7	386.2 ± 42.5	0.19 ± 0.03	0.66 ± 0.13	0.17 ± 0.06	5.96 ± 0.89	0.16 ± 0.08	0.007 ± 0.002	<0.001	<0.001
	2019	193.9 ± 17.5	415.0 ± 45.6	0.22 ± 0.05	0.31 ± 0.06	0.011 ± 0.005	6.78 ± 1.02	0.20 ± 0.10	0.009 ± 0.002	<0.001	<0.001

Note: 1 is Zheleznodorozhniy district; 2 is Kyibishevskiy district; 3 is Kyibishevskiy district (Volgar'); 4 is Krasnoglinskiy district (Novaya Samara); 5 is Krasnoglinskiy district (Koshelev); 6 is Krasnoglinskiy district (Krasnaya Glinka settlement); 7 is Samarskiy district; 8 is Leninskiy district; 9 is Promyshlenniy district; 10 is Kirovskiy district; 11 is Sovetskiy district; 12 is Yuzhniy gorod.

90-th percentiles were $3.0 \cdot 10^{-5}$ and $6.7 \cdot 10^{-5}$ accordingly) for children who lived on the examined territories in the city and corresponded to the second range or maximum permissible risk as per median and 90-th percentile according to R 2.1.10.1920–04 (Table 2). Also, in 2018 total carcinogenic risks for adults varied from $2.0 \cdot 10^{-5}$ to $4.5 \cdot 10^{-4}$ (the median was $1.0 \cdot 10^{-4}$; 10-th and 90-th percentiles were $1.3 \cdot 10^{-5}$ and $1.4 \cdot 10^{-4}$ accordingly) and corresponded to the third range as per the median and 90-th percentile (individual lifelong risk varied from $1 \cdot 10^{-4}$ to $1 \cdot 10^{-3}$); it was acceptable for occupational groups and unacceptable for population in general.

In 2019 corresponding median values calculated for individual carcinogenic risks amounted to $1.4 \cdot 10^{-4}$ and $6.4 \cdot 10^{-5}$ for adults and children respectively and there were no statistically authentic difference in these values against those obtained for 2018 ($p > 0.05$).

It was detected that in 2018–2019 individual carcinogenic risks were caused predominantly by impacts exerted by arsenic in all the examined city districts (Table 3). In 2018 lead made a contribution into total hazard index in three examined districts (Krasnaya Glinka settlements in Krasnoglinskiy district, Promyshlenniy district, and Kirovskiy district). The median of individual risk occurring due to effects produced by this contaminant amounted to $5.9 \cdot 10^{-7}$ (negligible risk) and $1.3 \cdot 10^{-6}$ (the second range) for children younger than 18 and adults respectively. In 2019 lead was detected in samples taken in Krasnaya Glinka settlement and Sovetskiy district in concentrations that caused median individual carcinogenic risk being equal to $7.2 \cdot 10^{-7}$ for children and $1.6 \cdot 10^{-6}$ for adults older than 18. Besides, in 2019 one sample taken in Krasnaya Glinka settlement contained cadmium in a concentration that caused median carcinogenic risk being equal to $2.0 \cdot 10^{-6}$ and $4.2 \cdot 10^{-6}$ (the second range) for children and adults older than 18 respectively.

We assessed health risks related to non-carcinogenic effects among population living in Samara caused by drinking water from centralized water supply; assessment was performed as per the same chemicals.

Calculated risks of non-carcinogenic effects were higher than permissible hazard levels: in 2018 median hazard index (range) amounted to 1.032 (0.384–3.024) and 2.407 (0.895–7.055) for adults and children respectively; in 2019, 1.055 (0.464–2.323) and 2.462 (1.082–5.419) respectively.

Total non-carcinogenic risk for children was higher than permissible levels in 2018 in 11 out of 12 examined districts (the median hazard index amounted to 2.407, the range was 0.895–7.055); the highest value was detected in Krasnaya Glinka settlement (7.055). We detected hazard quotients that were higher than permissible levels for certain critical organs and systems (the central nervous system, the range was 0.293–5.476; skin, 0.236–6.054; the cardiovascular system, 0.225–5.475; the kidneys, 0.341–1.44).

The greatest contribution here was made by arsenic since it was detected in doses higher than reference ones in all districts except Kirovskiy (the median value was 1.385 (range was 1.065–5.434)) (Table 4). Hazard quotients for petroleum products were also higher than permissible risk levels in three districts: Kyibishevskiy district, 1.065; Leninskiy district, 1.215; Promyshlennniy district, 1.440. Carcinogenic risk values were also within a range from 0.8 to 1.0 in another two districts, Krasnoglinskiy district – Novaya Samara and Koshelev. Individual hazard quotients calculated for sulfates, ammonium ions, nitrites, and nitrates were authentically higher in districts with drinking water supplied from underground sources than in districts where drinking water was supplied from surface ones ($p < 0.05$) (Table 4). Non-carcinogenic risks caused by iron amounted to 0.1 for children in 2018 excluding two territories (Kyibishevskiy district and Krasnaya Glinka settlement) where they amounted to 0.107 and 0.620 accordingly. Hazard quotients calculated for all other chemicals (copper, zinc, cadmium, and lead) were lower than 0.1.

In 2018 total non-carcinogenic risks for adults exceeded 0.8 excluding samples taken in Kirovskiy district where the total hazard index amounted to 0.384. Maximum hazard

Table 3

Concentrations of arsenic, lead, and cadmium in examined drinking water samples and individual carcinogenic risks caused by these contaminants in 2018–2019

District		CR (children younger than 18)				CR (adults)			
		As	Pb	Cd	Σ	As*	Pb	Cd	Σ
1	2018	5.34E-05	–	–	5.34E-05	1.14E-04	–	–	1.14E-04
	2019	6.49E-05	–	–	6.49E-05	1.39E-04	–	–	1.39E-04
2	2018	3.29E-05	–	–	3.29E-05	7.05E-05	–	–	7.05E-05
	2019	6.41E-05	–	–	6.41E-05	1.37E-04	–	–	1.37E-04
3	2018	6.74E-05	–	–	6.74E-05	1.44E-04	–	–	1.44E-04
	2019	6.41E-05	–	–	6.41E-05	1.37E-04	–	–	1.37E-04
4	2018	4.52E-05	–	–	4.52E-05	9.69E-05	–	–	9.69E-05
	2019	9.53E-05	–	–	9.53E-05	2.04E-04	–	–	2.04E-04
5	2018	2.96E-05	–	–	2.96E-05	6.34E-05	–	–	6.34E-05
	2019	3.53E-05	–	–	3.53E-05	7.57E-05	–	–	7.57E-05
6	2018	2.10E-04	5.92E-07	–	2.10E-04	4.49E-04	1.27E-06	–	4.50E-04
	2019	4.03E-05	1.13E-06	1.98E-06	4.34E-05	8.63E-05	2.43E-06	4.24E-06	9.30E-05
7	2018	4.11E-05	–	–	4.11E-05	8.81E-05	–	–	8.81E-05
	2019	2.79E-05	–	–	2.79E-05	5.99E-05	–	–	5.99E-05
8	2018	4.60E-05	–	–	4.60E-05	9.86E-05	–	–	9.86E-05
	2019	6.49E-05	–	–	6.49E-05	1.39E-04	–	–	1.39E-04
9	2018	6.41E-05	5.67E-07	–	6.47E-05	1.37E-04	1.21E-06	–	1.39E-04
	2019	3.53E-05	–	–	3.53E-05	7.57E-05	–	–	7.57E-05
10	2018	8.22E-06	1.13E-06	–	9.35E-06	1.76E-05	2.43E-06	–	2.00E-05
	2019	1.64E-05	–	–	1.64E-05	3.52E-05	–	–	3.52E-05
11	2018	5.10E-05	–	–	5.10E-05	1.09E-04	–	–	1.09E-04
	2019	1.73E-04	3.08E-07	–	1.74E-04	3.72E-04	6.62E-07	–	3.72E-04
12	2018	5.84E-05	–	–	5.84E-05	1.25E-04	–	–	1.25E-04
	2019	7.23E-05	–	–	7.23E-05	1.55E-04	–	–	1.55E-04

Note: 1 is Zheleznodorozhniy district; 2 is Kyibishevskiy district; 3 is Kyibishevskiy district (Volgar'); 4 is Krasnoglinskiy district (Novaya Samara); 5 is Krasnoglinskiy district (Koshelev); 6 is Krasnoglinskiy district (Krasnaya Glinka settlement); 7 is Samarskiy district; 8 is Leninskiy district; 9 is Promyshlenniy district; 10 is Kirovskiy district; 11 is Sovetskiy district; 12 is Yuzhniy gorod.

Table 4

Total non-carcinogenic risk indexes for children and adults as per priority chemicals

Parameter	2018		2019	
	Children	Adults	Children	Adults
Arsenic				
Median	1.257	0.539	1.662	0.712
Range	0.213–5.434	0.091–2.329	0.426–4.496	0.182–1.926
10-th percentile	0.767	0.329	0.725	0.310
90-th percentile	1.747	0.749	2.472	1.059
Petroleum products				
Median	0.797	0.342	0.448	0.192
Range	0.341–1.440	0.146–0.617	0.320–1.619	0.137–0.694
10-th percentile	0.354	0.152	0.320	0.137
90-th percentile	1.215	0.521	0.852	0.365
Total coefficient				
Median	2.407	1.032	2.462	1.055
Range	0.895–7.055	0.384–3.024	1.082–5.416	0.464–2.323
10-th percentile	1.8588	0.796	1.365	0.585
90-th percentile	3.357	1.439	3.937	1.687

Table 5

Non-carcinogenic risks indexes as per specific chemicals depending on water supply sources

Parameter	2018 г.				2019 г.			
	Children		Adults		Children		Adults	
	Underground	Surface	Underground	Surface	Underground	Surface	Underground	Surface
Sulfates	0.222 ± 0.067	0.035 ± 0.009	0.095 ± 0.029	0.015 ± 0.0004	0.141 ± 0.090	0.040 ± 0.008	0.061 ± 0.039	0.017 ± 0.003
Ammonium ions	0.033 ± 0.005	0.013 ± 0.003	0.014 ± 0.002	0.006 ± 0.001	0.010 ± 0.004*	0.009 ± 0.005*	0.010 ± 0.010*	0.004 ± 0.002*
Nitrites	0.092 ± 0.08	0.001 ± 0.00	0.039 ± 0.034	0.00 ± 0.00	0.023 ± 0.023	0.001 ± 0.00	0.157 ± 0.077	0.00 ± 0.00
Nitrates	0.268 ± 0.034	0.075 ± 0.008	0.115 ± 0.015	0.032 ± 0.003	0.367 ± 0.180	0.190 ± 0.017	0.157 ± 0.077	0.081 ± 0.007

index value was also detected for water samples taken in Krasnaya Glinka settlement (3.024); as for the other districts, this parameter was lower than 1.5 there. Hazards that critical organs or systems might be damages exceeded maximum permissible levels for the central nervous system (the range was 0.125–2.347), skin (0.101–2.595), and cardiovascular system (0.096–2.347).

Just as it was the case with risks for children, the greatest contribution into total non-carcinogenic risks was made by arsenic (the median was 0.539; the range, 0.091–2.329) and petroleum products (the median, 0.342; the range 0.146–0.617). As for the districts with underground drinking water supply, significant contributions were also made by sulfates and nitrates (Table 4).

In 2019 total non-carcinogenic risks for children were higher than permissible levels in all the examined districts and were equal to those calculated in 2018 (the median was 2.462 and the range was 1.082–5.419). Total non-carcinogenic health risks for adults were also higher than permissible levels in 10 out of all analyzed city districts. Just as in 2018, hazard indexes higher than maximum permissible levels were detected for the central nervous system (the range was 0.426–4.518 for children and 0.182–1.935 for adults), skin (0.481–4.562 and 0.206–1.954 accordingly), and cardiovascular system (0.435–4.521 and 0.26–2.007 accordingly).

We assessed hazard quotients for specific chemicals that made the greatest contributions into total risk (arsenic and petroleum products) in 2019; the results were similar to those obtained for 2018 (Table 5). Sulfates and nitrates also made substantial contributions into total health risks for children and adults in districts with underground drinking water supply. We should note that there was a more apparent spread in individual risk values calculated for sulfates and nitrogen compounds in districts where drinking water was supplied from underground sources than in districts where water sources were surface ones; apparently, it indicates that drinking water quality is primarily determined by water properties at water intake points and not by conditions of water distribution networks.

In 2019 non-carcinogenic health risk for children caused by iron in drinking water was higher than 0.1 in two districts (Zheleznodorozhniy district and Kyibishevskiy district). Non-carcinogenic risks for children caused by cadmium amounted to 0.121 in Krasnaya Glinka settlement. Other individual risks calculated for chemicals didn't exceed 0.1 either for children or adults.

Although drinking water quality is still rather unsatisfactory regarding non-carcinogenic health risks, we should note that that hazard quotients values improved in some districts (Krasnaya Glinka settlement), and there was also a decrease in risks caused by nitrates and ammonium ions. It probably indicates that drinking water quality may change over time due to influence exerted by different factors.

Therefore, non-carcinogenic effects might occur due to consuming drinking water from centralized communal and drinking water supply systems. Having assessed hazard quotients as per each examined chemicals and total hazard index as well, we revealed that substantial contributions into carcinogenic and non-carcinogenic effects related to long-term consumption of examined drinking water were made by arsenic, lead, and petroleum products.

According to literature data, an issue related to underground and surface waters being contaminated with arsenic has become significant worldwide and arsenic is now seen as the gravest and most hazardous non-organic contaminant occurring in drinking water. Arsenic compounds are widely spread in natural waters due to various factors, both natural and anthropogenic ones [7–12]. Natural geochemical soil leaching contributes significantly into underground waters contamination with arsenic compounds. Surface waters can also contain arsenic in low, though detectable, concentrations (from 10 to 60 % of the total arsenic quantity) including its organic compounds, such as monosodium methyl arsenates and disodium methyl arsenates [12].

Basic anthropogenic sources that make for arsenic compounds penetrating natural waters include mining, pharmaceutical industry, glass and ceramics production, production of herbicides, pesticides, and paints, wood-processing and oil-processing enterprises, as well as metal and alloy smelting etc. [7–12].

Arsenic occurring in drinking water is the most hazardous for human health [7, 10]. It is usually revealed when water that contains non-organic arsenic compounds in insignificant concentrations is consumed over a long-term period. Arsenic occurrence is thought to cause certain chronic diseases including oncologic diseases of the urinary bladder, kidneys, and lungs; blood-vessel diseases, diseases of the lower extremities, feet, and skin; probably, it can also cause diabetes, hypertension, reproductive disorders, and disorders of children's intellectual development [7–16]. There are data on a probable relation between arsenic in drinking water and endemic goiter development [13, 14].

Approximately 1 person out of 100 who consume dirking water with arsenic contents in it being 0.05 mg/dm^3 for a long-term period may die due to an oncologic disease. This share reaches 10 % in cases when arsenic contents exceed 0.05 mg/dm^3 [7].

Basing on hazard quotients calculated for arsenic we can assume that this chemical makes a contribution into a risk of chronic diseases among people living in Samara. We should note that this assumption is well in line with a cause-and-effect relation between morbidity with malignant neoplasms among children and teenagers in Samara and soil contamination, namely with arsenic, cadmium, zinc, and petroleum products; this relation was detected by experts from the Scientific Research Institute for Human Hygiene and Ecology, Samara State Medical University of the RF Public Healthcare Ministry[6]. It is also partially confirmed by research results published in Udmurtia [17]. At the same time we should note that arsenic contents didn't exceed maximum permissible concentration (0.05 mg/dm^3) in any examined sample.

There is a recently published work [18] that dwells on analyzing health risks for employable population caused by food products contamination and there are data in it that confirm a significant contribution made by alimentary introduced arsenic into the total hazard quotient of non-carcinogenic effects produced on population health in Samara.

Lead is another priority contaminant with carcinogenic effects and it is ranked by the World Health Organization among 10 chemicals that require special attention from public health authorities and certain actions aimed at protecting health of employable population, children, and women in their reproductive age. Epidemiologic research has revealed that effects produced by lead can result in elevated risks of lung cancer, stomach cancer, and brain cancer [19]. Nevertheless, lead contents didn't exceed MPC in any examined sample and car-

[6] Sazonova O.V., Sukhachyova I.F., Drozdova N.I. [et al]. The Report on scientific research work "The Complex approach to assessing ecological and hygienic safety on Samara territory" (State registration number 01201457241). Samara, Samara State Medical University of the RF Public Healthcare Ministry Publ., 2014, 261 p.

cinogenic risks caused by this chemical were within the first or second range (negligible or maximum permissible risks).

High concentrations of petroleum products are associated with risks of acute and chronic renal failure [20, 21]. Given that, we can assume that petroleum products exert their influence on morbidity with diseases of the urogenital system in Samara; however, additional population research on the matter is required.

Total carcinogenic and non-carcinogenic risks caused by contaminated drinking water can partly make a contribution into population morbidity; however, we should take into account variable environmental impacts including ambient air and contaminants introduced with food products as well.

Our results are in line with results obtained via analyzing health risks for population in Samara; the analysis was accomplished by Rospotrebnadzor Regional office in Samara as per data obtained via social and hygienic monitoring in 2013–2017 [22].

We should stress that our research has certain limitations; primarily, a number of examined samples is too small and it doesn't allow making a representative estimation of carcinogenic and non-carcinogenic risks for the whole population in Samara. A rather short observation period is another limitation since it doesn't allow estimating whether calculated risk levels will remain the same if taken in long-term dynamics. Nevertheless, the obtained results already indicate that risks for a part of the city population are higher than permissible levels. It seems advisable to performed wider-scale controlled examinations in several regions in order to assess significance of detected factors for morbidity among population.

Conclusion. The present research dwells on assessing carcinogenic and non-carcinogenic risks basing on actual data on quality of drinking water taken from centralized drinking and communal water supply systems.

We established that maximum total hazard quotient of non-carcinogenic effects was caused by arsenic and petroleum products introduced with drinking water. Assessment of carcinogenic risks caused by contaminants introduction with drinking water revealed that total health risk for children younger than 18 corresponded to the second range as per its median value; and total carcinogenic risks for adults were within the third range that was acceptable for occupational groups and unacceptable for population in general. At the same time we should stress that arsenic contents didn't exceed hygienic standards in any examined sample. Arsenic compounds are widely spread in natural waters and considerably hazardous for human health even in relatively small concentrations in drinking water; therefore, it is vital to conduct further research on developing efficient and economically feasible procedures for water purification from this element and its compounds.

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Research article

WATER PREAMMONIZATION AT CENTRAL WATER TREATMENT FACILITIES IN A LARGE CITY AS A WAY TO MINIMIZE HEALTH RISKS

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At present chlorine compounds are widely used to disinfect water during water treatment procedures; it stimulates occurrence of toxic chlorinated organic compounds. Water preammonization with ammonia sulfate was implemented at central water treatment facilities in Arkhangelsk.

Our research goal was to assess efficiency of water preammonization at central water treatment facilities in Arkhangelsk.

Our research involved analyzing drinking water quality at central water treatment facilities prior to preammonization was implemented (from January 2016 to July 2017) and after it was implemented (from June 2018 to December 2019). We examined 14,674 water samples prior to water preammonization implementation and 15,165 water samples after it. Water quality was analyzed as per 19 parameters. Non-carcinogenic effects caused by exposure to chemicals in drinking water, prior to and after preammonization, were estimated basing on calculating hazard quotients and indexes. To describe examined parameters, median and 90-th percentile was used. Wilcoxon signed-rank test was applied to reveal differences between water parameters prior to and after preammonization was implemented.

Water preammonization implemented at central water treatment facilities allowed improving drinking water quality at the second lifting and in distribution networks. After preammonization were implemented, aluminum concentration want down by 2.7 times at the second lifting; nitrates concentration, by 1.2 times; chloroform concentration, by 3.5 times ($p < 0.001$). Overall microbe number went down by 1.6 times ($p < 0.001$). After preammonization was implemented, water turbidity in distribution networks went down by 1.3 times, aluminum and chloroform concentrations fell by 1.7 and 7.3 times accordingly ($p < 0.001$). Contribution made by chloroform into hazard indexes decreased by 10–47 % after preammonization was implemented against water treatment performed according to conventional procedures (chlorination).

Water preammonization allowed achieving more qualitative and efficient operating of water supply systems and operational costs reduction; it also resulted in a decrease in concentrations of adverse side products occurring due to disinfection and in achieving higher drinking water quality.

***Key words:** water preammonization, ammonia sulfate, water treatment, disinfection products, chlorinated organic compounds, chloroform, drinking water quality, central water treatment facilities, Arkhangelsk.*

Drinking water quality is among the most essential factors affecting population health. High technogenic burden on the environment contributes significantly to the contamination of water bodies as indicated by chemical, biological and organoleptic properties of water [1–3]. Clean and safe drinking water supply and optimization of water usage are still ongoing tasks, despite improved water disinfection and purification technologies [3].

Sufficient drinking water disinfection and appropriate sanitary conditions at water treatment facilities are accomplished due to water chlorination, which is one of the most impor-

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tant stages in water conditioning and purification [4]. However, drinking water chlorination involves occurrence of disinfection by-products (DBPs). Water treatment using chlorine-containing reagents results in occurrence of more than 300 toxic chlorinated organic compounds, primarily those that belong to trihalomethanes (THMs) (chloroform, dichlorobromomethane, chlorodibromomethane, bromoform, and others) [4, 5]. And chloroform is one of the most common disinfection by-products with its concentration significantly exceeding contents of other chlorinated volatile organic compounds[1] [6–8]. In addition, even a small amount of chlorine in drinking water gives it a very distinctive odor that consumers can easily sense.

Chronic exposure to THMs poses a significant risk to population health as they are considered systemic toxicants, are mutagenic and carcinogenic [9–11], genotoxic, cause metabolic disorders [12], and contribute to an increase in overall and infant morbidity rates [13]. Even a small amount of THMs, in particular chloroform, in drinking water leads to elevated risks of carcinogenic and general toxic effects [14].

Contents of chlorinated organic compounds in drinking water can be decreased via preliminary ammonization, that is, water that is being chlorinated contains ammonium nitrogen [15]. The essence of the method lies in introducing ammonia or its salts into water before adding chlorine to it. The advantages of water preammonization are a decrease in chlorine consumption by 1.5–2 times, reduction in distinct chlorine odor from water, and increase in the concentration of residual chlorine in purified water, which contributes to a longer disinfection effect provided by combined chlorine (chloramines) [16, 17].

The practices in water preammonization in Moscow, St. Petersburg, Khabarovsk, Rostov-on-the-Don, and Nizhny Novgorod have shown a positive effect produced by this method for water conditioning and purification on quality of drinking water supplied to population, mainly due to reduction in the amount of chlorination by-products [4, 18–21].

This study was carried out on the territory of Arkhangelsk, the administrative center of the Arkhangelsk region, a city that is located in the Russian Arctic Zone[2]. The main source of centralized water supply in Arkhangelsk is the Northern Dvina with its channels with 10 waterworks being operated on them. The characteristic features of the Northern Dvina are low water temperature, low water salt and fluorine content, low total hardness, significant fluctuations in turbidity, intense color and high oxidizability[3].

Intense color of water – as much as 180° in the area at the water intake – is attributable to natural humic substances as well as to waste discharges from the Arkhangelsk Pulp and Paper Mill, with a share being no less than 60 % in total output of contaminated wastewater within the sanitary protection zone around the water source[4]. In addition, untreated or insufficiently treated municipal waste and storm water are discharged by sewage treatment plants of Arkhangelsk, housing without sewage, and enterprises operating in river and railway transport sectors.

The analysis of water quality in the Northern Dvina near Arkhangelsk revealed that a share of samples analyzed in 2017–2019 deviating from sanitary-hygienic standards as

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[1] Guidelines for drinking-water quality: fourth edition incorporating the first addendum. Geneva: World Health Organization, 2017, 470 p.

[2] Decree of the President of the Russian Federation issued on 2 May 2014 No. 296. On Land Territories of the Arctic Zone of the Russian Federation. *ConsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_162553/ (March 14, 2021).

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[4] Order of the Ministry of Natural Resources and Environment of Russia of 18 April 2018 No. 154. On approval of the list of facilities that have a negative impact on the environment, related to category I, whose contribution to the total emissions, discharges of pollutants in the Russian Federation is no less than 60 percent. *ConsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_301627/ (March 14, 2021).

per microbiological and sanitary-chemical indicators, was 48.8 and 56.3 %, respectively, and it was by 2–3 times higher than the same rates in the Russian Federation. A percentage of drinking water samples analyzed in 2017–2019 on the territory of Arkhangelsk, deviating from sanitary-hygienic standards as per microbiological and sanitary-chemical indicators was 6.3 and 30.7 %, respectively, and it was by 2.5 times higher than the same rates in the Russian Federation on the whole[5]. The assessment of water quality monitoring in centralized water supply systems on the territories included in the Russian Arctic Zone showed that chloroform was one of the key contaminants in drinking water in Arkhangelsk region [22]. Thus, to improve quality of drinking water supplied to the population in Arkhangelsk, it is required to upgrade the water treatment system.

Preammonization of water was introduced at the central water treatment facilities (CWTFs) that supplied water to 77 % of the population in Arkhangelsk. In 2017, Municipal Unitary Enterprise «Vodokanal» developed a pilot testing program for water ammonization technology that was approved by the Federal Service for Surveillance over Consumer Rights Protection and Human Well-being (Rospotrebnadzor) in Arkhangelsk Region. It was aimed at reducing contents of chlorinated organic derivatives remaining in drinking water due to its chlorination. In the period from August 2017 to May 2018, laboratory and pilot tests for implementing water ammonia technology were carried out using ammonium sulfate. In June 2018, preammonization of water at CWTFs was introduced on a permanent basis.

The **purpose of the study** is to assess the efficiency of water preammonization implementation at the central wastewater treatment plants in Arkhangelsk.

Materials and methods. The study analyzed quality of drinking water after water conditioning and purification at CWTFs prior to preammonization (from January 2016 to July 2017) and after it (from June 2018 to December 2019). 14,674 samples were analyzed prior to water preammonization was implemented, and 15,165 samples were analyzed after it was done. Exposed population involved in the study amounted to 273,624 people. The efficiency of preammonization implementation was assessed according to the data from in-process laboratory testing carried out by the organization operating CWTFs at re-lift pumping plants immediately after water conditioning and purification and at control points in the supply net, as well as according to the results obtained via supervisory activities performed by Rospotrebnadzor Department in Arkhangelsk region and laboratory investigations reports on drinking water quality completed by the Federal State-Funded Healthcare Institution "Centre for Hygiene and Epidemiology in Arkhangelsk Region" within socio-hygienic monitoring. The analysis included the data on consumption of chemicals prior to the implementation of preammonization and after it which were provided by the organizations (Municipal Unitary Enterprise "Vodokanal" and LLC RVK-Arkhangelsk) responsible for operating CWTFs.

The results of the study allowed the investigators to create a database on quality of drinking water supplied from CWTFs as per organoleptic, sanitary-chemical and microbiological indicators. Water quality was analyzed as per 19 indicators: organoleptic properties (odour at 20 °C, color, and turbidity), complex indices (hydrogen ion concentration, permanganate oxidizability, and total dissolved solids), inorganic substances (aluminum, iron, chlorides, sulfates, ammonia, nitrites, nitrates) and chemical compounds formed during water treatment (chloroform, free residual chlorine, residual combined chlorine) and microbiological indices (total coliforms, thermo-tolerant coliforms and total microbial count).

Non-carcinogenic effects caused by exposure to chemicals contained in drinking water, prior to the implementation of preammoniza-

[5] On the Sanitary and Epidemiological Wellbeing of the Population in the Russian Federation in 2019: State report. Moscow, Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor) Publ., 2020, 299 p.; On the Sanitary and Epidemiological Wellbeing of the Population of the Arkhangelsk region in 2019: State report. In: R.V. Buzinova ed. Arkhangelsk, 2020, 148 p.

tion and after it, were assessed via calculating hazard quotients (*HQ*) and hazard indices (*HI*) for substances with a unidirectional action. Hazard quotients were calculated for aluminum, iron, ammonia, nitrites, nitrates and chloroform in their median concentrations. To calculate a dose of chemicals taken with drinking water, a water intake rate for the average adult (2L per day for a person weighing 70 kg) was used. The total *HQ* and *HI* values lower than 1.0 were considered to be the minimum risk levels[6].

To describe the content of the analyzed indicators, the median (*Me*) and the 90-th percentile (P_{90}) were used. Differences between the indicators of drinking water quality prior to the implementation of preammonization and after it were detected with Wilcoxon two-sample test. The critical level of statistical significance, *p*, was equal to 0.05. Statistical data analysis was performed using STATA 14.2 software.

Results and their discussion. Currently, Arkhangelsk water supply services from CWTFs are being operated by LLC RVK-Arkhangelsk (previously, Municipal Unitary Enterprise "Vodokanal" till 20 December, 2018). CWTFs comprise two water treatment plants (No. 2 and 3) where water is prepared and disinfected, to be then supplied to a clean-water reservoir. On average, CWTFs produce 130–140 thousand m^3/day.

CWTFs use two methods to purify water: coagulation in a free volume at plant No. 2, and coagulation in a filtering layer at plant No. 3. During water conditioning and purification at plant No. 2, water from the Northern Dvina comes to a vortex mixer, and then goes into water conduits, where ammonium sulfate is added to react with free chlorine to form bound chlorine. After that, to ensure primary disinfection, sodium hypochlorite and soda ash, coagulant and flocculant, are added into water. The ratio of ammonium nitrogen to active chlorine is 1:4. Further, water mixed with the chemicals arrives at high-speed filters through the reaction chambers, and then undergoes secondary disinfection and enters reservoirs with pure drinking water.

During water conditioning and purification at plant No. 3, water from the Northern Dvina is fed into a contact chamber, where ammonium sulfate solution, sodium hypochlorite (primary chlorination) and coagulant are added. When water leaves the contact chamber, it is mixed with the flocculant and enters contact coagulation pre-filters (contact flocculators). In addition, a micro-dose of flocculant is introduced into purified water. Then the second dose of sodium hypochlorite and soda ash solution are added into the water. After rapid filters, purified water undergoes final disinfection and is pumped into reservoirs with pure drinking water, where it is mixed with water coming from plant No. 2.

Assessment of water quality at the re-lift pumping plant of CWTFs. A comparative assessment of drinking water quality sampled at the re-lift pumping plant of CWTFs, taken as per average values of the indicators, showed an increase in color by 1.1 times ($p = 0.027$) and an increase in ammonia concentration (in terms of nitrogen) by 3.8 times ($p < 0.001$). At the same time, color and ammonia content at the median level did not exceed the threshold limit values (Table 1).

The quality of drinking water at the re-lift pumping plant of CWTFs at the median level for such indicators as odor, turbidity, pH value, permanganate oxidizability, iron and nitrites content did not change after preammonization was implemented ($p > 0.05$).

After water preammonization was implemented, the content of substances in drinking water decreased statistically significantly as to the following values: aluminum, by 2.7 times ($p < 0.001$); chlorides, by 1.7 times ($p < 0.001$); nitrates, by 1.2 times ($p < 0.001$). The concentration of chloroform at the re-lift pumping plant of CWTFs decreased by 3.5 times at the *Me* level, and by 5.5 times at the P_{90} level ($p < 0.001$) after water preammonization was implemented. It was not possible to assess effects produced by

[6] Guide on Health Risk Assessment under Exposure to Chemicals that Pollute the Environment. Moscow, Federal Center of Rosepidnadzor of the Ministry of Health of Russia Publ., 2004, 143 p.

Table 1

Laboratory tests results showing drinking water quality at the re-lift pumping plant of CWTFs in Arkhangelsk

Indicator	Prior to preammonization		After preammonization		p	Normal value[7]
	Me	P_{90}	*Me*	P_{90}		
Organoleptic indicators						
Odor at 20 °C, points	1	2	1	2	0.466	2
Color (colority), degrees	12	18	13	21	0.027	20
Turbidity, mg/L (Kaolin)	0.58	1.10	0.58	0.62	0.106	1.5
Complex indicators						
Hydrogen ion concentration, pH units	6.9	7.4	6.8	7.3	0.742	6–9
Permanganate oxidizability, mg/L	4.1	5.0	4.3	5.0	0.369	5
Total dissolved solids (solid residue), mg/L	268	362	209	322	0.008	1000
Inorganic substances						
Aluminum (Al (3+)), mg/L	0.32	0.46	0.12	0.24	< 0.001	0.5
Iron (Fe, total), mg/L	0.1	0.14	0.1	0.15	0.107	0.3
Chlorides (in terms of CL), mg/L	16.05	20.3	9.7	13.8	< 0.001	350
Sulfates (SO_4), mg/L	77.9	116.4	83.3	113.5	0.650	500
Ammonia (in terms of nitrogen)	0.10	0.38	0.38	0.60	< 0.001	2.0
Nitrites (in terms of NO_2), mg/L	0.02	0.02	0.02	0.03	0.014	3.0
Nitrates (in terms of NO_3), mg/L	0.55	1.44	0.45	1.04	0.024	45
Chemical compounds occurring during water treatment						
Chloroform, mg/L	0.07	0.11	0.02	0.02	< 0.001	0.2
Free residual chlorine, mg/L	0.94	1.17	0.05	0.27	0.317	NA
Residual combined chlorine, mg/L	0.59	0.95	1.16	1.40	0.317	0.8–1.2
Microbiological indices						
Total coliforms, in 100 mL	0	0	0	0	x	None
Thermo-tolerant coliforms, in 100 mL	0	0	0	0	x	None
Total microbial count (TMC), number of colony forming bacteria in 1 mL	0.03	0.41	0	0.26	< 0.001	Not more than 50

Table 2

Laboratory tests results showing drinking water quality supplied to population through the Central Water Treatment Facilities in Arkhangelsk

Indicator	Prior to preammonization		After preammonization		p	Normal value[6]
	Me	P_{90}	*Me*	P_{90}		
Organoleptic indicators						
Odor at 20 °C, points	1	1.3	1	1.3	0.114	2
Color (colority), degrees	15	20	18	23	< 0.001	20
Turbidity, mg/L (Kaolin)	0.86	1.47	0.66	1.02	0.002	1.5
Complex indicators						
Hydrogen ion concentration, pH units	6.9	7.4	6.9	7.3	0.684	6–9
Permanganate oxidizability, mg/L	4.1	5.2	4.4	4.8	0.547	5
Total dissolved solids (solid residue), mg/L	277	363	199	310	0.023	1000
Inorganic substances						
Aluminum (Al (3+)), mg/L	0.25	0.42	0.15	0.24	< 0.001	0.5
Iron (Fe, total), mg/L	0.31	0.48	0.32	0.64	0.576	0.3
Chlorides (in terms of CL), mg/L	17.35	22.30	10.73	15.88	< 0.001	350

[7] SanPiN (Sanitary Rules and Norms) 2.1.4.1074-01. Drinking Water. Hygienic Requirements for the Quality of Water from Centralized Drinking Water Supply Systems. Quality control. Moscow, Ministry of Public Health of Russia, 2002,103 p.

Indicator	Prior to preammonization		After preammonization		p	Normal value[6]
	Me	P_{90}	*Me*	P_{90}		
Sulfates (SO_4), mg/L	71.8	122.6	74.7	105.6	0.327	500
Ammonia (in terms of nitrogen)	0.11	0.22	0.43	0.66	< 0.001	2.0
Nitrites (in terms of NO_2), mg/L	0.02	0.02	0.03	0.12	< 0.001	3.0
Nitrates (in terms of NO_3), mg/L	0.73	1.42	0.54	1.38	0.31	45
Chemical compounds formed during water treatment						
Chloroform, mg/L	0.066	0.085	0.009	0.043	< 0.001	0.2
Free residual chlorine, mg/L	0.10	0.25	0.01	0.14	< 0.001	NA
Residual combined chlorine, mg/L	0.11	0.15	0.50	0.64	< 0.001	NA
Microbiological indices						
Total coliforms, in 100 mL	0	0.04	0	0.04	0.888	None
Thermo=tolerant coliforms, in 100 mL	0	0.03	0	0.02	0.829	None
Total microbial count (TMC), number of colony forming bacteria in 1 mL	0.05	0.68	0.05	0.36	0.580	Not more than 50

water preammonization on the content of free residual chlorine and residual combined chlorine due to the low number of observations before it was implemented ($n = 4$).

At the median level, the total microbial count (TMC) was not found after water preammonization was implemented; the TMC at the P_{90} level decreased by 1.6 times ($p < 0.001$) at the re-lift pumping plant of CWTFs.

Assessment of water quality in the supply net. Comparative assessment of quality of drinking water sampled in the supply net prior to preammonization and after it, did not reveal any changes in odor and hydrogen ion concentration ($p > 0.05$).

It was found that after preammonization was implemented, colority increased by 1.2 times at the median level, the ammonia concentration increased by 3.9 times ($p < 0.001$), and nitrites concentration increased by 1.5 times ($p < 0.001$) (Table 2). At the same time, the values of these indicators did not exceed the threshold limit values, with the exception of colority at the P_{90} level.

In the supply net, after preammonization was implemented, water turbidity decreased by 1.3 times ($p = 0.002$), the solid residue decreased by 1.1 times ($p = 0.023$), and concentration of aluminum and chlorides decreased by 1.7 and 1.6 times, respectively ($p < 0.001$). The average content of chloroform decreased by 7.3 times, and free residual chlorine decreased by 10 times ($p < 0.001$). An average concentration of residual bound chlorine increased by 4.5 times ($p < 0.001$). An increase in contents of residual bound chlorine in the supply net and a decrease in free residual chlorine indicate that chlorine remains in the supply net for a longer period, and it determines longer bactericidal effects produced by chlorine in the water supply net.

In comparison with the re-lift pumping plant, quality of water in the supply net in terms of iron content deteriorated owing to significant wear and tear of the water supply network in Arkhangelsk (70.7 %) and the large number of accidents in it. However, the iron content in water in the supply net prior to preammonization was implemented and after it did not show statistically significant differences.

A decrease in concentrations of solid residue, chlorides, nitrates and sulfates in drinking water at the re-lift pumping plant of CWTFs and in the supply net in Arkhangelsk is associated with water natural composition. A decrease in concentration of aluminum at the re-lift pumping plant of CWTFs and in the supply net doesn't result from water preammonization implementation.

After preammonization was implemented, contents of thermo-tolerant coliforms (TTCs) and TMC in water in the supply net decreased by 1.5 and 1.9 times, respectively, while the total coliforms number (TCs) remained unchanged.

The characteristics risks that developing general toxic effects would develop showed that values of the hazard quotients for all analyzed substances and the hazard indices for critical organs and systems, both prior to the implementation of preammonization and after it, did not exceed 1.0. Nevertheless, after the preammonization was implemented, the hazard indices for the blood and skin systems decreased by 3.2 times, and they decreased by 5–7 times for the circulatory system, central nervous system and digestive organs (figure).

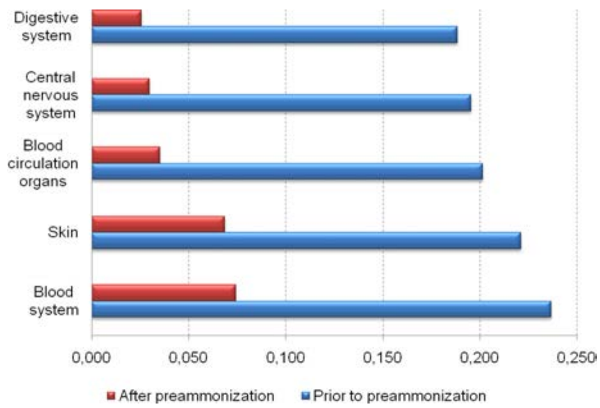

Figure. Hazard indices for critical organs and systems when exposed to chemicals contained in drinking water, prior to preammonization and after it was implemented

A decrease in a risk of developing general toxic effects on critical organs and systems was primarily attributable to a fall in contents of chloroform in drinking water after preammonization was implemented. A contribution made by chloroform in the hazard indices after preammonization was implemented went down by 10–47 % as compared to water treatment based on traditional chlorination.

The major outcome gained via implementing water preammonization in Arkhangelsk was a decrease in chloroform contents in drinking water at the re-lift pumping plant from 0.07 to 0.02 mg/L and in the supply net from 0.066 to 0.009 mg/L. The results of this study are consistent with the data obtained in St. Petersburg, where tests on implementing water ammonization with ammonium sulfate were carried out. As a result of preammonization at the water treatment facilities in St. Petersburg, chloroform contents in drinking water decreased from 90–120 to 1–5 μg/dm^3 [18].

In Khabarovsk, implementation of water preammonization with the use of ammonium sulfate allowed preventing drinking water quality form further deterioration as per microbiological indicators in the supply net and reducing contents of chlorinated organic compounds in drinking water lower than hygienic standards [19]. Water preammonization with ammonium sulfate became an effective way to reduce concentrations of chlorinated volatile organic compounds up to seven times in water supplied to population of Rostov-on-the-Don, Taganrog and Azov [20].

The implementation of water preammonization and the use of sodium hypochlorite at the Sludinskaya waterworks in Nizhny Novgorod made it possible to reduce concentrations of chloroform to no more than 0.01 mg/L, as well as to reduce concentrations of disinfection by-products (DBPs) in drinking water by 60–80 % [21]. Employees of OJSC "Mosvodokanal" carried out a study on implementation of water preammonization as a part of water treatment in Moscow; as a result chloroform concentrations decreased from 50–87 to 6–15 μg/L [4].

To reduce contents of chlorinated organic compounds in drinking water, preliminary ammonization and chlorination are the most efficient technology, but it results in occurrence of chloramines which diminish the effect of discoloration. This explains more intense color of water at the re-lift pumping plant of the wastewater treatment facilities (1°) and in the supply net (3°). OJSC "Mosvodokanal" carried out a number of laboratory tests to determine dependence between colority value on a dose and the order in which chlorine and ammonia were introduced into water. As a result, color reducing was not achieved: when ammonia was added 5 minutes after chlorine, color decreased only by 2° [4].

According to data provided by LLC RVK-Arkhangelsk that operates CWTFs in Arkhangelsk, the total consumption of a chemical reagent (sodium hypochlorite) amounted to 318.2 tons in 2019. Prior to the implementation of water ammonization, the total consumption of the reagent was 666 tons per year. Therefore, after water preammonization was implemented, the consumption of this chemical reagent decreased by 2.1 times and it means reagent saving and economic efficiency of implemented water preammonization. At the Sludinskaya waterworks in Nizhny Novgorod, the implementation of preammonization helped reduce the chlorine consumption by 40–50 % [21].

Conclusions. The use of ammonium sulphate for preliminary ammonization as part of water conditioning and drinking water purification at CWTFs in Arkhangelsk helped significantly improve quality of drinking water supplied to population. A positive effect achieved due to preammonization was a reduction in the amount of chlorination by-products and improved microbiological quality of drinking water. A reduction in chloroform contents decreases the risk of developing general toxic effects on critical organs and systems. Water preammonization as a new technology used at the stage of water treatment made it possible to improve quality of waterworks operation, reduce operating costs, decrease the amount of disinfection by-products (DBPs) and improve drinking water quality.

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Research article

ASSESSING ACUTE INHALATION HEALTH RISK CAUSED BY EXPOSURE TO PRODUCTS CREATED BY NICOTINE-CONTAINING STUFF CONSUMPTION IN ENCLOSED SPACES

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Contemporary research reveals that electronic devices for nicotine consumption produce not so negative effects on health due to adverse chemicals being emitted in substantially lower quantities. Nevertheless, such consumption still results in emission of various organic and non-organic substances with their effects on health being rather unpredictable. It is necessary to conduct additional studies, including those focusing on passive smoking of electronic cigarettes and assessing health risks caused by exposure to them.

Our research goal was to assess acute health risks caused by passive consumption of tobacco and nicotine-containing products.

We built a model for tobacco or nicotine consumption by actual consumers (volunteers) and the process was evened as per a number of consumption sessions. We examined three products: tobacco cigarettes (cigarettes), electronic nicotine delivery system (ENDS), and a tobacco heating system (IQOS). Background air quality parameters were measured in a specifically organized enclosed space prior to each study session. We also conducted experiments in so called «reference groups» when research participants didn't consume the examined products but were in the same conditions. Health risks were assessed as per the Guide R 2.1.10.1920-04 «The Guide on assessing health risks caused by exposure to chemicals that pollute the environment».

Use of ENDS and IQOS does not result in significant changes in air composure and does not cause unacceptable acute health risk. Combined effects produced by contaminants on organs and systems resulted in health risks for respiratory organs, eyes, and body as a whole being insignificantly higher than permissible levels; these risks were practically the same as those detected for a reference group. Tobacco smoking resulted in unacceptable acute risks 1.5 hours after an experiment started; these risks were caused by elevated concentrations of such contaminants as acetaldehyde, formaldehyde, $PM_{2.5}$, PM_{10}, and carbon monoxide.

Key words: *health risk, acute risk, acute additional risk, passive smoking, tobacco, nicotine-containing products, cigarettes, electronic nicotine delivery systems, electronic tobacco heating devices.*

According to data provided by the RF Public Healthcare Ministry, in Russia annually up to 300 thousand people die due to smoking-related diseases [1, 2]. As per data provided by the WHO, tobacco smoking is among the most significant threats for human health that causes approximately 7 million death cases every year all over the world; 890 thousand out of them are non-smokers who were exposed to tobacco smoke [3, 4].

According to the Concept on the state policy aimed at fighting against consumption of tobacco and other nicotine-containing products for a period up to 2035[1], the RF Public Health-

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[1] The Concept on the state policy aimed at fighting against consumption of tobacco and other nicotine-containing products for a period up to 2035 and further: The RF Government Order dated November 18, 2019 No. 2732-r. Garant: the information and legal portal. Available at: https://www.garant.ru/products/ipo/prime/doc/72943536/ (January 27, 2021).

care Ministry aims to reach maximum possible decrease in mortality and morbidity caused by smoking-related diseases as well as to prevent nicotine-containing products from further spread among population. To achieve the goals set by the Concept a system for managing its implementation is being created; this system involves developing mechanisms for risk monitoring, assessment, and minimization.

According to the Concept, by 2035 a number of smokers among adult population should go down to 21 %. Initial parameters are fixed as in December 2018 when smokers accounted for 29 % among adult population in Russia.

It should be noted that recently new smoking products have been becoming more and more popular among population, namely electronic nicotine delivery systems (ENDS) and electronic tobacco heating systems (ETHS) [5, 6]. It is especially true for young people aged 18–24 since approximately 19.1 % people in this age group use such products and it is 10 times higher than in other age groups [7]. Electronic vaping is already widely spread all over the world and many countries introduce strict rules for it given new available actual data on negative effects produced by vaping on health [8–12]. But at present it is still rather difficult to issue legislative acts regarding a ban on use of electronic cigarettes in public places; although such an initiative was introduced to the State Duma, an absence of evidence base proving that "passive consumption" of nicotine-containing products causes health risks doesn't allow determining what limitations should be imposed on distribution of such products which are considered an alternative to tobacco products [13–21].

Besides, there were some studies [22] on electronic cigarettes and a medicinal nicotine inhalator as an etalon product performed in the USA, Great Britain and Poland; they revealed that ENDS produced certain toxicants but their levels were from 9 to 450 times lower than in cigarette smoke. But still, a mix that was inhaled via using ENDS contained small quantities of 1,2-propanediol, 1,2,3-propanetriol, diacetyl, flavor additives, and also nicotine in trace quantities [23].

Given all the above mentioned, additional studies are required including those focusing on "passive consumption" of electronic cigarettes; it is also vital to assess health risks caused by exposure to them.

Our research goal was to assess acute health risk caused by passive consumption of tobacco in nicotine-containing products.

Data and methods. 3 types of nicotine-containing products were examined as sources of adverse chemicals emission, namely cigarettes, an electronic nicotine delivery system (ENDS), and an electronic tobacco heating system (ETHS). Volunteers that had been smoking for not less than three years prior to our experiment took part in it; they all gave their informed consent to participate. To achieve greater representativeness in our research, we examined each product for three days and each examination involved three volunteers participating in it. A reference group was made up of non-smokers who stayed in an experiment room for four and a half hours. All examinations were performed in a specifically prepared room.

Background air quality was estimated prior to the experiment started. Air samples were taken thrice during the experiment, 1.5, 3 and 4.5 hours after it had started. Sampling devices and a meteometer gauge were placed at a height where a sitting person breathed.

Air samples were analyzed at "Arbitrazh" certified laboratory chemical and analytical center in conformity with the requirements fixed in the valid regulatory and methodical documents[2]. All obtained results were statistically processed with IBM SPSS Statistics, v. 22.

[2] Methodical guidelines 4.1.1673-03. Chromato-mass-spectrometric determination of substances that are contained in tobacco and tobacco dust in ambient air; M-21. The procedure for measuring nicotine mass concentration in industrial emissions into ambient air, in working area air and in ambient air, with gas chromatography; M-MVI-198-07. The procedure for measuring carbonyl-containing substances in ambient air in settlements and working area air via HPLC using active sampling device; RD 52.04.830-2015. Mass concentration of particulate matter PM_{10} and $PM_{2,5}$ in ambient air. The gravimetric procedure; "Methodical guidelines on analyzing objects with unknown structure with GLC, CMS, HPLC, GC/IR/PS, AE-ICP, MS-ICP" D.I. Mendeleev's Russian Metrology Scientific and Research Institute No. 01-07. *KonsultantPlus*. Available at: https://docs.cntd.ru (January 26, 2021).

Our research was given the following methodical grounds: the Guide R 2.1.10.1920-04 "The Guide on assessing health risks under exposure to chemicals that pollute the environment"[3], guidelines developed by the US Environmental Protection Agency[4] and the Office of Environmental Health Hazard Assessment[5], Integrated Risk Information System, (IRIS).

Risks were assessed by an organization certified in this sphere in the System for voluntary certification of institutions dealing with health risk assessment (Conformance Certificate No. SDS 062, registered in the System database on December 26, 2018).

We considered short-term (acute) exposure lasting for several hours in our research. This scenario was selected due to the following factors:

– the experiment involved modeling an exposure scenario taking into account potential inhalation of contaminant with air in a closed room (so called "passive consumption") and not its direct (or "active") consumption;

– "passive consumers" had to spend limited amount of time in the experiment room according to the experiment design;

– there was no possibility to predict periodicity of contacts an exposed person would have with the examined substances in real conditions during the whole life span; consequently, it was impossible to calculate chronic dose exposure [11, 16, 17, 19].

As for this experimental situation, we modeled 4.5-hour exposure to contaminants in the air in the closed experimental room and it was considered short-term and acute exposure.

Reference concentrations under acute inhalation exposure, ARfC, were applied to assess acute risks caused by exposure to contaminants. Their values were taken from the Appendix 2 to the Guide R 2.1.10.1920-04 as well as from USEPA and OEHHA databases.

We applied a standard formula for calculating an acute risk (hazard quotient HQ_R) in our research:

$$HQ_R = C/ARfC,$$

where C is concentration of a substance, $ARfC$ is a reference concentration under acute exposure.

In addition to acute risk assessment and according to the Guide R 2.1.10.1920-04 we also calculated some parameters that described difference between an acute risk caused by exposure to a certain chemical among people who consumed tobacco or nicotine at a specific moment of time during the experiment and an acute risk that occurred for the reference group at the same moment. A term "acute additional risk" (HQ_{R_add}) was applied for this parameter in the present work; it was calculated as per the following formula:

$$HQ_{R\_add} = HQ_{R\_t} - HQ_{R\_bkgd},$$

where HQ_{R_t} is an acute risk at a certain moment of time during the experiment (when samples were being taken); HQ_{R_bkgd} is a background acute risk for the reference group at the same moment of time during the experiment.

Results and discussion. The hazard identification stage involved estimating a structure of contaminants in the air in the closed room that occurred due to different tobacco- and nicotine-containing products consumption (Table 1).

Acute health risks were assessed basing on results obtained via laboratory tests performed on the air in the closed room; the assessment revealed that air quality became unacceptable already after 1.5 hours when cigarette smoking was modeled in the experiment. It was primarily due to elevated concentrations of acetaldehyde, formaldehyde, and particulate matter that

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[3] R 2.1.10.1920-04. The Guide on assessing health risks caused by exposure to chemicals that pollute the environment. Moscow, The Federal Center for State sanitary and Epidemiologic Surveillance of the RF Public Healthcare Ministry Publ., 2004, 143 p.

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[5] Environmental Topics. The Office of Environmental Health Hazard Assessment (OEHHA). Available at: https://oehha.ca.gov/environmental-topics (January 26, 2021).

were 1.5–2 times higher than permissible ones after 1.5 hours. Acute risks caused by acetaldehyde and formaldehyde contents didn't exceed permissible levels during the whole experiment when ENDS and ETHS consumption was modeled (Tables 2 and 3).

Overall, we can state that air contamination in the closed room caused by ENDS and ETHS consumption didn't cause unacceptable acute health risks even after a long period of time spent in that room without any air ventilation; meanwhile, cigarette smoking caused unacceptable health risk already 1.5 hour after the experiment started (Table 2).

Taking into account data on effects produced by various chemicals on a body as a whole or organs and systems in particular provided in Appendix 2, the Guide R 2.1.10.1920-04, we created a list of critical organs and systems that were target ones for adverse impacts exerted by the examined chemicals (Table 4).

Table 1

Priority contaminants in the air in the experimental room and hygienic standards regulating them

Contaminant	ARfC, mg/m^3
Formaldehyde	0.048
Acetaldehyde	0.115
Buta-1,3-dien (Divinyl)	0.11
Benzene	0.15
Methylbenzene (Toluene)	3.8
Carbon oxide	23
Nitrogen dioxide (Nitrogen (IV) oxide)	0.47
Nitrogen (II) oxide (Nitrogen oxide)	0.72
$PM_{2,5}$	0.065
PM_{10}	0.15

Note:

ARfC are reference concentrations under acute exposure;

PM_{10} are particulate matter with mass concentrations of particles smaller than 10 μm in diameter;

$PM_{2,5}$ are particulate matter with mass concentrations of particles smaller than 2.5 μm in diameter.

Table 2

Concentrations of contaminants and acute and acute additional risks caused by specific contaminants occurring due to tobacco or nicotine consumption in the air in the closed room at different moments of time during the experiment

Components	Experiment	Concentrations (average values, mg/m³) and risk levels										
		Background values (sampling time 8:00–9:30)		After 1.5 hours (sampling time 9:40–11:10)			After 3 hours (sampling time 11:20–12:50)			After 4.5 hours (sampling time 13:00–14:30)		
		Concentration	Acute risk	Concentration	Acute risk	Acute additional risk	Concentration	Acute risk	Acute additional risk	Concentration	Acute risk	Acute additional risk
1	2	3	4	5	6	7	8	9	10	11	12	13
Benzene	Reference	0.0011	0.007	0.0016	0.01		0.011	0.07		0.009	0.06	
	Cigarettes	0.0009	0.006	0.014	0.09	0.083	0.027	0.18	0.107	0.034	0.23	0.17
	ENDS	0.0009	0.006	0.0022	0.02	0.004	0.0029	0.02	-0.054	0.0029	0.02	-0.04
	ETHS	0.0013	0.009	0.0015	0.01	-0.001	0.0015	0.01	-0.063	0.0018	0.01	-0.05
Toluene	Reference	0.0034	0.001	0.0053	0.001		0.0054	0.001		0.0052	0.001	
	Cigarettes	0.0019	0.001	0.023	0.01	0.005	0.041	0.01	0.009	0.053	0.01	0.01
	ENDS	0.0022	0.001	0.0057	0.002	0	0.0083	0.002	0.001	0.0088	0.002	0.001
	ETHS	0.0044	0.001	0.0045	0.001	0	0.004	0.001	0	0.0051	0.001	0
Formaldehyde	Reference	0.024	0.5	0.035	0.73		0.038	0.79		0.044	0.92	
	Cigarettes	0.026	0.542	0.072	1.50	0.771	0.1	2.08	1.292	0.106	2.21	1.29
	ENDS	0.024	0.5	0.033	0.69	-0.042	0.042	0.88	0.083	0.044	0.92	0.00
	ETHS	0.022	0.458	0.029	0.60	-0.125	0.031	0.65	-0.146	0.036	0.75	-0.17
Acetaldehyde	Reference	0.008	0.07	0.014	0.12		0.017	0.15		0.018	0.16	
	Cigarettes	0.009	0.078	0.125	1.09	0.965	0.262	2.28	2.13	0.332	2.89	2.73
	ENDS	0.008	0.07	0.017	0.15	0.026	0.03	0.26	0.113	0.248	2.16	2.00
	ETHS	0.009	0.078	0.02	0.17	0.052	0.031	0.27	0.122	0.042	0.37	0.21
Particulate matter $PM_{2,5}$	Reference	0.034	0.523	0.048	0.74		0.044	0.68		0.053	0.82	
	Cigarettes	0.026	0.4	0.68	10.46	9.723	1.2	18.46	17.785	1.2	18.46	17.65
	ENDS	0.045	0.692	0.065	1.00	0.262	0.078	1.20	0.523	0.084	1.29	0.48
	ETHS	0.039	0.6	0.071	1.09	0.354	0.071	1.09	0.415	0.07	1.08	0.26

1	2	3	4	5	6	7	8	9	10	11	12	13
Particulate matter PM_{10}	Reference	0.048	0.32	0.042	0.28		0.047	0.31		0.0513	0.34	
	Cigarettes	0.035	0.233	0.66	4.40	4.12	1.2	8.00	7.687	1.1333	7.56	7.21
	ENDS	0.053	0.353	0.066	0.44	0.16	0.097	0.65	0.333	0.0903	0.60	0.26
	ETHS	0.038	0.253	0.073	0.49	0.207	0.075	0.50	0.187	0.0747	0.50	0.16
Carbon oxide	Reference	0.467	0.648	0.967	1.34		0.967	1.34		1.167	1.62	
	Cigarettes	0.367	0.509	8.167	11.34	10	10.633	14.77	13.426	13.333	18.52	16.90
	ENDS	0.467	0.648	1.9	2.64	1.296	2.967	4.12	2.778	3.3	4.58	2.96
	ETHS	0.467	0.648	1.167	1.62	0.278	1.033	1.44	0.093	1.2	1.67	0.05
Nitrogen (II) oxide (Nitrogen oxide)	Reference	0.041	0.056	0.043	0.06	0	0.048	0.07	0	0.049	0.07	0.00
	Cigarettes	0.049	0.068	0.196	0.27	0.213	0.293	0.41	0.34	0.314	0.44	0.37
	ENDS	0.014	0.019	0.02	0.03	-0.032	0.029	0.04	-0.025	0.034	0.05	-0.02
	ETHS	0.053	0.074	0.053	0.07	0.013	0.056	0.08	0.012	0.056	0.08	0.01
Nitrogen dioxide (Nitrogen (IV) oxide)	Reference	0.005	0.01	0.001	0.001	0	0	0.00	0	0	0.000	0.00
	Cigarettes	0.003	0.006	0.003	0.01	0.004	0.002	0.004	0.004	0.001	0.003	0.003
	ENDS	0.006	0.013	0	0.001	-0.001	0	0.00	0	0	0.000	0.000
	ETHS	0.012	0.026	0.001	0.001	0	0.002	0.004	0.004	0.001	0.001	0.001

Table 3

Contaminants concentrations and acute risk caused by specific substances occurring due to tobacco or nicotine consumption in the air in the closed room after 4.5 hours of the experiment

Components	Experiment	Contaminants concentrations, mg/m³		Acute risk	
		Me	$Q_{0.25–0.75}$*	*Me*[8]	$Q_{0.25–0.75}$[9]
Formaldehyde	Reference	0.0365	0.03225–0.0395	0.76	0.67–0.82
	Cigarettes	0.086	0.0605–0.1015	1.79	1.26–2.11
	ENDS	0.0375	0.03075–0.0425	0.78	0.64–0.89
	ETHS	0.03	0.02725–0.03225	0.63	0.57–0.67
Acetaldehyde	Reference	0.0155	0.0125–0.01725	0.14	0.11–0.15
	Cigarettes	0.1935	0.096–0.2795	1.68	0.83–2.43
	ENDS	0.0235	0.01475–0.0845	0.20	0.13–0.74
	ETHS	0.0255	0.01725–0.03375	0.22	0.15–0.29
Buta-1,3-dien (Divinyl)	Reference	0.0002	0.0002–0.0002	0.00	0.002–0.002
	Cigarettes	0.049	0.02705–0.0675	0.45	0.25–0.61
	ENDS	0.001	0.000575–0.001525	0.01	0.005–0.01
	ETHS	0.0004	0.00035–0.0004	0.00	0.003–0.004
Benzene	Reference	0.0053	0.001475–0.0095	0.04	0.01–0.06
	Cigarettes	0.0205	0.010725–0.02875	0.14	0.07–0.19
	ENDS	0.00255	0.001875–0.0029	0.02	0.01–0.02
	ETHS	0.0015	0.00145–0.001575	0.01	0.01–0.01
Methylbenzene (Toluene)	Reference	0.00525	0.00475–0.005325	0.001	0.001–0.001
	Cigarettes	0.032	0.017725–0.044	0.01	0.005–0.01
	ENDS	0.007	0.004825–0.008425	0.002	0.002–0.002
	ETHS	0.00445	0.0043-0.00465	0.001	0.001–0.001
Carbon oxide	Reference	0.967	0.842–1.017	1.34	1.17–1.41
	Cigarettes	9.4	6.217–11.308	13.06	8.63–15.71
	ENDS	2.4335	1.54175–3.05025	3.38	2.14–4.24
	ETHS	1.1	0.8915–1.17525	1.53	1.23–1.63
Nitrogen dioxide (Nitrogen (IV) oxide)	Reference	0.0005	0–0.002	0.0005	0–0.003
	Cigarettes	0.0025	0.00175–0.003	0.005	0.003–0.006
	ENDS	0	0–0.0015	0.0005	0–0.004
	ETHS	0.0015	0.001–0.0045	0.003	0.001–0.01
Nitrogen (II) oxide (Nitrogen oxide)	Reference	0.0455	0.0425–0.04825	0.06	0.06–0.1
	Cigarettes	0.2445	0.15925–0.29825	0.34	0.22–0.41
	ENDS	0.0245	0.0185–0.03025	0.03	0.03–0.04
	ETHS	0.0545	0.053–0.056	0.08	0.07–0.08

Components	Experiment	Contaminants concentrations, mg/m³		Acute risk	
		Me	$Q_{0.25–0.75}$*	*Me*[8]	$Q_{0.25–0.75}$[9]
$PM_{2,5}$	Reference	0.046	0.0415–0.04925	0.71	0.64–0.76
	Cigarettes	0.94	0.5165–1.2	14.46	7.95–18.46
	ENDS	0.0715	0.06–0.0795	1.10	0.92–1.22
	ETHS	0.0705	0.06225–0.071	1.08	0.96–1.09
PM_{10}	Reference	0.0475	0.04575–0.048825	0.32	0.30–0.33
	Cigarettes	0.89665	0.50375–1.149975	5.98	3.36–7.67
	ENDS	0.07815	0.06275–0.091975	0.52	0.42–0.61
	ETHS	0.07385	0.06425–0.074775	0.49	0.43–0.50

N o t e : *Me* means median; * is interquartile range.

T a b l e 4

A list of critical organs and systems and chemicals that exert their impacts on them

Critical organs and systems	A number of chemicals targeting a certain organ or a system	Chemicals
Respiratory organs	6	Toluene, Formaldehyde, Particulate matter $PM_{2,5}$, PM_{10}, Nitrogen oxide, Nitrogen dioxide
Nervous system	1	Toluene
Development	2	1,3-butadien, Carbon monoxide
Eyes	3	Toluene, Formaldehyde, Acetaldehyde
Blood	1	Carbon oxide
Impacts on a body as a whole	2	Particulate matter $PM_{2,5}$, PM_{10}

Having analyzed impacts exerted by different chemicals that targeted the same organs and systems and having calculated *HI* for them, we revealed that the highest acute risks were caused by cigarette smoking for the respiratory organs and overall impacts on a body as a whole, risk values being 28.68 and 26.02 taking background concentrations into account and 26.54 and 24.86 without them (acute additional risk) accordingly (Tables 5 and 6). We should note that acute risks for all organs and systems that were sensitive to the examined chemicals were the lowest in case ETHS was used and they practically didn't differ from those detected for the reference group.

Analysis of acute risks and acute additional risks indicated that background contamination didn't make any significant contribution into acute risks as it was confirmed by negligible differences in risk levels (Tables 5 and 6).

Despite there were several measures taken for providing purity of the experiment, we should mention several objective factors that create certain difficulties in assessing the experimental results:

1. It would be advisable to unify quantity of different consumed nicotine-containing products for proper comparative assessment of chemicals emission. However, we modeled actual tobacco or nicotine consumption by actual people who consume such products and this consumption was leveled off as per a number of consumption cases. Due to it this uncertainty can be considered negligible.

2. We detected "marker-substances" in the air in the experimental room during the experiment for the reference group and at a stage when background (initial) concentrations were determined.

3. Some "marker-substances" occur in ambient air and can influence the experimental results.

4. The air in the experimental room was not ventilated during the whole experiment so that "marker-substances" could be efficiently determined via laboratory tests. Due to it the obtained absolute values can be different from similar data obtained by other researchers.

Additional acute risks were analyzed in dynamics and this analysis revealed that the greatest additional acute risks occurred due to cigarettes smoking (Figures 1–8). Overall, consumption of all tobacco or nicotine-containing produces resulted in additional risks during the experiment due to an increase

Table 5

Hazard indexes for acute non-carcinogenic risk (*HI*) caused by combined exposure to different chemicals for various organs and systems taking background concentrations into account

Experiment	Acute non-carcinogenic risks for specific organs and systems (hazard index *HI*) under 4.5-hour exposure					
	Respiratory organs	Systemic impacts	Nervous system	Develop-ment	Eyes	Blood
Reference group (non-smokers)	2.14	1.16	0.001	1.62	1.08	1.62
Cigarette smoking	28.68	26.02	0.014	18.52	5.11	18.52
ENDS consumption	2.86	1.89	0.002	4.58	3.08	4.58
ETHS consumption	2.41	1.58	0.001	1.67	1.12	1.67

Table 6

Hazard indexes for acute non-carcinogenic risk (*HI*) caused by combined exposure to different chemicals for various organs and systems without taking background concentrations into account

Experiment	Additional acute non-carcinogenic risks for specific organs and systems (hazard index *HI*) under 4.5-hour exposure					
	Respiratory organs	Systemic impacts	Nervous system	Development	Eyes	Blood
Reference group (non-smokers)	–	–	–	–	–	–
Cigarette smoking	26.54	24.86	0.01	16.90	4.04	16.90
ENDS consumption	0.72	0.74	0.001	2.96	2.00	2.96
ETHS consumption	0.26	0.42	0.00	0.05	0.04	0.05

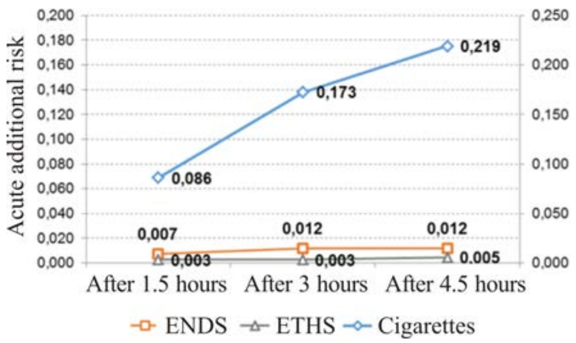

Figure 1. Acute additional risk caused by exposure to benzene for different consumed tobacco- or nicotine-containing products

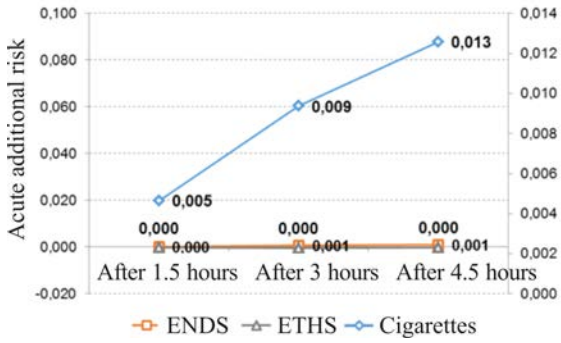

Figure 2. Acute additional risk caused by exposure to toluene for different consumed tobacco- or nicotine-containing products

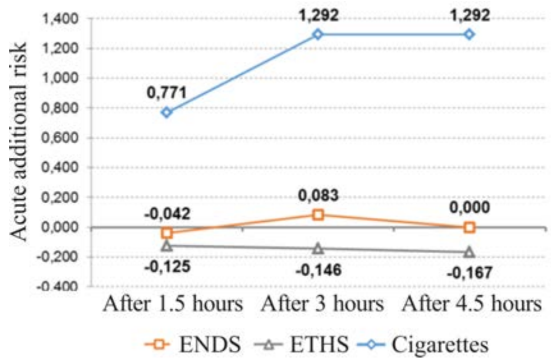

Figure 3. Acute additional risk caused by exposure to formaldehyde for different consumed tobacco- or nicotine-containing products

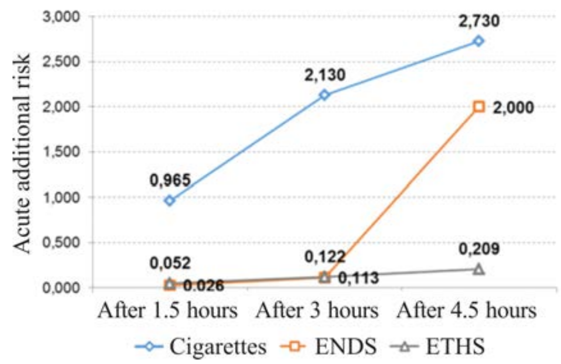

Figure 4. Acute additional risk caused by exposure to acetaldehyde for different consumed tobacco- or nicotine-containing products

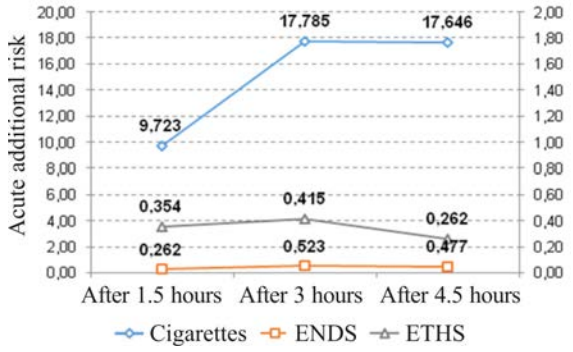

Figure 5. Acute additional risk caused by exposure to particulate matter $PM_{2,5}$ for different consumed tobacco- or nicotine-containing products

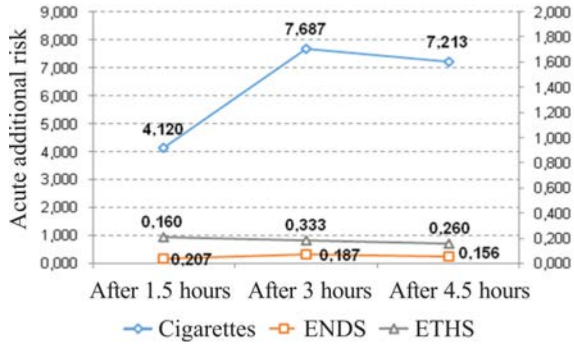

Figure 6. Acute additional risk caused by exposure to particulate matter PM_{10} for different consumed tobacco- or nicotine-containing products

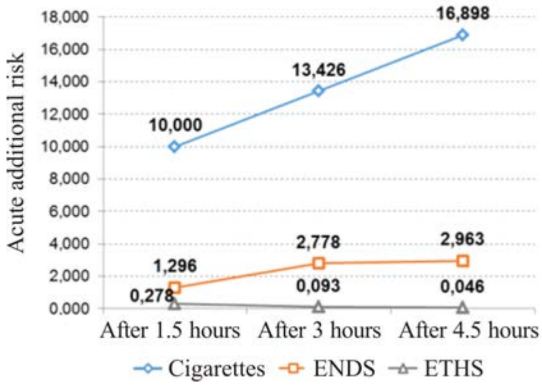

Figure 7. Acute additional risk caused by exposure to carbon oxide for different consumed tobacco- or nicotine-containing products

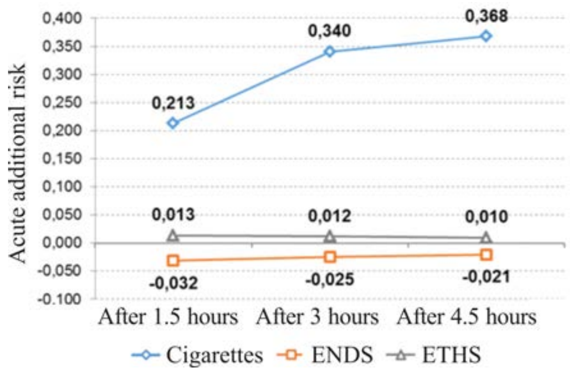

Figure 8. Acute additional risk caused by exposure to nitrogen oxide (II) for different consumed tobacco- or nicotine-containing products

in adverse chemicals concentrations. But at the same time, this growth in additional risks was the most apparent in case of cigarette smoking as it can be seen in Figures 1–8. This dynamics in additional risk growth was substantially lower in case ENDS or ETHS were used; it was equal to zero or even negative in some cases.

Conclusion. Health risks were assessed basing on the results obtained via laboratory tests performed on the air samples taken inside the closed room under 4.5-hour exposure that was modeled in the experiment. The assessment revealed that ENDS and ETHS consumption didn't result in any significant changes in air composure and didn't cause any unacceptable acute health risks. When examining combined exposure to contaminants on organs and systems, we established that actual risks were slightly higher than permissible ones for the respiratory organs, eyes, and overall impacts on a body as a whole but they practically didn't differ from those detected for the reference group. At the same time cigarette smoking caused unacceptable acute risks already 1.5 hours after the experiment started; those risks occurred due to elevated concentrations of acetaldehyde, formaldehyde, particulate matter $PM_{2,5}$ and PM_{10}, and carbon monoxide. Elevated risk levels caused by ENDS consumption were reached only after 3 hours and occurred due to exposure to only two chemicals, acetaldehyde and carbon oxide.

Our experimental data gave ground for recommending separate places to be organized for ENDS and ETHS consumption and tobacco smoking since ENDS and ETHS consumers may be exposed to additional risks caused by effects produced by tobacco smoke.

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Research article

A SYSTEM FOR CREATING HEALTHY LIFESTYLE IN EDUCATIONAL ESTABLISHMENTS AS A WAY TO PREVENT HEALTH DISORDERS IN CHILDREN

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The paper focuses on morbidity among children that was examined as per medical aid appealability and prevailing behavioral factors among children aged 10–14 who attended schools with different systems for healthy lifestyle creation. In 2008, when a continuous system for healthy lifestyle formation was just being introduced, there were only slight differences in primary and overall morbidity among children aged 10–14 who attended test schools and reference ones; 10 years later, in 2018, primary and overall morbidity was substantially lower among children who attended tests schools than among those who went to reference ones. Primarily, it concerns such «school-induced» diseases as diseases of the eye and adnexa; diseases of the respiratory system; gastric diseases; diseases of the musculoskeletal system and the connective tissue; injury, poisoning and certain other consequences of external causes. Data obtained via questioning that was performed among schoolchildren and concentrated on them assessing their health are well in line with official data on morbidity obtained as per medical aid appealability. Children from test schools estimated their health as poor much less frequently than children from reference schools; they were significantly less irritable, and bad mood was also not so frequent among them.

Healthy lifestyle recommended for children included an obligatory combination of 5 basic components: fruit and vegetables should be consumed every day; sleep should be not shorter than 8 hours; physical activity was to be 1 hour a day or longer not more than 2 hours a day should be spent working or playing on a PC, laptop, or a smartphone; no alcohol intake and no smoking either. Assessment of this lifestyle revealed that a share of children who pursued it was higher in test schools than in reference ones; in the 5–6th grades, 18.7±1.62 % and 11.0±1.43 % (t=3.56) accordingly; in the 7–8th grades, 19.2±2.09 % and 11.8±1.41 % (t=2.93).

Key words: *children, secondary schools, a continuous system for healthy lifestyle formation, morbidity, questioning, health self-assessment, behavioral factors prevalence, healthy habits.*

At present primary and secondary prevention unfortunately don't provide the results they should [1]; it is confirmed, among other things, by absence of any positive trends regarding schoolchildren's somatic and mental health [2–4]. Given that, it seems vital to make the school environment a useful resource for improving their health and increasing welfare for everyone [5, 6]; to achieve that, greater attention should be paid to examining and analyzing various factors that provide children's and teenagers' health instead of simple risks reduction [7].

Factors that can be considered as a resource for schoolchildren's health improvement primarily include the following: medical support provided at an educational establishment [8, 9], creating a motivation among

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schoolchildren to pursue healthy lifestyle [10–13], supporting positive changes in behavior, physical activity, nutrition, and health self-assessment [14, 15].

Sanitary and hygienic education provided by educational establishments (EE) via building up knowledge and convictions, developing abilities and skills to make a choice on healthy behavior can prevent multiple behavioral risk factors from occurring [10, 16]. A success here depends on interaction between EE and primary medical care [17], families and variable partners [18].

Children should be introduced to preserving and improving their health via creating attitudes towards healthy lifestyle and it should be done staring from early age in the course of their education taking into account peculiarities of their behavioral attitudes towards their own health and places where they live [19–21]. Given that, it seems vital to examine experience gained in organizing an educational process in such a way so that it helps preserve health of schoolchildren who attend secondary schools. It can allow determining what interventions or adjustments are necessary in the sphere.

Our research goal was to comparatively assess two educational processes that were organized in a different way regarding medical support and a system for healthy lifestyle creation.

Data and methods. Our research objects were 6 educational establishments located in Penza city; and schoolchildren who attended these establishments were our units under observation. In accordance with the set goal, we examined morbidity among children in 2008 and 2018 via analyzing data taken from statistical reports (Statistical Form No. 025/u "Medical records of a patient who applies for outpatient care"). We performed a retrospect study of morbidity among children aged 10–14 who attended three test schools (1,087 people in 2008; 1,126 in 2018) and three reference schools (982 and 1,018 people accordingly). Morbidity parameters were calculated as per data on applications for medical aid. In November and December 2018 a questioning was performed at the same schools; a questionnaire consisted of 30 questions on lifestyle, screening assessments of health, and attitudes towards school (as per an international questionnaire entitled Health Behavior in School-aged Children). 1,935 schoolchildren took part in voluntary anonymous questioning; 1,054 out of them attended the test schools (TS) (579 attended the 5–6th grades; 475, 7–8th grades); 881 attended the reference schools (RS) (355 attended the 5–6th grades; 526, the 7–8th grades).

The test schools were the Secondary School No. 74, "SAN" Gymnasium, and Gymnasium No. 13; in 2008 prevention and rehabilitation offices were opened in all three of them [22], and in the same year a system for continuous education on healthy lifestyle creation was implemented in the educational processes in all three TS. Schoolchildren got access to health-improving procedures, dentist's aid, and consultations on behavior corrections via visiting a physiotherapeutic or a massage room, training facilities and facilities for exercise therapy that were opened in the TS; it could be done basing on a therapist's recommendations and without any breaks in the educational process. These test schools where medical support, together with conventional medical offices, includes additional prevention and rehabilitation facilities can be considered a resource for health improvement and it allows providing a health-preserving educational process and preserving schoolchildren's health that is ranked among the most important tasks the state has to fulfill [23].

Attitudes towards healthy lifestyle are created among schoolchildren attending the TS basing on interdepartmental interactions and sectoral partnership and with parents actively participating in the process; necessary components in healthy lifestyle creation are built into children's activities during classes, beyond them, and in their project activities (Figure).

In the TS there is a system for continuous education on healthy lifestyle creation including classes on "Healthy lifestyle" in junior

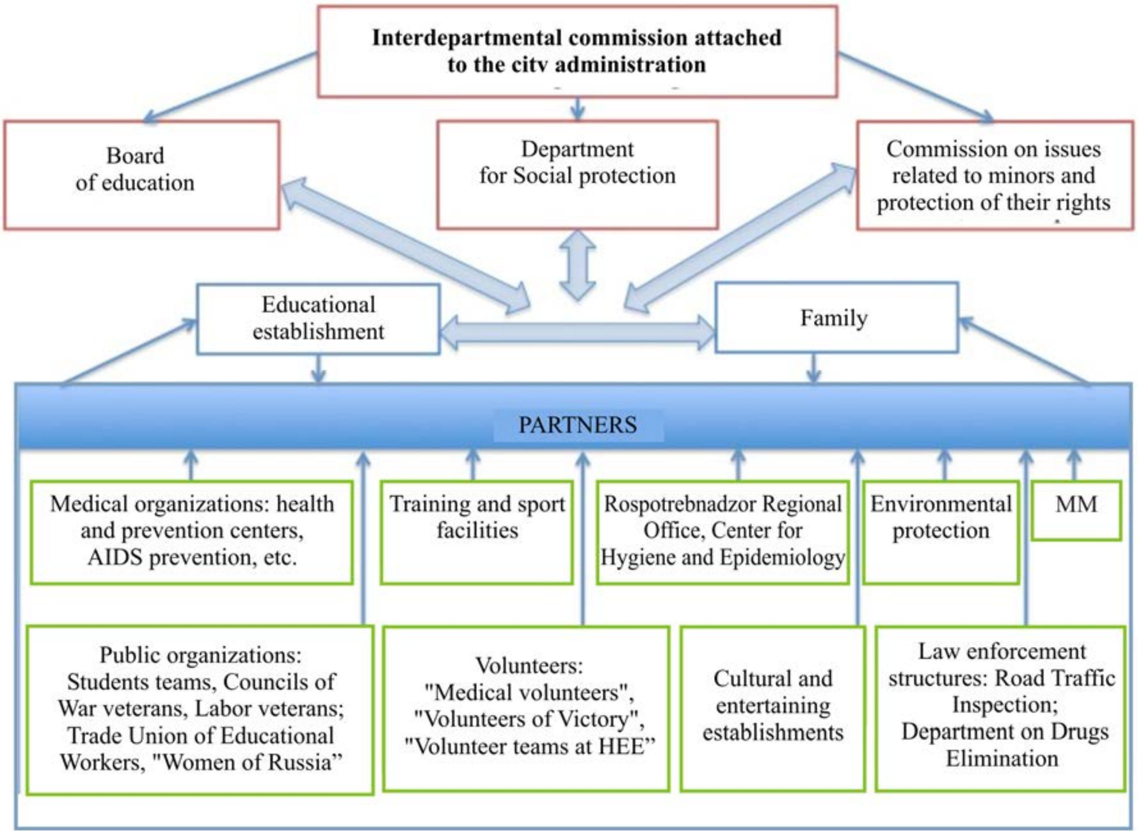

Figure. Interdepartmental interaction and social partnership in creating hygienic culture and healthy lifestyle

and middle grades and "Basics of healthy lifestyle" in senior grades; these classes are taught within a regional component in educational programs. Skills and abilities regarding healthy lifestyle are also trained during lessons in ordinary school subjects such as physical training, biology, chemistry, physics, geography, as well as basics of safe life activities. Continuous education on healthy lifestyle creation is aimed at developing value orientation at health and relevant behavioral stereotypes. Continuous education provided for schoolchildren from the 1st to 11th grade is based on an author's methodology approved by the Penza regional administration and developed by scientists in a close cooperation with experts from Rospotrebnadzor's regional office in Penza and schoolteachers. In 2008–2009 the authors' team created a teaching methodological complex consisting of 11 manuals and textbooks including electronic ones that contained developing and role games. Apart from conventional education techniques, the educational process utilizes variable technologies such as communication, volunteering, and partnership. All this together allows better communication on risk factors for schoolchildren and their parents, teachers, and school personnel and provides motivation and creating conditions for developing skills of healthy lifestyle.

Our reference schools were the Secondary School No. 52, Secondary School No. 56, and Gymnasium No. 42 where the educational process didn't provide available prevention and rehabilitation facilities (medical support at school was provided via conventional medical offices) and there was no continuous education on healthy lifestyle creation.

All six schools were located in the Oktyabrskiy district in the city where there were no industrial enterprises and medical aid for minors was provided at a single polyclinic for children, namely the municipal children's polyclinic No. 6.

All the data were statistically processed with a statistics calculator. Student's t-test was applied to determine statistical significance of values obtained for the examined samplings.

Results and discussion. Having examined applications for medical aid by children in 2008, we detected that primary morbidity and overall morbidity among children aged 10–14 didn't have authentic differences between the test and reference schools (t_1=1.67; t_2=1.22). Primary morbidity among children aged 10–14 in 2018 went down authentically against 2008, both among schoolchildren from the test schools and the reference ones (Table 1). But morbidity growth in 2018 against 2008 amounted to (-6.47 %) among children attending the TS whereas it was only (-1.37 %) among those attending the RS. Overall morbidity also decreased over 10 years and its growth amounted to (-6.61 %) among children from the TS and only (-3.11 %) among those from the RS.

In 2018 primary and overall morbidity were authentically lower among children attending the test schools than among those from the reference ones (Tables 2 and 3). Primary morbidity among children attending the test schools was significantly lower than among their counterparts attending the RS as per such nosologies as diseases of the eye and adnexa; diseases of the respiratory system; diseases of the digestive system; diseases of the musculoskeletal system and connective tissue; injury, poisoning and certain other consequences of external causes (Table 2). We didn't reveal any authentic differences in morbidity among children as per other nosologies.

Table 1

Morbidity among children aged 10–14 in 2008 and 2018 (per 1,000 children of the relevant age)

Morbidity	*TS*		*t*	*RS*		*t*
	2008	2018		2008	2018	
Primary	2,547.43 ± 60.22	2,382.54 ± 54.08	15.4	2,528.91 ± 62.75	2,494.31 ± 60.50	3.1
Overall	3,056.27 ± 76.03	2,854.17 ± 68.65	16.8	3,071.52 ± 80.49	2,976.19 ± 76.01	7.6

Table 2

Morbidity among children aged 10–14 first detected in their life in 2018 (per 1,000 children of the relevant age)

Nosology	*TS*	*RS*	*t*
	M ± *m*	*M* ± *m*	
Diseases cases, overall	2382.54 ± 54.08	2494.31 ± 60.50	10.44*
Certain infections and parasitic diseases	69.06 ± 7.55	67.42 ± 7.8	0.42
Neoplasms	4.63 ± 2.02	5.13 ± 2.24	0.24
Diseases of the blood and blood-forming organs	3.46 ± 1.75	3.86 ± 1.94	0.20
Endocrine, nutritional, and metabolic disorders	10.90 ± 3.09	13.72 ± 3.64	1.09
Diseases of the nervous system	29.22 ± 5.02	30.87 ± 5.42	0.51
Diseases of the eye and adnexa	68.16 ± 7.51	87.03 ± 8.83	4.67*
Diseases of the ear and mastoid process	48.0 ± 6.37	44.14 ± 6.44	1.08
Diseases of the circulatory system	11.25 ± 3.14	12.98 ± 3.55	0.67
Diseases of the respiratory system	1,483.86 ± 25.25	1,519.26 ± 27.84	4.86*
Diseases of the digestive system	247.77 ± 12.86	266.53 ± 13.86	3.63*
Diseases of the skin and subcutaneous tissue	61.73 ± 7.17	62.07 ± 7.56	0.30
Diseases of the musculoskeletal system and connective tissue	66.61 ± 7.43	81.56 ± 8.58	3.73*
Diseases of the genitourinary system	73.02 ± 7.75	68.13 ± 7.90	1.23
Congenital malformations	6.73 ± 2.43	6.65 ± 2.58	0.19
Injury, poisoning and certain other consequences of external causes	198.14 ± 11.8	224.96 ± 13.09	5.37*

Note: here and in the table 3 * means there are authentic differences in morbidity among children from the TS and RS ($t > 2$).

Table 3

Overall morbidity among children aged 10–14 in 2018 (per 1,000 children of the relevant age)

Nosology	*TS*	*RS*	*t*
	$M \pm m$	$M \pm m$	
Diseases cases, overall	2.854,17 ± 68.65	2.976,19 ± 76.01	10.15*
Certain infections and parasitic diseases	88.31 ± 8.45	79.04 ± 8.46	1.09
Neoplasms	7.44 ± 2.56	8.18 ± 2.82	0.32
Diseases of the blood and blood-forming organs	8.08 ± 2.66	7.59 ± 2.72	0.21
Endocrine, nutritional, and metabolic disorders	31.16 ± 5.18	35.52 ± 5.80	1.31
Diseases of the nervous system	41.08 ± 5.91	45.56 ± 6.53	1.27
Diseases of the eye and adnexa	96.47 ± 8.80	107.17 ± 9.69	2.48*
Diseases of the ear and mastoid process	48.26 ± 6.38	44.49 ± 6.46	1.05
Diseases of the circulatory system	28.09 ± 4.92	25.38 ± 4.93	0.86
Diseases of the respiratory system	1,542.4 ± 27.25	1,598.59 ± 30.66	7.38*
Diseases of the digestive system	441.36 ± 14.79	470.14 ± 15.64	5.22*
Diseases of the skin and subcutaneous tissue	74.18 ± 7.81	70.56 ± 8.02	0.91
Diseases of the musculoskeletal system and connective tissue	96.67 ± 8.80	111.34 ± 9.86	3.39*
Diseases of the genitourinary system	130.38 ± 10.03	121.39 ± 10.23	1.99
Congenital malformations	22.15 ± 4.38	23.28 ± 4.72	0.37
Injury, poisoning and certain other consequences of external causes	198.14 ± 11.8	224.96 ± 13.09	5.37*

Prevalence of such disorders as diseases of the eye and adnexa, diseases of respiratory system, diseases of the digestive system, diseases of the musculoskeletal system and connective tissue, injury, poisoning and certain other consequences of external causes was authentically lower among children who attended the test schools than among those from the reference ones (Table 3).

Therefore, school-related diseases were much less frequent in 2018 than in 2008 among children who attended the test schools where a contemporary model of school medical aid was implemented into the educational process starting from 2008 than among those who attended the reference ones. This model envisages opening prevention and rehabilitation facilities at an EE together with a conventional medical office and providing continuous education on healthy lifestyle creation from the 1st to 11th grade. We should note that primary morbidity among children aged 10–14 who are classified as junior teenagers by the World Health Organization was substantially higher than among senior teenagers (aged 15–17); in Penza primary morbidity among the latter amounted to 1,495.2 and 2,308.7 per 1,000 teenagers of the relevant age on average in 2016 and in 2017. It calls for greater attention being paid to health of children aged 10–14, including studying and analyzing factors that influence their health.

Our questioning revealed that health parameters of children from two compared types of schools had certain differences regarding some questions; thus, 16.4 % children from the 5–6th grades and 18.3 % children from the 7–8th grades in the TS assessed their health rather as “poor” than “satisfactory” and the share of such children was even higher in the RS, 25.6 % and 24.9 % accordingly (t = 3.67 and t = 2.37). Neurotic disorders were more frequent among 5–6th grade children in the RS: one third of them had bad mood or felt irritated more often than one a week whereas it was so only for each forth child in the 5–6th grades in the TS (t = 4.65); anxiety appeared in 29.8 % and 24.8 % accordingly (t < 2). Each third schoolchild (33.8 %) from the 7–8th grades in the RS mentioned bad mood and irritability; in the TS, only each forth (24.4 %) (t = 3.03); anxiety was mentioned by 26.0 % and 28.5 % children accordingly (t < 2). Gender analysis revealed that girls from the 7–8th grades, both in the TS and RS, tended to have bad moods and headaches and feel irritated more frequently than boys

($t = 2.19$); they also gave lower assessments of their health ($t = 3.15$).

Having assessed what complaints about health schoolchildren usually had, we didn't reveal any authentic differences excluding headaches prevalence among children from 5–6th grades, 17.6 % and 22.8 % ($t = 2.06$); overall, regardless of age, almost each fifth child complained about headaches; each tenth had difficulty in falling asleep. Aches in other places were mentioned by 15.7 % children from the 5–6th grades in the TS and 16.9 % in the RS ($t < 2$); 15.4 % and 17.5 % accordingly among children from the 7–8th grades ($t < 2$) (Tables 4 and 5).

Self-assessment of health by children from the 5–6th grades coincided with their mental perception of their school: schoolchildren from the TS had positive attitudes towards school much more frequently (75.8 %) than their counterparts from the RS (67.0 %) ($t = 3.17$). Answers to questions regarding difficulties in the educational process differed only slightly between respondents from the TS and RS. Children from the 7–8th grades in both types of schools stated that the educational program was difficult more frequently than children from the 5–6th grades ($t = 3.06$ and $t = 2.47$).

Optimal nutrition should always include meat and milk products consumed 5 days a week or more and fruit and vegetables consumed daily. Our questioning results indicate that only two thirds of respondents consumed milk products and meat 5 days a week or more. There were no authentic differences regarding meat and milk products consumption by children form the 5–6th grades in the TS and RS. But a share of children from the 7–8th grades who consumed meat not less than

Table 4

Attitudes to educational activities among children from the 5–6th grades and data on their health and prevalence of factors that influence it, %

Parameters	*TS*	*RS*	*t*
Poor health	16.40 ± 1.54	25.63 ± 2.00	3.67*
Headaches (more often than once a week)	17.61 ± 1.58	22.81 ± 1.92	2.06*
Other aches (more often than once a week)	15.71 ± 1.51	16.90 ± 1.72	0.49
Bad mood, irritability (more often than once a week)	25.56 ± 1.81	38.87 ± 2.24	4.65*
Anxiety (more often than once a week)	24.87 ± 1.80	29.86 ± 2.10	1.82
Insomnia (more often than once a week)	10.01 ± 1.25	12.95 ± 1.54	1.43
Positive attitudes towards school	75.82 ± 1.78	67.04 ± 2.16	3.17*
Difficulties in studies	14.16 ± 1.45	17.46 ± 1.74	1.46
Everyday breakfast on workdays	77.20 ± 1.74	77.75 ± 1.91	0.19
Hot meals 2 times a day or more	69.77 ± 1.91	54.46 ± 2.28	5.12*
Fruit consumed every day	72.54 ± 1.85	62.25 ± 2.22	3.53*
Vegetables consumed every day	69.95 ± 1.91	59.72 ± 2.25	3.45*
Milk products consumed 5 days a week or more	67.36 ± 1.95	63.38 ± 2.21	1.35
Meat consumed 5 days a week or more	68.05 ± 1.94	63.94 ± 2.19	1.10
Daily physical activities (1 hour and longer)	67.0 ± 1.95	54.46 ± 2.28	4.15*
Every day sleep for less than 8 hours	42.66 ± 2.06	47.89 ± 2.29	1.67
More than 2 hours every day spent with a PC or a gadget	51.64 ± 2.08	56.34 ± 2.28	1.55
Smoking every week	1.38 ± 0.49	4.22 ± 0.92	2.72*
Drinking beer every week	1.9 ± 0.57	2.82 ± 0.75	0.89
Drinking strong spirits every week	1.21 ± 0.45	1.97 ± 0.63	0.89
Participating in fights over the previous year	23.66 ± 1.64	23.67 ± 1.95	1.66
Bullied their classmates over the last 3 months	19.17 ± 1.64	21.97 ± 1.90	1.09
Were victims of bullying in school	18.65 ± 1.62	21.13 ± 1.87	0.97

Note: here and then in Table 5 * means there are authentic differences between answers given by respondents from the TS and RS ($t > 2$);

Table 5

Attitudes to educational activities among children from the 7–8th grades and data on their health and prevalence of factors that influence it, %

Parameters	*TS*	*RS*	*t*
Poor health	18.31 ± 2.05	24.90 ± 1.89	2.37*
Headaches (more often than once a week)	16.74 ± 1.98	19.23 ± 1.72	0.99
Other aches (more often than once a week)	15.47 ± 1.92	17.56 ± 1.66	0.79
Bad mood, irritability (more often than once a week)	24.47 ± 2.28	33.84 ± 2.06	3.03*
Anxiety (more often than once a week)	26.07 ± 2.33	28.52 ± 1.97	0.85
Insomnia (more often than once a week)	10.10 ± 1.60	12.23 ± 1.43	0.94
Positive attitudes towards school	75.47 ± 2.28	73.54 ± 1.92	0.64
Difficulties in studies	22.26 ± 2.21	23.89 ± 1.86	0.59
Everyday breakfast on workdays	76.84 ± 2.24	64.83 ± 2.08	3.95*
Hot meals 2 times a day or more	66.74 ± 2.50	60.84 ± 2.13	1.8
Fruit consumed every day	79.58 ± 2.15	59.70 ± 2.14	6.52*
Vegetables consumed every day	74.74 ± 2.31	60.46 ± 2.13	4.52*
Milk products consumed 5 days a week or more	66.32 ± 2.51	67.30 ± 2.13	1.74
Meat consumed 5 days a week or more	66.53 ± 2.51	56.84 ± 2.16	2.91*
Daily physical activities (1 hour and longer)	42.68 ± 2.62	35.70 ± 2.09	2.03*
Every day sleep for less than 8 hours	50.99 ± 2.65	56.27 ± 2.16	1.54
More than 2 hours every day spent with a PC or a gadget	51.83 ± 2.65	58.94 ± 2.15	2.08*
Smoking every week	2.21 ± 0.79	5.09 ± 0.96	2.32*
Drinking beer every week	2.8 ± 0.88	3.80 ± 0.83	0.81
Drinking strong spirits every week	1.64 ± 0.68	2.17 ± 0.62	0.43
Participating in fights over the previous year	16.84 ± 1.99	23.73 ± 1.86	2.52*
Bullied their classmates over the last 3 months	14.31 ± 1.86	22.51 ± 1.82	3.10*
Were victims of bullying in school	14.53 ± 1.86	15.32 ± 1.57	0.42

5 days a week was substantially higher in the TS than in the RS, 66.5 % and 56.8 % accordingly ($t = 2.91$). Children from the TS consumed fruit more frequently than their counterparts from the RS: 72.5 % and 62.2 % accordingly in the 5–6th grades ($t = 3.53$) and 79.5 % and 59.7 % in the 7–8th grades ($t = 6.52$); and vegetables, 69.9 % and 59.7 % in the 5–6th grades ($t = 3.45$) and 74.7 % and 60.4 % in the 7–8th grades ($t = 4.52$). When fruit and vegetables are not consumed in sufficient quantities, it can result in so called latent hunger or micronutrients deficiency and cause a risk of cardiovascular diseases, cancer, diabetes, and obesity. Children from the 7–8th grades in the TS had breakfast on workdays more frequently than their counterparts from the RS, 76.8 % against 64.8 % ($t = 3.95$). A share of schoolchildren from the 5–6th grades who had breakfast every day on workdays didn't differ between the compared schools. A number of schoolchildren from the 5–6th grades who had hot meals 2 times a day or more was significantly higher among children from the TS than RS, 69.7 % and 54.4 % accordingly ($t = 5.12$). A share of schoolchildren from the 7–8th grades who had hot meals 2 times a day or more amounted to 66.7 % in the TS and 60.8 % in the RS ($t < 2$).

Health of children in puberty is influenced significantly by such behavioral factors as intensity of physical activity, amount of time spent with a PC or a gadget, and amount of sleep [17, 24]. There were significantly more children with moderate physical activity (not less than 1 hour a day) in the TS than in the RS: 5–6th grades, 67.0 % and 54.4 % accordingly ($t = 4.15$); the 7–8th grades, 42.6 % and 35.7 % ($t = 2.03$). A share of children with daily physical activity being longer than 1 hour was lower among children from the 7–8th grades than among those from the 5–6th grades in both types of EE ($t = 7.39$ and $t = 6.07$ accordingly). Each second schoolchild spent more than 2 hours with a PC or any other digital device. A difference in this parameter was only slight for children from the 5–6th grades but it was authentic for children from the 7–8th grades, 51.8 % in the TS and 58.8 % in the RS (t = 2.08). Each second child from the 7–8th grades, 51 % in the TS and 56.3 % in the RS slept for less than 8 hours and it was authentically different from figures obtained for children from the 5–6th grades, 42.6 % and 47.8 % (t = 2.48 and t = 2.69).

Our study on behavioral risk factors revealed that more children from the TS smoked every week against the same parameter in the RS, accordingly in the 5–6th grades (t = 2,72); in the 7–8th grades, (t = 2.32). We didn't reveal any authentic differences as per weekly intake of beer or strong spirits in two compared types of schools.

The data on health and prevalence of factors that influence it as well as on schoolchildren's attitudes towards school studies that we obtained via questioning schoolchildren in Penza predominantly coincide with data obtained via questioning performed by S.B. Sokolova among schoolchildren from 7–8th grades in Moscow [25].

Aggressive behavior that is typical for two out of ten respondents is rather alerting. Schoolchildren from the 7–8th grades in the RS participated in fights (t = 2.52) and bullied their classmates (t = 3.10) more frequently than their counterparts from the TS. Meanwhile, health self-assessment, contentment with life, and subjective complaints about one's health are closely connected with psychosocial environment at school and relationships between classmates [19, 26]. As per data obtained via questioning, 81.7 % schoolchildren from the 5–6th grades in the TS and 72.2 % in the RS (t = 3.63) were quite content with their life; 77.9 % and 70.4 % accordingly in the 7–8th grades (t = 2.59). As it has already been mentioned, health self-assessment was higher among children who attended the TS and they had subjective complaints less frequently than their counterparts from the RS. It indicates that psychosocial environment at school plays an exceptionally vital role in maintaining children's health and it is advisable to examine it in detail when characterizing schoolchildren's health.

Healthy lifestyle that children should pursue involves daily consumption of fruit and vegetables, night sleep lasting not less than 8 hours, physical activity for not less than 1 hour a day, time spent with a PC or any other electronic device not exceeding 2 hours, and total abstention from alcohol and smoking. Having performed complex assessment of children's actual lifestyles, we revealed that a number of children who adhered to all the above-mentioned behavior patterns was significantly higher in the TS than in the RS: 18.7±1.62 % and 11.0±1.43 % accordingly in the 5–6th grades (t = 3.56); 19.2±2.09 % and 11.8±1.41 % accordingly in the 7–8th grades (t = 2.93). These parameters obtained via questioning performed among schoolchildren in Penza differ from results obtained via questioning performed among junior schoolchildren in Europe and America where only about 5 % children aged 11 and 35 children aged 13 adhered to all 5 above mentioned components of healthy lifestyle every day [20, 27].

Conclusion. Our research allowed determining that implementation of a new model for school medicine and a system of continuous education on healthy lifestyle creation into the educational process in a secondary school yielded certain positive results. Thus, 10 years after the system for healthy lifestyle creation had been implemented there were more children aged 10–14 pursuing healthy lifestyle in the test schools than in the reference ones. It concerned nutrition in particular since there was a greater share of children who had breakfast every day on workdays, had hot meals two times a day or more and consumed fruit and vegetables in the test schools. The share of children who had physical activities for 1 hour a day or longer was also higher in the tests schools; and the share of children with such behavioral risk as tobacco smoking was lower among them. Aggressive behavior was equally frequent among children from the 5–6th grades in both types of schools, but the share of such children was authentically lower in the

7–8th grades in the test schools than in the reference ones.

An increase in number of children who pursued healthy lifestyle allowed achieving prevention effects that became apparent via a decrease in morbidity. Thus, in 2008 there was only slight difference in primary morbidity among children aged 10–14 from both test and reference schools; in 2018 morbidity among children who attended the TS was significantly lower than among their counterparts from the RS. We detected authentic differences in primary and overall morbidity among children from the compared groups as per such school-related diseases as diseases of the eye and adnexa, diseases of the respiratory system, diseases of the digestive system, diseases of the musculoskeletal system and connective tissue, injury, poisoning, and certain other consequences of external causes. Data obtained via questioning schoolchildren regarding their health coincided with morbidity that was officially registered as per applications for medical aid: children from the TS assessed their health as poor much less frequent that their counterparts from the RS, they also had bad mood and got irritated less frequently; children from the 5–6th grades in the TS complained about headaches more rarely.

Healthy lifestyle includes 5 obligatory components that should be pursued: daily physical activity for not less than 1 hour, night sleep being not less than 8 hours, daily consumption of fruit and vegetables, less than 2 hours spent every day with a PC or any other electronic device, and total abstention from alcohol and tobacco. Having assessed actual children's lifestyle, we revealed that there were still a lot of reserves for preserving children's health due to potential decrease in morbidity since a share of children who pursued healthy lifestyle in its integrity as a combination of 5 basic components was rather low even in the test schools, namely 18.7±1.62 % of children from the 5–6th grades and 19.2±2.09 % among children from the 7–8th grades. It was even lower in the reference schools, 11.0±1.43 % and 11.8±1.41 % accordingly.

Conclusions:

1. When a system for continuous education on healthy lifestyle formation was implemented into the educational process at secondary schools via opening prevention and rehabilitation facilities in them, it resulted in an increase in a share of children who pursued healthy lifestyle and a decrease in a share of children with risky behavior. It allowed achieving prevention effects that became apparent via a significant decrease in primary and overall morbidity, predominantly with school-related diseases, taken in dynamics over 10 years.

2. In order to preserve schoolchildren's health, it is advisable to use this experience of opening prevention and rehabilitation facilities and implementing a system for continuous education on healthy lifestyle creation in other cities in the region and other regions in the country as well.

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Research article

RISKS RELATED TO COGNITIVE DISORDERS DEVELOPMENT IN WORKERS WITH DIFFERENT WORK EXPERIENCE EMPLOYED AT AN OIL EXTRACTING FACILITY

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Our research goal was to examine cognitive functions parameters in dynamics among workers employed at an oil extracting facility depending on their work experience under exposure to adverse occupational factors.

We estimated cognitive functions in 292 oil and gas extraction operators who were exposed to adverse occupational factors (aromatic hydrocarbons, hydrogen sulphide, occupational noise, labor hardness, and adverse microclimate). The reference group consisted of 65 administrative workers employed at the same enterprise. All the examined people were males aged 20–65; they were divided into several sub-groups depending on their work experience: the 1st subgroup, work experience shorter than 10 years; the 2nd subgroup, 10–20 years; the 3rd sub-group, longer than 20 years. All the subgroups were comparable as per average age ($p > 0.05$). Nervous systems diseases that caused cognitive deficiency were a criterion for exclusion from the research groups. We performed neural-psychological examination using «NS-Psychotest» computer complex («Concept exclusion», short term memory tests for pictures and figures, square number test). To analyze dependence between cognitive disorders and work experience duration in the test and reference groups, we calculated relative risk and its 95 % confidence interval (results are given as RR (95 % CI)). We also performed one-factor linear regression analysis of dependence on work experience separately for each parameter of examined cognitive functions.

Oil and gas extraction operators tended to have 1.3–1.6 times lower cognitive flexibility, picture and number memory, and attention than people who worked under permissible working conditions at their work places. Oil and gas extraction operators with their work experience being equal or exceeding 10 years ran more than 5 times higher risk of cognitive disorders; memory, attention, and analytical activity parameters were lower among them 2–3 times more frequently. Basing on relative risk calculation and one-factor linear regression analysis, we established a correlation between cognitive disorders development and work experience duration. Periodical medical examinations provided for oil and gas extraction operators should include neural-psychological tests that assess memory, attention, and cognitive flexibility since it will allow diagnosing cognitive dysfunction at an early (pre-dementia) stage and revealing people with its minimal signs for further profound examination, prevention activities, and occupational examination.

***Key words**: cognitive functions, number and picture memory, attention, cognitive flexibility, cognitive deficiency, neural-psychological testing, oil extracting industry, occupationally induced pathology, adverse occupational factors, work experience.*

The Economic Safety Strategy approved in the Russian Federation for a period up to 2030 lists an issue related to longer life expectancy and extended period of employment (in particular, for workers who have to work under adverse and hazardous working condi-

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tions) among priority tasks the state is to solve[1].

Cognitive disorders among employable population are a vital task that is to be solved by contemporary medicine. Sub-clinical (pre-dementia) cognitive disorders that occur among employable population become apparent via memory disorder, poorer ability to focus one's attention, and greater fatigue at the end of a working shift [1, 2]. Apparent cognitive disorders disrupt every day and occupational activities and result in lower life quality. It has been shown that as a person grows older, cognitive disorders become more and more frequent with their frequency growing progressively and reaching 20 % among people aged 60–69 [3, 4]. Adequate functioning and plasticity of synapses in the central nervous system (CNS) is among factors that determine cognitive and neuroplastic potential and support learning processes and memory [5, 6]. A substantial loss of these neuronal structures caused by ageing, various diseases, or exposure to toxic agents can has such clinical manifestation as cognitive disorders syndrome [7–9].

As per data provided by G.V. Timasheva et al., working under adverse working conditions is a risk factor that may cause cognitive disorders [10]. It was established that toxic effects might be produced on a body by a wide range of chemicals under certain conditions. These conditions include a dose, exposure duration, as well as a way through which a chemical is introduced into a body [11]. At present workers employed at oil extracting enterprises are exposed to such adverse chemicals as sulfur dioxide, carbon oxide, and aromatic hydrocarbons [12]. Chronic exposure to chemical factors in low doses that is typical for oil extraction causes disorders in the nervous system[2] [13]; these disorders are further aggravated due to impacts exerted by additional occupational factors (occupational noise, labor hardness and intensity)[3] [14–16].

Workers employed at an oil extracting enterprise are exposed to several adverse occupational factors at their workplaces (chemical factors and noise) and these factors can be seen as risk factors that might cause cognitive disorders. At the same time, so far there hasn't been sufficient research on parameters of cognitive functions taken in dynamics that is related to work experience duration. This issue becomes especially vital since technological processes are getting faster and more complicated and it makes greater demands of workers to be precise in their actions and to be able to make quick decisions when performing production operations. Any mistake can result in an emergency including those when people's lives are threatened [14].

Our research goal was to examine cognitive function parameters among workers employed at an oil extracting enterprise and to develop feasible criteria for early diagnostic of functional disorders in the brain. These parameters were taken in dynamics depending on duration of work experience under exposure to adverse occupational factors.

Data and methods. Our examined sampling was made up of 357 workers employed at an oil-extracting enterprise; 292 were oil and gas extraction operators (the test group) and 65 administrative workers (the reference group). Workers in both groups were males, aged 20–65, and their working experience at the examined enterprise was longer than 1 year. Both groups were divided into three subgroups according to duration of their working experience; subgroup I included workers with their working experience being shorter than 10 years; subgroup II, 10–20 years; subgroup III, longer than 20 years. All subgroups were comparable in terms of average age and working experience ($p > 0.05$). Results obtained via special assessment of working conditions (hereinafter SAWC) allowed establishing that all the

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workers from the test group had to work under "adverse" working conditions with 3.1–3.2 hazard category. Technological operations involved chemicals emissions into working area air with prevailing saturated aliphatic hydrocarbons C1-10 (recalculated as per C) in concentrations that didn't' exceed hygienic standards and dihydrosulfate mixed with hydrocarbons C1-5 (hydrogen sulfate) in concentrations that were up to 1.2 times higher than MPC (10 mg/m^3). Noise at working places was 1.1 times higher than maximum permissible level for workers from the test group and reached 87–88 dB. Working conditions for workers from the reference group corresponded to hazard category 2 (permissible).

Our research program included analysis of working conditions as per SAWC results and assessment of workers' cognitive functions as per results obtained via neural-psychological examination that was performed with "NS-Psychotest" computer complex ("Neurosoft", Russia, SN 0384UX). The research involved estimating such intellectual operations as classification and analysis via "Concepts exclusion" test; image memory was estimated with "Image memory" test; number memory, "Number memory" test; and attention, "Number square" test[4] .

All the data were accumulated, adjusted, processed and analyzed with IBMSPSS Statistics 22 software for statistical analysis. Analysis was performed with non-parametric statistic techniques. Data obtained for different groups are given in tables as median values (*Me*) and 25–75 percentiles. Quantitative attributes were compared as per Mann – Whitney test. Differences were considered authentic at $p < 0.05$[5] . Qualitative attributes were assessed with Fischer's z-test.

To analyze dependence between cognitive disorders and duration of working experience in the test and reference group, we calculated relative risk and its 95 % confidence interval (the results are given as (95 % *CI*)); also, we performed one-factor linear regression analysis separately for each parameter of examined cognitive functions. This analysis allowed estimating parameters of a model given as per the following formula (1):

$$y = b_0 + b_1 \cdot x + \varepsilon, \quad (1)$$

where

y is resulting quantitative attribute;

b_1 is model coefficient;

b_0 is model constant;

ε is random error in the model;

x is working experience under exposure to a set of adverse working conditions (the test group) or without such exposure at a workplace (the reference group).

To assess quality of the linear function, we calculated F-criterion and a square of linear correlation coefficient R^2 (determination coefficient).

The present research work was accomplished in conformity with ICHGCP Rules and with adherence to ethical standards stipulated by Helsinki Declaration (edited in 2008) and the RF National Standard GOST-R 52379-2005 "Good clinical practice" (ICH E6 GCP)[6]. The research program was approved by the Ethical Committee of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies (The meeting report No. 55 dated December 20, 2018). All the workers were informed about research goals and gave their voluntary informed consent to take part in the research.

Results and discussion. Having assessed abilities to classify and analyze among workers from all the subgroups, we revealed authentic differences between the groups, namely fewer correct answers given by workers from the test group against those from the reference one (13 (10; 15) against 14 (13; 15), $p = 0.003$). A share of people with low cognitive flexibility was 5 times higher in the test group than in the reference one (25.2 % and 4.5 %, $p = 0.003$) (Table 1).

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Table 1

Comparative analysis of data obtained via "Concepts exclusion" tests among all the examined workers

Data obtained via "Concepts exclusion" test	Test group $n = 210$	Reference group $n = 44$	Validity of differences between groups, $p < 0.05$
Correct answers, number	13 (10; 15)	14 (13; 15)	0.003
Frequency of detected cognitive flexibility, %			
Low cognitive flexibility, 1–3 scores	25.2	4.5	0.002
Average cognitive flexibility, 4–7 scores	61.0	75.0	0.08
High cognitive flexibility, 8–9 scores	13.8	20.5	0.26

Table 2

Relative risk of cognitive disorders among workers employed at an oil-extracting enterprise as per data obtained via neural-psychological testing

Tests	Test group $n = 209$	Reference group $n = 44$	*RR* (*CI* 95 %)
"Concepts exclusion"	25.2 %	4.5 %	*RR* = 5.55; 95 % *CI* = 1.4–21.9
"Number memory"	52.9 %	34.1 %	*RR* = 1.6; 95 % *CI* = 1.0–2.4
"Number square"	19.3 %	12.1 %	*RR* = 1.59. 95 % *CI* = 0.60–4.20

Relative risk that low cognitive flexibility might occur was 5.6 times higher in the test group than in the reference one (*RR* = 5.55; 95 % *CI* = 1.4–21.9) (Table 2).

19 % workers from the test group, subgroup I, had low cognitive flexibility; and there were no such workers in the same subgroup from the reference group ($p = 0.03$). Having analyzed data obtained via "Concepts exclusion" test, we revealed authentically fewer correct answers among workers from the test group, subgroup II, against the same subgroup in the reference group, (13 (15; 12) against 15 (14; 16), $p = 0.03$). 21.3 % workers from the test group, subgroup II, had low cognitive flexibility and it was 3.2 times higher than in the same subgroup in the reference group where it was equal to 6.6 % (*RR* = 3.2; 95 % *CI* = 0.45–22.55); high cognitive flexibility was 1.5 times less frequent (18.8 % in the test group, subgroup II, against 26.6 % in the reference group, subgroup II, $p = 0.45$). "Concepts exclusion" test revealed authentically fewer correct answers among workers from the test group, subgroup III, against their counterparts from the reference group, subgroup III (11 (7; 14) against 14 (12; 15), $p = 0.04$). 42.9 % workers from the test group, subgroup III, had low cognitive flexibility against 11.1 % in the same subgroup in the reference group (*RR* = 3.9; 95 % *CI* = 0.59–25.18). Having assessed dynamics related to working experience we noticed that there was an authentic 1.3-time decrease in a number of correct answers given by workers from the test group, subgroup III, against their counterparts from the same group, but subgroup I (11 (7; 14) against 14 (12; 15), $p = 0.001$) whereas these attributes were quite similar in the reference group (14 (13; 15.5) against 14 (12; 15), $p = 0.64$) (Table 3).

Image memory was assessed with "Image memory" test; the assessment revealed fewer correct answers in the test group than in the reference one (8 (6; 10) against 10 (7; 12), $p = 0.01$), and capacity of image memory was by 13 % lower in the test group than in the reference one (43.8 % against 56.3 %, $p = 0.01$) (Table 4).

Having compared data obtained for subgroups II in both groups, we also revealed fewer correct answers in the test group (9 (7; 10) against 11 (9; 13), $p = 0.02$); besides, median value of image memory capacity turned out to be 1.4 times lower in the test group, subgroup II,

Table 3

Comparative analysis of data obtained via "Concepts exclusion" test among workers with different working experience

"Concepts exclusion" test data	Test group, subgroup I $n = 100$	Test group, subgroup II $n = 61$	Test group, subgroup III $n = 49$	Ref.group, subgroup I $n = 20$	Ref.group, subgroup II $n = 15$	Ref.group, subgroup III $n = 20$	p^1	p^2	p^3
Correct answers, number	14 (12; 15)	13 (12; 15)	11 (7; 14)	14 (13; 15.5)	15 (14; 16)	14 (12; 15)	0.32	0.03	0.04
Frequency of different cognitive flexibility, %									
Low cognitive flexibility, 1–3 scores	19	21.3	42.9	0	6.6	11.1	0.03	0.19	0.07
Average cognitive flexibility, 4–7 scores	64	60.7	55.1	75	66.7	88.9	0.34	0.67	0.06
High cognitive flexibility, 8–9 scores	17	18.0	2.0	25	26.6	0.0	0.39	0.45	0.67

Note: p^1 is validity of differences between the test group, subgroup I, and the reference group, subgroup I; p^2 is validity of differences between the test group, subgroup II, and the reference group, subgroup II; p^3 is validity of differences between the test group, subgroup III, and the reference group, subgroup III.

Table 4

Comparative analysis of data obtained via "Image memory" test among all the examined workers

"Image memory" test data	The test group $n = 209$	The reference group $n = 44$	Validity of differences between groups, $p < 0.05$
Correct answers, number	8 (6; 10)	10 (7; 12)	0.009
Mistakes, number	1 (0; 2)	1 (0; 1)	0.21
Memory capacity, %	43.8 (25; 62.5)	56.3 (34.4; 71.9)	0.007
Frequency of accuracy in reproducing images, %			
Low image reproduction accuracy (from 0 to 5)	21.5	15.9	0.40
Standard image reproduction accuracy (more than 5)	86.9	84.1	0.40

than in the same subgroup in the reference group (43.8 % against 62.5 %, $p = 0.03$). We didn't detect any authentic differences between subgroups I and III regarding image memory capacity; however, there was an authentic 1.2-time decrease in a number of correct answers given by workers from the test group, subgroup III, against subgroup I in the same group (7 (4; 9) against 9 (7; 11), $p = 0.001$). Low image reproduction accuracy was also 3 times more frequent in the test group, subgroup III, than in subgroup I (36.4 % and 13.1 %, $p = 0.001$). There were no authentic differences between subgroups in the reference group (Table 5).

Having assessed number memory as per results obtained via "Number memory" test, we established a statistically significant decrease in a number of correct answers given by workers from the test group than by those from the reference one (7 (6; 8) and 8 (7; 9.5), $p = 0.002$). Besides, capacity of number memory was by 8.3 % lower in the test group than in the reference one (50 (33.3; 66.7) and 58.3 (41.7; 75), $p = 0.03$) (Table 6). Low accuracy in reproducing numbers was detected in more than half of workers from the test group and it was 1.6 times higher than in the reference group (52.9 % against 34.1 %; $RR = 1.6$; 95 % $CI = 1.0–2.4$) (Table 6).

Comparative analysis of data obtained via this test revealed authentically fewer correct answers given by workers from the test group, subgroup I, against workers from the same

Table 5

Comparative analysis of data obtained via “Image memory” test among workers with different working experience

“Image memory” test data	Test group, subgroup I $n = 99$	Test group, subgroup II $n = 61$	Test group, subgroup III $n = 66$	Ref.group, subgroup I $n = 20$	Ref.group, subgroup II $n = 15$	Ref.group, subgroup III $n = 9$	p^1	p^2	p^3
Correct answers, number	9 (7; 11)	9 (7; 10)	7 (4; 9)	10.5 (9; 11.5)	11 (9; 13)	6 (5; 10)	0.27	0.02	0.57
Mistakes, number	1 (0; 2)	1 (0; 2)	1 (0; 3)	1 (0; 2)	1 (0; 3)	1 (0; 1)	0.86	0.32	0.13
Memory capacity, %	50 (31.3; 62.5)	43.8 (25; 62.5)	31.3 (18.8; 50)	56.3 (40.7; 68.8)	62.5 (43.8; 81.3)	31.3 (25; 62.5)	0.31	0.03	0.21
Frequency of accuracy in reproducing images, %									
Low image reproduction accuracy (from 0 to 5)	13.1	13.1	36.4	10	13.3	33.3	0.7	0.98	0.86
Standard image reproduction accuracy (more than 5)	86.9	86.9	63.6	90	86.7	66.7	0.7	0.98	0.86

Note: p^1 is validity of differences between the test group, subgroup I, and the reference group, subgroup I; p^2 is validity of differences between the test group, subgroup II, and the reference group, subgroup II; p^3 is validity of differences between the test group, subgroup III, and the reference group, subgroup III.

Table 6

Comparative analysis of data obtained via “Number memory” test among all the examined workers

“Number memory” test data	Test group $n = 210$	Reference group $n = 44$	Validity of differences between group, $p < 0.05$
Correct answers, number	7 (6; 8)	8 (7; 9.5)	0.002
Mistakes, number	1 (0; 2)	1 (0; 2)	0.71
Memory capacity, %	50 (33.3; 66.7)	58.3 (41.7; 75)	0.03
Frequency of accuracy in reproducing numbers, %			
Low accuracy in reproducing numbers (from 0 to 7)	52.9	34.1	0.02

subgroup in the reference group (7 (6; 8.5) and 8 (7; 10) accordingly, $p = 0.01$) and a share of workers with low accuracy in reproducing numbers was 1.4 times higher in the test group, subgroup I (55.0 % and 40.0 %; $RR = 1.37$; 95 % $CI = 0.78$–2.42). There were no statistically significant differences in “Number memory” test results between subgroups II in the test group and the reference group ($p = 0.14$–0.65); however, a share of workers with low accuracy in reproducing numbers was 1.3 times higher in the test group, subgroup II, than in the same subgroup in the reference group (42.6 % and 33.3 % accordingly; $RR = 1.3$; 95 % $CI = 0.6$–2.8). Test results didn’t reveal any statistically significant differences between subgroups III in both examined groups; more than half workers from the test group, subgroup III, had low accuracy in reproducing numbers and it was authentically 2.7 times higher than in the reference group, subgroup III (61.22 % and 22.2 % accordingly; $RR = 2.8$; 95 % $CI = 0.79$–9.54). Having assessed dynamics related to working experience we detected an authentic decrease in a number of correct answers given by workers from the test group, subgroup III, against subgroup I in the same group (6 (5; 8) against 7 (6; 8), $p = 0.02$) whereas there were no statistically significant difference revealed in the reference group (8 (8; 8) against 8 (7; 10), $p = 0.49$) (Table 7).

Table 7

Comparative analysis of data obtained via “Number memory” test among workers with different working experience

“Number memory” test data	Test group, subgroup I $n = 100$	Test group, subgroup II $n = 61$	Test group, subgroup III $n = 49$	Ref.group, subgroup I $n = 20$	Ref.group, subgroup II $n = 15$	Ref.group, subgroup III $n = 9$	p^1	p^2	p^3
Correct answers, number.	7 (6; 8.5)	8 (7; 9)	6 (5; 8)	8 (7; 10)	8 (7; 10)	8 (8; 8)	0.01	0.14	0.07
Mistakes, number	1 (0; 2)	1 (0; 2)	1 (0; 2)	1.5 (0.5; 2.5)	1 (0; 2)	1 (1; 2)	0.52	0.65	0.56
Memory capacity, %	50 (41.7; 66.7)	50 (41.7; 66.7)	41.7 (33.3; 58.3)	58.3 (37.5; 75)	58.3 (50; 75)	50 (41.7; 58.3)	0.2	0.16	0.26
Frequency of accuracy in reproducing numbers, %									
Low accuracy in reproducing numbers (from 0 to 7)	55.0	42.6	61.2	40.0	33.3	22.2	0.22	0.51	0.03
Standard accuracy in reproducing numbers (more than 7)	45.0	57.4	40.9	60.0	66.7	77.8	0.22	0.51	0.03

N o t e : p^1 is validity of differences between the test group, subgroup I, and the reference group, subgroup I; p^2 is validity of differences between the test group, subgroup II, and the reference group, subgroup II; p^3 is validity of differences between the test group, subgroup III, and the reference group, subgroup III.

Attention was assessed with “Number square” test; the assessment revealed fewer correct answers in all subgroups in the test group against the reference group (11 (7; 13) and 13 (10; 14) accordingly; *RR* = 1.59, 95 % *CI* = 0.60–4.20) (Tables 2 and 8).

Comparative analysis of data obtained for different subgroups revealed that workers from the test group, subgroup II, gave authentically fewer correct answers (11 (8; 12) and 13.5 (10.5; 14.5), $p = 0.02$) than their counterparts from the same subgroup in the reference group; they also made more mistakes (7 (5; 11) and 5 (2.5; 7), $p = 0.03$). We didn’t detect any statistically significant differences between subgroups I and subgroups III in both examined groups ($p = 0.28$–0.91); however, having assessed dynamics related to working experience, we detected an authentic decrease in a number of correct answers given by workers from the test group, subgroup III, against workers form the same group, but subgroup I (9 (6; 11) against 12 (9; 14), $p = 0.002$). There were no authentic differences in these attributes between subgroups in the reference group (Table 9).

The next stage in our research involved assessing cognitive state of workers from the examined groups as per a number of test parameters that were lower than the standard level detected in each examined workers employed at an oil-extracting enterprise (Table 10). Our comparative analysis revealed that a share of workers without low parameters as per any test tended to be lower among oil and gas extraction operators, (*RR* = 0.64 (95 % *CI* 0.44–0.92); also, this share was lower regarding low parameters as per just one test (*RR* = 0.97 (95 % *CI* 0.66–1.44). However, a relative risk that low results would be obtained in 2 or 3 tests was 2.0–3.0 times higher in this group than in the reference one (*RR* = 2.05 (95 % *CI* 0.77–5.45) and *RR* = 2.9 (95 % *CI* 0.39–21.8) accordingly). Results that were lower than standard levels as per all 4 tests were revealed in 4.3 % oil and gas extraction operators whereas there were no such results revealed in the reference group. Having analyzed cognitive functions in subgroups I, we revealed that a share of workers without lower results as per any test was a bit lower in the test group (*RR* = 0.59 (95 % *CI* 0.37–0.92); however, relative risk that lower results would be detected in 1 and 2 tests tended to increase and was *RR* = 1.12 (95 % *CI* 0.55–2.26) and *RR* = 2.52 (95 % *CI* 0.65–9.82) accordingly. And quite the contrary, relative risk of low results obtained in 1 and 2 tests was lower in the test group, subgroup III, than in the same subgroup in the reference group

Table 8

Comparative analysis of data obtained via "Number square" test among all the examined workers

"Number square" test data	Test group, $n = 166$	Reference group. $n = 33$	Validity of differences between groups, $p < 0.05$
Correct answers, number	11 (7; 13)	13 (10; 14)	0.02
Mistakes, number	7 (5; 11)	7 (4; 9)	0.11
Frequency of different attention levels, %			
Low attention (from 0 to 5 correct answers)	19.3	12.1	0.33

Table 9

Comparative analysis of data obtained via "Number square" test among workers with different working experience

"Number square' test data	Test group, subgroup I $n = 77$	Test group, subgroup II $n = 53$	Test group, subgroup III $n = 46$	Ref.group, subgroup I $n = 15$	Ref.group, subgroup II $n = 12$	Ref.group, subgroup III $n = 20$	p^1	p^2	p^3
Correct answers, number	12 (9; 14)	11 (8; 12)	9 (6; 11)	13 (11; 13)	13.5 (10.5; 14.5)	10.5 (7; 14)	0.78	0.02	0.29
Mistakes, number	7 (5; 10)	7 (5; 11)	8.5 (6; 12)	8 (4; 10)	5 (2.5; 7)	8 (7; 10)	0.91	0.029	0.95
Frequency of different attention levels, %									
Lowe attention (from 0 to 5 correct answers)	16.9	18.9	23.9	13.3	8.3	16.7	0.73	0.38	0.69
Standard attention (more than 5 correct answers)	83.1	81.1	76.1	86.7	91.7	83.3	0.73	0.38	0.69

Note: p^1 is validity of differences between the test group, subgroup I, and the reference group, subgroup I; p^2 is validity of differences between the test group, subgroup II, and the reference group, subgroup II; p^3 is validity of differences between the test group, subgroup III, and the reference group, subgroup III.

and amounted to $RR = 0.58$ (95 % CI 0.29–1.20) and $RR = 0.64$ (95 % CI 0.16–2.61). However, results lower than standard levels in 3 and 4 tests were detected in 20.4 % and 18.4 % workers in this subgroup accordingly whereas there were no such workers in the reference group, subgroup III (Table 10).

Table 11 contains the results obtained via linear regression analysis of a probable deterioration in cognitive functions among oil and gas extraction operators depending on their working experience. We revealed statistically significant dependence between working experience under exposure to adverse occupational factors for oil and gas extraction operators and probable low results obtained via "Concepts exclusion" test ($b_0 = 13.46$; $b_1 = –0.97$; $F = 15.85$; $R^2 = 0.071$; $p = 0.0001$), "Image memory" test ($b_0 = 9.96$; $b_1 = –0.13$; $F = 36.78$; $R^2 = 0.151$; $p = 0.0001$), "Number memory" test ($b_0 = 7.75$; $b_1 = –0.04$; $F = 9.91$; $R^2 = 0.045$; $p = 0.002$), "Number square" test ($b_0 = 11.03$; $b_1 = –0.11$; $F = 9.95$; $R^2 = 0.057$; $p = 0.002$). We didn't detect any similar statistically significant dependence in the reference group.

Cognitive disorders become apparent via cognitive functions dropping lower than their standard levels; they can develop both due to natural ageing of a body and due to exposure to various occupational factors (noise, vibration, etc.). Effects produced by neurotoxicants on the nervous system become apparent via diffuse damage to the brain that is accompanied with occurring brainstem–hypothalamic syndrome, and syndrome related to cerebral and psychoneurological disorders[2]. Impacts exerted by adverse occupational factors (chemical factors, noise, vibration, and labor intensity) on cognitive functions have been examined by many authors [11, 17–19]. As per data obtained by M. Reale et al., 80 examined workers employed in oil extraction had increased anxiety levels and occupational stress signs [20]. However, research

Table 10

Results obtained via neural-psychological tests that were lower than standard levels

Tests	Test group, *n* = 209	Reference group, *n* = 44	*RR* (*CI* 95 %)
Attributes in the test and reference groups			
Absent, %	64 (30.6)	21 (47.7)	0.64 (0.44–0.92)
1 test, %	83 (39.7)	18 (40.9)	0.97 (0.66–1.44)
2 tests, %	39 (18.7)	4 (9.1)	2.05 (0.77–5.45)
3 tests, %	14 (6.7)	1 (2.3)	2.9 (0.39–21.8)
All 4 tests	9 (4.3)	0	–
Attributes in subgroups I (99/20)			
Absent, people (%)	35 (35.4)	12 (60.0)	0.59 (0.37–0.92)
1 test, people (%)	37 (37.4)	6 (30.0)	1.12 (0.55–2.26)
2 tests, people (%)	25 (25.3)	2 (10.0)	2.52 (0.65–9.82)
3 tests, people (%)	2 (2.0)	0	–
All 4 tests	0	0	–
Attributes in subgroups II (61/15)			
Absent, people (%)	22 (36.1)	7 (46.7)	0.77 (0.41–1.46)
1 test, people (%)	30 (49.2)	7 (46.7)	1.05 (0.58–1.92)
2 tests, people (%)	7 (11.5)	0	–
3 tests, people (%)	2 (3.3)	1 (6.7)	0.49 (0.05–5.07)
All 4 tests	0	0	–
Attributes in subgroups III (49/9)			
Absent, people (%)	7 (14.3)	2 (22.2)	0.64 (0.16–2.61)
1 test, people (%)	16 (32.7)	5 (55.6)	0.58 (0.29–1.20)
2 tests, people (%)	7 (14.3)	2 (22.2)	0.64 (0.16–2.61)
3 tests, people (%)	10 (20.4)	0	–
All 4 tests	9 (18.4)	0	–

Table 11

"Working experience – cognitive functions parameters" liner regression: attributes

Exposure marker	Effect marker	A trend of a change in parameters	b_0	b_1	*F*	R^2	*p*
Test group							
Working experience under adverse working conditions	"Concepts exclusion"	Descending	13.46	-0.97	15.85	0.071	0.0001
	"Image memory"	Descending	9.96	-0.13	36.78	0.151	0.0001
	"Number memory"	Descending	7.75	-0.04	9.91	0.045	0.002
	"Number square"	Descending	11.03	-0.11	9.95	0.057	0.002
Reference group							
Working experience without exposure to adverse working conditions	"Concepts exclusion"	Descending	14.07	-0.16	0.209	0.005	0.65
	"Image memory"	Descending	10.32	-0.041	0.592	0.014	0.45
	"Number memory"	Descending	8.53	-0.16	0.38	0.009	0.54
	"Number square"	Descending	11.93	-0.06	0.45	0.014	0.51

performed by S.V. Tsyrempilov et al. didn't reveal any authentic deviations in cognitive functions among 56 workers who were occupationally exposed to neurotoxicants (aromatic hydrocarbons, toluene, and benzine) [21]; it may be due to selected diagnostic tests not being specific enough. To achieve relevant accuracy in research, O.I. Shevchenko et al. recommend applying several most informative diagnostic psychological tests simultaneously and these tests should be specific in terms of revealing damage done to specific brain structures by this or that neurotoxicant [22].

Our research results revealed that oil and gas extraction operators who had to work under exposure to several adverse occupational factors (chemicals and noise) had 1.3–1.6 times lower cognitive flexibility, image/number memory, and attention; lower memory capacity, attention, and analytical abilities were 2-3 times more frequent among them, and a risk of a decrease in synthetic and analytical activity was more than 5 times higher (*RR* = 5.55; 95 % *CI* = 1.4–21.9) than among workers with permissible working conditions at their workplaces. Results obtained via linear regression analysis revealed dependence between cognitive disorders occurrence in oil and gas extraction operators and their working experience under adverse working conditions; we didn't reveal any similar dependence in the reference group. A set of neural-psychological tests ("Concepts exclusion", "Image memory", "Number memory", and "Number square") was applied for assessing cognitive functions; the assessment revealed their availability, reproducibility and objectivity of their results even at early stages in cognitive dysfunction development (pre-dementia stage). It allows using these tests in periodical medical examinations for detecting people with minimal cognitive dysfunctions and further profound examinations, prevention activities, and finding solutions to issues detected due to medical inspections.

Conclusions

1. We detected authentic dependence between disorders in cognitive functions and duration of working experience under exposure to adverse occupational factors (chemical factor and occupational noise) for oil and gas extraction operators. Their cognitive flexibility (synthetic and analytical activity), image and number memory capacity, and attention were 1.3–1.6 times lower than among workers who had permissible working conditions at their workplaces.

2. Oil and gas extraction operators had 5 times higher relative risk of cognitive disorders occurrence, and low memory capacity, attention, and analytical activity were 2–3 times more frequent among them than among workers from the reference group (permissible working conditions at workplaces).

3. Using a set of neural-psychological tests ("Concepts exclusion", "Image memory", "Number memory", and "Number square") during periodical medical examinations provided for oil and gas extraction operators allows diagnosing cognitive dysfunction already at an early stage (pre-dementia stage) in its development (when working experience already exceeds 10 years) and revealing people with its minimal signs for further prevention activities and finding solutions to issues detected due to medical inspections.

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Research article

DETECTING AND PREDICTING RISKS RELAYED TO SPREAD OF NATURAL FOCI INFECTIONS ON FLOOD-AFFECTED TERRITORIES IN IRKUTSK REGION

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In summer 2019 in western Irkutsk region abundant and long rainfall caused a catastrophic flood that became a federal emergency.

It resulted in a threat that natural infection foci would be activated in that emergency zone; given that, the Irkutsk Anti-plague Institute, together with Rospotrebnadzor territorial offices and regional veterinary authorities, conducted an epizootologic-epidemiologic study on affected territories in order to detect and predict possible epidemiologic risks.

Totally, the study covered 30 socially significant objects and natural biotopes in three municipal districts in the region. We tested blood serum of people (244 samples), farm and home animals (253), and organs taken from caught small mammals aiming at determining natural foci infections in them with bacteriologic, serologic, and PCR procedures; overall. 4,370 examinations were performed.

Share of immune people amounted to 13.1 % regarding tularemia; 17.5 %, tick-borne encephalitis; yersiniosis, 10.8 %; leptospirosis, 3.1 %; tick-borne borreliosis, 7.1 %. Antibodies to pathogenic leptospira were detected in 36.0–81.3 % farm animals and it can indicate there is a latent epizootic process. In July 2019 there was low population of synanthropic rodents in socially significant objects on affected territories and small mammals population also decreased in natural foci with high contagion rate for tularemia agent (down to 17.9 %). In September 2019 rats were detected to inhabit food-related objects and small mammals migrated actively in natural stations, contagion rate with tularemia agent going down among them whereas there was a growth in contagion rate with leptospira (up to 40.0 %). We also revealed new natural tularemia and leptospirosis foci.

Activity in natural infections foci didn't exceed long-term average level just after the flood; still, there are persisting risks on affected territories in Irkutsk region that an epidemiologic situation might get worse there. The paper contains recommendations on further epizootologic-epidemiologic monitoring and organizing prevention activities such as control over sanitary situation at socially significant objects, local deratization, and sanitation in natural foci of animal leptospirosis.

Key words: *emergency, flood, epidemiologic risks, natural foci infections, zoonosis, leptospirosis, tularemia, Irkutsk region.*

At the end of the XX and beginning of the XXI century, a number of floods increased worldwide and their destructive force and inflicted economic loss also grew considerably. In Russia, annually more than 50 thousand square kilometers are exposed to flooding. The threat of flooding exists for more than 300 cities, dozens of thousands of other settlements, and industrial enterprises [1]. So, the main task that is to be solved by Rospotrebnadzor, medical and veterinary services on territories that suffered from flooding is to provide sanitary well-being based on epidemiological risk assessment for appropriate responding to a deteriorating sanitary situation [2].

Over the last decade experts at the Irkutsk Antiplague Research Institute have accumulated considerable experience in providing sanitary-epidemiological well-being in emergency zones including those that occurred due to floods in Amur region, Khabarovsk region and Jewish Autonomous Area in 2013; in the Republic of Khakassia and the Altai Republic in 2014 [2, 3]. The same situation connected with abnormal hydrometeorological conditions was observed in Irkutsk region in summer 2019.

On June 25, 2019 water-level started to grow in Angara river feeders after abundant and long rainfall in the western Irkutsk region. In the morning on June 27 six settlements of Nizhneudinsky and Taishetsky district were already underflooded, in the evening of the same day another nine settlements of Tulunsky district [4]. On June 28, 20 settlements were impacted by the flood, more than 800 people were evacuated from their homes, and 17 places of temporary accommodation were organized with a total capacity of 6,500 places; also the federal road R-255 to Tulun was closed for the traffic [5, 6]. In the morning of June 29 31 settlements in Nizhneudinsky, Taishetsky, Tulunsky and Chunsky districts were underflooded. To the noon of the same day, the extremely high water level of the Ia river was 13.8 meters whereas its critically permissible limit was only 7 meters. On June 30, 28 settlements remained underflooded in the Nizhneudisky, Chunsky, Taishetsky, Tulunsky and Ziminsky districts [4, 6].That situation was announced to be a federal emergency by the RF Presidential Order[1].

About 10.9 thousand houses in 109 settlements where 42.7 thousand people lived were flooded during the 1st flood wave. During the second wave (in late July – early August), 1.9 thousand houses with 5.4 thousand people living there were flooded in 58 settlements. Totally 49 sections of highways and 22 local road bridges were damaged. The stream of water demolished 1.3 thousand houses; almost more than 7 thousand buildings were damaged and could not be restored. 26 people were killed, 4 people were gone missing [7].

The rapid development of the flood situation in Irkutsk region at the beginning of July 2019, a sharp deterioration in the living conditions of the affected population, insufficient provision of high-quality drinking water, an increased number of contacts people had with livestock and wild animals that died from the flood in private farmsteads and natural stations resulted in risks related to epidemic manifestations of acute infectious diseases, including natural focal ones and those common for humans and animals. The experience gained by sanitary anti-epidemic teams (SAET) from the Irkutsk Antiplague Research Institute during the flood in the Amur region in 2013 showed the effectiveness of timely accomplished preventive measures aimed at preventing complications of the epidemiological situation [2].

By the order signed by the Head of the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing (Rospotrebnadzor), an emergency operations center was created at the Irkutsk Antiplague Research Institute of Rospotrebnadzor to promptly respond to a worsening flood situation and to coordinate the activities performed by SAET with other services. Previously, we considered its algorithm for taking actions and making organizational decisions [8].

Our research goal was to analyze the data obtained via an epizootologic and epidemiological survey on the flood-affected territories in Irkutsk region, carried out by the operations group of the Irkutsk Antiplague Research Institute in cooperation with the Rospotrebnadzor's territorial bodies and institutions, healthcare and veterinary organizations.

Data and methods. Given the existing situation, the Irkutsk Antiplague Research Institute prepared and conducted two visits by the operation group in July–September 2019 to assess the epidemiological situation with natural focal infectious diseases in the emergency zone in the Irkutsk region that occurred due to a catastrophic summer flood.

The initial phase of work (July 01, 2019 – July 12, 2019) in the emergency zone was carried out immediately after the first flood wave, when many areas were still flooded. The second stage (September 18, 2019 – September 28, 2019) was performed when all affected areas, except for the Chunsky district, were freed from flooding.

The retrospective analysis of the epizootological and epidemiological situation was based on the materials provided by the Reference Center for Monitoring over Natural Focal Diseases (since 2018 – the Scientific and Methodological Center for Monitoring over II–IV Risk Group Pathogens) of the Irkutsk Antiplague Research Institute, archive data and reports issued by Rospotrebnadzor Office in the Irkutsk region, Center for Hygiene and Epidemiology in Irkutsk region, and veterinary stations in Irkutsk region. The operational analysis of the situation was carried out basing on information from territorial institutions and departments, as well as their data obtained during the survey performed in the areas affected by the flood.

Sanitary situation at 30 socially significant objects was assessed as per their population with synanthropic rodents via visual observation and use of control-track sites (CTS),

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[1] On activities aimed at eliminating consequences of the flood in Irkutsk region: The RF President Order dated July 3, 2019 No. 316 (with alterations made on August 2, 2019). *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/560536767 (March 03, 2021).

Gero break-back traps and steel traps. The abundance of small mammals (s/m) in natural stations was tracked as per a number of animals per 100 trap-days (t/d) using Gero break-back traps. The definition of s/m species was given in accordance with descriptions in the monographs [9, 10]

Blood sampling from the population was carried out in conformity with the decision made by the emergency operations center of the territorial healthcare institutions.

Obtained samples (n = 4,370) were examined at laboratories in the Irkutsk Antiplague Research Institute. Blood serum and small mammals' organs were frozen and stored at the temperature 20 °C below zero, the filter paper was juiced with small mammals' blood, dried and stored at 4–8 °C. Before the examination, the small mammals' organs were thawed and suspensions were prepared with a Tissue Lyser LT homogenizer (Qiagen, Germany).

A random sampling made up of 244 blood serum samples taken from people living in Irkutsk region were examined to detect specific antibodies (IgG, IgA and agglutinins) to infectious agents causing tularemia, leptospirosis, hemorrhagic fever with renal syndrome (HFRS), tick-borne viral encephalitis (TBE), tick-borne borreliosis (ITB), West Nile fever (WNF), brucellosis, and yersiniosis. 222 samples out of them were obtained from the state-funded healthcare facility “Nizhneudinsk community hospital” (Nizhneudinsky district); 22 samples, from a branch of the Center for Hygiene and Epidemiology in Irkutsk Region in Tulunsky and Kuytunsky districts (Tulun city).

195 bovine blood serum samples were obtained from regional state-funded institutions including animal health centers in Nizhneudinsky district (66), Taishetsky district (99), and Tulun city (30); 32 small cattle blood serum samples were obtained from Nizhneudinsky district; 22 samples from horses, from Nizhneudinsky district (18) and Taishetsky district (4); 4 blood serum samples from dogs from Nizhneudinsk. All the samples were examined to detect specific antibodies to causative agents of leptospirosis and brucellosis.

Organs (kidneys, spleen, lungs, and brains) and blood of 237 captured small mammals (205, Nizhneudinsky district; 15, Taishetsky district; and 17, Tulunsky district) were tested to detect antibodies to causative agents of tularemia, leptospirosis, TBE, tularemia antigen, DNA of tularemia, leptospirosis causative agents, TBE virus antigen and RNA of the WNF virus and hantaviruses. Intestine samples of 69 small mammals (52 from Nizhneudinsky district and 17 from Tulunsky district) were investigated for yersiniosis via bacteriologic procedures and PCR; six combined spleen samples were investigated for tularemia via biological procedures using outbred white mice.

Anti-tularemia antibodies were determined in human serum and small mammals blood using the “RNGA-Tul-Ag-StavNIPCHI” (StavNIPCHI, Stavropol) and chromatic tularemia diagnosticum (Irkutsk Antiplague Research Institute) for agglutination micro response (MRA). Tularemia antigen in spleen suspensions of small mammals was detected using “RNGA-Tul-Ig-StavNIPCHI” (StavNIPCHI, Stavropol).

Anti-leptospirosis agglutinins in all serum and blood taken from small mammals were detected by MAT (Microscopic Agglutination Test) with a set of 11 reference leptospira strains; immunoglobulin, using “Leptospirosis-ELISA-IgG”, “Leptospirosis-ELISA-IgA” test systems (“Omniks”, St. Petersburg).

IgG to hemorrhagic fever with renal syndrome, tick-borne encephalitis, tick-borne borreliosis in samples from humans were detected via using “LymeBest-IgG”, “VectoTBEV-IgG”, “VectoHanta-IgG” test-systems; IgG to pathogenic Yersinia, using “Yersinia-IgG-EIA-BEST” test-system (“VECTOR-BEST”, Novosibirsk).

Antigens to TBE and WNF in small mammals’ brains were detected via immunofluorescence assay using ELISA reagent kit for detecting antigens to tick-borne encephalitis in field samples and ELISA reagent kit for detecting antigens to West Nile virus in field samples (“Bioservice”, Moscow).

Nucleic acid extraction was made with “RIBO-prep”, nucleic acid in pathogenic leptospira was detected via real-time PCR with "AmpliSens® Leptospira-FRT" test-system. Pathogenic yersinia were detected with "AmpliSens® Yersinia enterocolitica / Y.pseudotuberculosis – FRT" PCR kit; West-Nile Fever virus was detected with " AmpliSens® WNV-FRT" ("InterLabService", Moscow); tularemia causative agent was detected with PCR kit «Gen Francisellatularensis – RGF» (RusRAPI "Microbe") using Rotor-GeneQ amplifier (Qiagen, Germany). Hantavirus DNA was detected via using "Reverta-L" detection kit ("InterLabService", Moscow). PCR was performed with using primers that encode L-exon in hanta-virus [11] with CFX96 (Bio-Rad, USA); all results were accounted for via agarose gel electrophoresis. Positive samples were sequenced with "ABIPrism" 3500XL (Applied Biosystems / Hitachi, Japan) using Big Dye Terminator Cycle Sequencing Kit v 1.1 (Applied Biosystems, USA) to define hantavirus genotype. Nucleotide sequence was processed with Bio Edit program V.7.0.9 [12].

All obtained results were statistically processed with standard variation statistics procedures with calculating arithmetic mean values and their error, as well as via comparing individual samples using Student's t-test for qualitative features [13].

Results and discussion. Retrospective analysis of the epidemiological situation in the flood zone showed that natural foci of tularemia and leptospirosis occurred in Nizhneudinsky district. Thus, in 1937 an outbreak of tularemia was registered here; and in 1994, an outbreak of leptospirosis [14]. Natural infection foci are very stable and can exist for decades without showing themselves in any way [15]; therefore, in 2012–2014 a planned survey of the natural foci in Nizhneudinsky district was performed and the results indicated their activity was low [14]. Over five years preceding the flood, focal diseases of tularemia and leptospirosis were not registered on the territories in the emergency zone; no unfavorable events with farm animals were detected. The last cases of brucellosis in cattle, small cattle and horses were registered in Irkutsk region in 2004–2011 [16]. In general, the epidemiological and epizootic situation was safe in Irkutsk region before the flood[2] [17].

The laboratory base used by the operation group at the Irkutsk Antiplague Institute was organized in the building where the veterinary laboratory of "Nizhneudinsky district animal health center", the regional state-funded institution, was located. It was flooded during the first wave, but quickly restored its work and performed all the tasks assigned to the Veterinary Service in Irkutsk Region to eliminate the consequences of emergency. First of all, all dead animals' corpses were collected and destroyed. According to operational data as on August 28, 2019 4,736 corpses were collected in the emergency zone; poultry accounted for the biggest share (3,113 corpses); small domestic animals followed (rabbits, 885; dogs and cats, 250); and large farm animals were the next (cattle, 115; small cattle, 103; pigs, 260; horses, 10). In Tulunsky district, about three thousand animal corpses were collected; in Nizhneudinsky district, about a thousand. All dead animals were burned in specially prepared places. The veterinary service also took necessary actions to catch, treat, vaccinate and provide temporary keeping for neglected small animals. During the emergency period, 744 animals were caught; in Chunsky district, 175; Taishetsky, 90; Nizhneudinsky, 123; across Tulun and Tulunsky district, 356. 7,349 animals were vaccinated against rabies. Ultimate disinfection was provided for livestock buildings and walking yards, livestock enterprises and personal subsidiary farms affected by the flood. Overall, 913 objects were disinfected in a total area being equal to 165,948 square meters. Deratization was carried out at 263 objects (73,419 square meters). We emphasize that all veterinary care provided during the period of flood for private appeals was free of charge.

The tasks performed by the operation group at the Irkutsk Antiplague Institute in-

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[2] On the sanitary-epidemiologic situation and prevetive and anti-epidemic activities being accomplished in the zone of underflooding. Rospotrebnadzor Regional office in Irkutsk region, 2019. Available at: http://38.rospotrebnadzor.ru/ (November 25, 2020).

cluded an epizootologic and epidemiological examination, analysis of the epidemiological situation and forecasting its changes, as well as preventive work with the population and the development of guidelines on how to reduce risks that the epidemiological situation would deteriorate.

Particular attention was paid to examining socially significant facilities (places of temporary accommodation, food facilities, schools, and kindergartens), which provided the affected population with necessary services. It was important to prevent small mammals and rodents from penetrating into these objects and timely take preventive measures. A total of 549 break-back traps were installed, and 5.8 ± 1.0 % of them turned out to be tracked. At socially significant objects, 168 traps per day were worked out, 6.5 ± 1.9 % of hits of synanthropic rodents were detected. The presence of rodents was established at six sites (see Table 1), and their supervisors were recommended to immediately carry out unscheduled deratization.

Data on a share of population being immune to tularemia, TBE, yersiniosis, leptospirosis and borreliosis are given in Table 2. In Shumsky settlement in Nizhneudinsky district, people were identified who responded positively to brucellosis. In two cases also antibodies to Hantavirus were detected; this seems important since Irkutsk region is considered non-endemic as per HFRS [18, 19]. High immune layer to tularemia that amounted to 17.5 ± 4.2 % in Shumsky settlement where this disease was not previously registered and the population was not covered by preventive immunization could indicate a recent contact that people had with the infection in natural sites and thus an existing natural focus.

Epizootologic survey of natural biotopes involved working out a total of 2,080 trap-days. The abundance of small mammals was 11.4 ± 0.7 % of hits. In July the East Asian mice prevailed in the capture in the vicinity of Shumsky settlement (83.3 ± 6.8 %) and they had previously been very rare there (2012, 3.5 ± 2.0 %; $p < 0.01$). Laboratory studies revealed a high infection of small mammals by the causative agent of tularemia and relatively low infection by leptospira, which was also uncharacteristic for this area in 2012–2014 (see Table 3).

Table 1

Socially significant facilities with detected rodent presence

№	Facility	Date	Survey method	Results
July 2019				
1.	"Boarding school No. 26" Russian Railways affiliate, place of temporary accommodation in Nizhneudinsk	July 03–04, 2019	43 control-track sites, visual observation	9.3 % of control-track site tracked (mice), one rat corpse found
2.	Confectionary factory "Siberia", Nizhneudinsk	July 06–07, 2019	50 control-track sites, visual observation	4.0 % of control-track site tracked (mice)
3.	Shumsky municipal hospital, Shumsky	July 02–03, 2019	30 control-track sites, visual observation	6.7 % of control-track site tracked (mice)
September 2019				
4.	Tulun Grain delivery station, Tulun	September 17–18, 2019	8 steel traps; 20 control-track sites, visual observation	3 grey rats caught; 100 % of control-track sites tracked
5.	Taishet bakery complex, Taishet	September 19–20, 2019	20 control-track sites, visual observation	20.0 % of control-track sites tracked; one rat corpse found
6.	Central food market, Nizhneudinsk	September 26–27, 2019	25 break-back traps, visual observation	0 collected rodents; inhabited rat burrows found

Table 2

Serological screening of the population regarding zoonotic diseases in flood-affected districts in Irkutsk region

Infection	Method	Quantity of investigations / % of positive results (reaction titer)	
		July, 2019	September, 2019
Leptospirosis	MAT	94 / **2.1** ± 1.5 (1:20)	114 / **2.6** ± 1.5 (1:20-100)
	ELISA, IgG	130 / **3.1** ± 1.5	41 / **0**
	ELISA, IgA	80 / **0**	n/i
Tularemia	RNGA, *MRA	130 / **13.1** ±3.0 (1:20–80)	*106 / **4.7** ± 2.1 (1:20)
HFRS	ELISA, IgG	80 / **0**	99 / **3.0** ± 1.6
TBE		80 / **17.5** ± 4.2	99 / **9.1** ± 2.9
TBB		80 / **0**	99 / **7.1** ± 2.4
Yersiniosis		130 / **10.8** ± 2.7	41 / **9.8** ± 4.6
Brucellosis	ELISA, IgG	130 / **0**	105 / **1.9** ±1.3
	Heddlson's reaction	105 / **0**	105 / **1.0** ±1.0 (0.04+++; 0.02+++; 0.01+++)

N o t e s : n/i means not investigated;

Description: HFRS is hemorragis fever with renal syndrome; TBE, tick-borne encephalitis; TBB, ixodic tick-borne borreliosis; MAT, Microscopic Agglutination Test; * MRA, micro-reaction of agglutination.

Table 3

The results of small mammals' investigation to detect tularemia and leptospira causative agents in the flood-affected districts in Irkutsk region

Survey territory	Date of survey	Totally investigated / positive results (%)			
		Tularemia			Leptospirosis
		AB	AG	DNA	DNA/RNA
Shumsky municipal district	2012–2014	53/ **11.3**± 4.2	5*/ **60.0** ±21.9	n/i	105/ **17.1** ± 3.7
	July 2019	30/ **40.0** ± 8.9	17*/ **23.5** ±10.3	17*/ **5.9** ± 5.4	30 / **3.3** ± 3.3
	September 2019	77/ **1.3**±0.9	19*/**10.5**±2.3	19*/ **0**	77 / **6.5** ± 2.8
Nizhneudinsky district (including Shumsky municipal district)	2012–2014	53/ **11.3**± 4.2	5*/**60.0** ± 6.4	n/i	105/ **17.1** ± 3.7
	July 2019	58 / **31.0** ± 6.1	28*/ **32.1** ± 8.8	28*/ **17.9** ± 7.2	61 / **1.6** ± 1.6
	September 2019	144/ **1.4** ±0.9	46*/ **15.2**±2.7	46*/ **0**	144 / **10.4**±5.9
Tulunsky district	September 2019	17/ **5.9**±5.7	6*/**16.7**±9.0	6*/ **0**	17 / **17.6** ± 9.2
Taishetsky district		3*/ **33.3**±12.2	15/ **0**	3*/ **0**	15 / **40.0**±12.6

N o t e : * means combined probes; n/i, not investigated; AB, antibodies; AG, antigen.

In July 2019, anti-tularemia antibodies were found in more than a third of small mammals captured in the vicinity of Shumsky settlement, which could be a sign of a fading epizooty [2]. High epizootic activity detected in Shumsky municipal district's natural focus of tularemia was confirmed with an immune layer being present among local residents. Detection of antigen and DNA of the tularemia causative agent in small mammals in Nizhneudinsky district, including those which were captured within the city of Nizhneudinsk, indicated a risk that an epizooty would develop further provided there was a sufficient number of susceptible individuals. The situation was aggravated by animals migrating actively and occurring reserves with a high number of blood-sucking mosquitoes in numerous temporary wet biotopes. However, in September 2019, despite an increase in the number of carriers (from 8.8 ± 1.1 to 15.4 ± ± 1.1 % of hits, $p < 0.01$), their infection with tularemia causative agent sharply decreased in comparison with July ($p < 0.01$). Also in September, the ratio of small mammals' species changed significantly and approached the levels that were observed in the area in 2012–2014. While exploring the surroundings of Shumsky settlement, experts didn't detect any small mammals on the outskirts. In the vicinity of the settlement, as before, animals were concentrated in the reserve stations (hills, forest belts). However, the root vole began to predominate in the catches (45.4 ± ± 5.7 %, in 2012 9.4 ± 5.4 %), and the proportion of East Asian mice decreased 2.5 times falling to 31.2 ± 5.3 % ($p < 0.01$).

In September 2019, seven house mice and one gray rat were captured in the residential sector of Nizhneudinsk. In natural stations on the outskirts of Nizhneudinsk, the root vole (33.9 ± 6.2 %) and field mouse (22.0 ± ± 5.4 %) prevailed in the catches. When examining Taishet district in the flood plain area on the right bank of the Biryusa river, experts detected that shrews and red voles prevailed there (46.7 ± 12.9 % each). Their infection with leptospirosis was unexpectedly high, which is consistent with the results obtained via serological screening performed over livestock animals. When examining the outskirts of Tulun in forest-shrub biotope on the left bank of the Ia river, experts didn't find any small mammals. This place was completely submerged in both the first and second flood waves. The surroundings of the Bulushkin settlement were also strongly flooded in the first wave of flood, but the second wave practically did not affect them, and there a high number of small mammals was revealed (14.0 ± 3.5 % of hits), mostly shrews (64.3 ± 12.8 % of the catch), and their high infection with tularemia and leptospirosis pathogens was confirmed (see Table 4).

Small mammals infected with WNF and TBE viruses were not identified.

RNA of Hantavirus Seewis was detected in samples from Tulunsky and Nizhneudinsky districts and it is consistent with detection of antibodies in humans and is of great scientific interest. The pathogen of tularemia was not isolated in six PCR-positive spleen samples.

The DNA of the pseudotuberculosis and intestinal yersiniosis causative agents was found in 52.2 ± 6.0 % of the small mammals' kidney samples. Besides, in Nizhneudinsky district experts detected three cultures of Yersinia pseudotuberculosis and five pathogenic Y.enterocolitica belonging to 0:3 serovars.

Serological screening of animals revealed a high percentage of cattle that reacted positively with leptospira serogroups Tarassovi and Hebdomadis (see Table 4), in the Tulunsky district in unvaccinated cattle, in addition to Bataviae and Grippotyphosa, and in Nizhneudinsk – Canicola, with the absence of sick animals; it could indicate there was a latent epizootic process. When it comes down to small cattle, the situation is similar to that of

Table 4

The results of livestock animals' serological screening for leptospirosis in Irkutsk region districts affected by flood (%)

Serogroup	Taishetsky district (*n*=99)	Tulunsky district (*n*=30)	Nizhneudinsky district		Reaction titre
			July (*n*=50)	September (*n*=16)	
*Grippotyphosa**	11.2 ± 3.2	40.0 ± 8.9	4.0 ± 2.8	25.0 ± 10.8	1:20–1:100
*Sejroe**	17.2 ± 4.0	0	0	0	1:20–1:100
*Tarassovi**	52.5 ± 5.0	63.4 ± 8.8	20.0 ± 5.6	50.0 ± 12.5	1:20–1:100
*Pomona**	11.2 ± 3.2	0	0	68.8 ± 11.6	1:20–1:100
Icterohaemorrhagiae	1.0 ± 1.0	0	4.0 ± 2.8	12.5 ± 8.3	1:20
Hebdomadis	17.2 ± 4.0	10.0 ± 5.5	6.0 ± 3.4	18.8 ± 9.8	1:20–1:100
Javanica	0	0	0	0	–
Bataviae	12.1 ± 3.3	23.4 ± 7.7	4.0 ± 2.8	12.5 ± 8.3	1:20
Canicola	1.0 ± 1.0	0	14.0 ± 4.9	31.3 ± 11.6	1:20–1:200
Autumnalis	5.1 ± 2.2	3.4 ± 3.3	0	25.0 ± 10.8	1:20
Australis	1.0 ± 1.0	3.4 ± 3.3	0	6.25 ± 1.2	1:20
Total %	71.2 ± 4.5	76.7 ± 7.7	36.0 ± 6.8	81.3 ± 9.8	1:20–1:200

Note: * means included in vaccine.

cattle; horses, in addition to all of the above, can become infected with leptospira serogroups Autumnalis (40.9 ± 10.5 %, titers 1:20–1:100), Javanica (36.4 ± 10.3 %, titer 1:20) and Bataviae (27.3 ± 9.5 %, titer 1:20).

Conclusions. Summing up the results obtained via the epizootologic survey, they can be briefly presented in the following way. After the first wave of flood in July 2019, on the affected territories there was a low population of socially significant objects by rodents (mice) and a number of small mammals was depressed in natural sites with their high infection with tularemia causative agent and low infection with leptospira. In September 2019, there was a high population of rats in some food premises in the cities of Tulun, Taishet and Nizhneudinsk; small mammals quantity recovered in natural sites with a decrease in their infection with the causative agent of tularemia and an increase with leptospira. A natural focus of tularemia was revealed in the vicinity of Shumsky settlement in Nizhneudinsky district. Also it has been established there were of agricultural and natural foci of leptospirosis in Tulunsky and Taishetsky districts.

Sanitary and epidemiological situation on the affected territories remained stable; the levels of infectious morbidity were within the mean long-term values. Group and outbreak morbidity has not been registered [20].

Forecast for natural focal infections and zoonoses is relatively favorable for the coming years for Nizhneudinsky district. Complicated epidemiological situation can be caused by massive reproduction of small mammals, however, but there are no prerequisites for this. Stronger monitoring is needed first to detect the natural focus of tularemia in the vicinity of Shumsky settlement. A situation that is emerging in Tulunsky and Taishetsky districts in connection with previously identified unregistered foci of leptospirosis remains unclear. The detection of antigen and antibodies to hanta viruses requires further examination.

The main preventive measures that need to be carried out basing on the results of the survey include the following: leptospirosis foci of farm animals should be sanitized; control should be performed over socially significant objects with identified violations; further epizootologic and epidemiological monitoring is required. Significant small mammals' infection with pathogenic Yersinia requires intensified preventive measures aimed at excluding animals' contacts with food and drinking water provided for people: local deratization measures in places of small mammals finding, control over rodent population at socially significant objects (primarily those associated with food production and distribution), control over measures taken to ensure rodent impermeability into food objects, strict adherence to the conditions and terms of food products storage, control over water intakes, drinking water quality control.

Thus, we can say that the flood wave extinguished the epizootic process in natural foci, causing a depression in the number of carriers. Biotic communities are being renewed on flood-affected territories in Irkutsk region, small mammals are migrating and inhabiting vacated natural niches, and also new natural foci of tularemia and leptospirosis have been revealed and it means that there are still risks that natural foci infections might spread in the area.

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Research article

ENDOTHELIN-1 AS A RISK FACTOR CAUSING CARDIOVASCULAR PATHOLOGY IN YOUNG AND MIDDLE-AGED PEOPLE EMPLOYED UNDER HAZARDOUS WORKING CONDITIONS

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Our research goal was to reveal peculiarities related to changes in endothelin-1 contents in blood serum in young and middle-aged people exposed to occupational noise and industrial welding and silicon-containing aerosols with fibrogenic effects. Another goal was to establish a correlation between endothelin-1 contents and blood pressure, body mass, and dyslipidemia.

We examined workers employed at a metallurgic plant in Nizhniy Novgorod region. Endothelin-1 concentration in blood serum was determined with «Endothelin (1–21)», a reagent kit for ELISA produced by «Biomedica Medizinprodukte GmbH & Co KG» (Austria). We detected certain group differences in endothelin-1 contents in blood serum and frequency of its elevated concentrations between workers who had to work under different working conditions. We established a direct correlation between endothelin-1 and blood pressure, total cholesterol, and body mass index. Elevated endothelin-1 contents in people suffering from arterial hypertension can indicate a higher risk of complications this disease might have. People who have elevated endothelin-1 contents but normal blood pressure, total cholesterol within physiological standard and normal body mass index can be recommended to have regular medical check-ups focusing on functional state of their cardiovascular system; endothelin-1 in this case should be considered a risk factor that might cause cardiovascular pathology occurrence. An individual approach is required when assessing elevated endothelin-1 contents and probable use of this parameter as a risk factor that might cause cardiovascular pathology in young and middle-aged people employed under hazardous working conditions.

Key words: *adverse occupational factors, endothelin-1, blood pressure, total cholesterol, body mass, cardiovascular pathology, risk factor, biomarker.*

Over recent years, experts' attention has been concentrated on searching for biochemical markers that could indicate there was a cardiovascular pathology at an early stage in its development in young and middle-aged people. And it is especially vital when it comes down to men rather than women since signs of atherosclerotic diseases tend to appear

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earlier among them. Risk factors that may cause cardiovascular pathology are smoking, overweight, low physical activity, blood pressure, and hereditary predisposition [1]. A significant contribution is also made by adverse occupational factors [2, 3]. By now, there are several known biochemical parameters; analysis of changes in them together with examining functional and clinical parameters provides an insight into atherosclerotic process development and subsequent occurrence of cardiovascular pathology [4]. Such parameters as overall cholesterol and dextrose are to be determined during any periodical medical examination (according to the Order by the RF Ministry for Public Healthcare and Social Development issued on April 12, 2011 No. 302n[1]). Changes in these biomarkers together with EKG readings, body mass index (BMI), and blood pressure (BP) reflect only one side in pathogenesis of cardiovascular pathology, namely, a role probably played in this pathogenesis by metabolic disorders that contribute significantly into development of atherosclerosis and cardiovascular pathology[2]. However, pathogenetic mechanisms of cardiovascular pathology development are more complicated and it is a vital task to manage to reveal them at initial stages, especially among young people with their bodies still being highly adaptable to environmental factors [5]. Endothelin-1 (ET-1) is a marker that can be useful here since it is a marker of endothelial dysfunction that becomes apparent via changes in vascular tonus and damage to vessel walls making them thicker and thus resulting in vasoconstriction. All this plays a significant role in pathogenesis of atherosclerosis and arterial hypertension (AH) development [6, 7]. It was established that elevated overall peripheral vascular resistance (OPVR) was a significant pathogenetic component in AH occurrence; this resistance, in its turn, is closely connected with vascular endothelium condition and with excessive ET-1 formation in particular [8]. According to some authors, OPVR remains pathologically high among those young people who are prone to AH. Some research works revealed that 25 % people living in the USA aged 20 and older suffered from hypertension since their systolic blood pressure (SBP) was 120–139 mm Hg; and diastolic blood pressure (DBP), 80–89 mm Hg. A probability that essential hypertension would develop was 11 times higher among young people with such blood pressure than among those with optimal blood pressure (SBP being lower than 120 mm Hg and DBP lower than 80 mm Hg) [9]. A relation between ET-1 and AH is confirmed by many researchers [10, 11]; but relations between ET-1 and dyslipidemia and overweight require further investigation [12] and it provides an opportunity to consider ET-1 a risk factor that can cause cardiovascular pathology.

Workers employed at metallurgic and metal-processing productions are exposed to a set of adverse occupational factors [13, 14]. As a rule, they are young and middle-aged people who start their career at such enterprises at 23–25; it is extremely important to monitor their health, to provide timely prophylaxis for them in order to prevent work-related and occupationally induced pathologies since it will make their period of employment longer and result in longer life expectancy [15]. Issues related to examining endothelial dysfunction among young and middle-aged people and its relation with AH, dyslipidemia, and overweight among workers exposed to adverse occupational factors at their workplaces have not been studied in detail and require special attention by researchers and physicians.

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[1] On approving the list of adverse and (or) hazardous occupational factors and works which require obligatory preliminary and periodical medical examinations (checkups) and the Procedure for performing obligatory preliminary and periodical medical examinations (checkups) of workers who deal with hard labor and adverse and (or) hazardous working conditions at their workplaces: The Order by the RF Ministry for Pubic Healthcare and Social Development issued on April 12, 2011 No. 302n (last edited on May 18, 2020). *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_120902/ (January 29, 2021).

[2] Diagnostics and correction of lipid metabolism disorders for atherosclerosis prevention and treatment. Russian recommendations: the VI revisions by D.M. Aronov, G.G. Arabidze, N.M. Akhmedjanov, T.V. Balakhonova, O.L. Barbarash, S.A. Boitsov [et al.]. Moscow, 2017, 44 p.

Our research goal was to detect peculiarities related to changes in Endothelin-1 contents in blood serum among young and middle-aged workers exposed to occupational noise and welding and silicon-containing aerosols with predominantly fibrogenic effects and to reveal a relation between endothelin-1 contents and blood pressure, body weight, and dyslipidemia.

Data and methods. We examined 87 workers employed at a metallurgic plant in Nizhniy Novgorod region; they were all men aged from 25 to 51.Their working experience at this enterprise varied from 5 to 15 years. All these workers had a profound medical examination at an advisory polyclinic of Rospotrebnadzor's Scientific and Research Institute for Hygiene and Occupational Pathology. All the examined workers dealt with producing big-diameter metal pipes. They were divided into 2 groups depending on a type and essence of adverse occupational factors at their workplace; the first group (32 people aged 38.6 ± 8.3) was exposed to occupational noise (crane operators, pipe elector-welding mill operators, metal sorters, repairmen, and control unit operators); the second group (55 people aged 39.1 ± 9.5) were exposed to welding and silicon-containing aerosols with predominantly fibrogenic effects (pipe electro-welders, strop operators, metal cutters, milling machine operators, and rollers).

Working conditions were assessed according to the FZ-426 issued on December 28, 2013 "On special assessment of working conditions"[3]. According to this assessment, occupational noise at workplaces exceeded permissible levels (more than 80 dBA, and it even reached 83–85 dBA in some areas at production facilities). Aerosol contents in working area air exceeded maximum permissible concentrations and were within ranges that corresponded to working conditions belonging to 3.1 hazard category ("hazardous", the first degree).

The reference group (the third group) was made up of men (31 people aged 43.3 ± 9.6) who were not exposed to any adverse occupational factors at their workplaces; they were employed at an advertising agency and dealt with placing street advertising in the regional center and region. All three groups were comparable as per age, sex, and working experience ($p > 0.05$).

We excluded people with acute respiratory and inflammatory diseases, malignant neoplasms, type II pancreatic diabetes and exacerbation of chronic diseases from our research. All participants gave their voluntary informed consent to be examined and examination results to be published. Our research didn't infringe on rights of the examined people and didn't impose any threats for them in conformity with biomedical ethics requirements fixed by Helsinki Declaration issued by the World Medical Association (2000) and The Order by the RF Public Healthcare Ministry issued on June 19, 2003 No. 266[4].

Endothelin-1 concentration in blood serum was determined with "Endotelin (1-21)" reagent kit for ELISA tests produced by "Biomedica Medizinprodukte GmbH & Co KG" (Austria). A range of reference values for ET-1 concentrations in blood serum of healthy donors amounted to 1–3.5 pg/ml. Concentrations of cholesterol (CS), low density lipoproteins (LDLP-CS), high density lipoproteins (HDLP-CS), and triglycerides (TG) in blood serum were determined with "Thermo Fisher Scientific Oy" reagent kit (Finland) and "Konelab 20" biochemical analyzer produced by Thermo Fisher Scientific Oy" (Finland). CS, LDLP-CS, HDLP-CS and TG levels determined in the examined people were analyzed taking into account risks of cardiovascular pathology occurrence according to recommendations by experts from the Russian Society of Cardiology and the European Society of Cardiology / European Society of Hy-

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[3] On special assessment of working conditions: The Federal Law No. 426 issued on December 28, 2013. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_156555/ (January 29, 2021).

[4] On approving Rules for Clinical Practice in the Russian Federation: The Order by the RF Public Healthcare Ministry issued on June 19, 2003 No. 266 (Registered by the RF Ministry of Justice on June 20, 2003 No. 4808). *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_43346/ (January 29, 2021).

pertension (2018) [16]. Overweight and obesity were classified as per BMI in accordance with guidelines given by the WHO, 1997. BP levels were assessed according to "Clinical guidelines on diagnosing and treating arterial hypertension": optimal level for systolic BP was < 120 mm Hg; for diastolic BP, < 80 mm Hg; normal and elevated levels were 120–139 mm Hg and 80–89 mm Hg; AH, 140 mm Hg and higher than 90 mm Hg and above [17].

All the data were statistically processed with "Statisitca 6.1". We applied Shapiro – Wilk test to analyze whether parameters were distributed normally and dispersions were equal. All further statistical analysis was performed according to the results with non-parametric processing techniques. Data are given as *Med* ± *IQR* (25–75 %). We applied Kruskal – Wallis test to perform multiple comparison of the examined groups; to describe differences more precisely, we applied Mann – Whitney U-test that allowed assessing differences in parameters when a pair of group was compared; Bonferroni correction was used when *p* value were estimated. Differences between independent samplings were assessed as per a frequency of an examined parameter basing on Pearson's χ^2 test [18]. Critical significance of the results was taken at $p < 0.05$. When *p* varied from 0.05 and up to 0.1 inclusive, it was considered to be a trend.

Results and discussion. Table 1 contains data on ET-1 contents in blood serum and frequency of its occurrence in different concentrations in the examined groups.

Having compared ET-1 contents in three groups, we detected authentic differences between them ($p = 0.013$, H = 8.58, Kruskal – Wallis test). Pair analysis revealed statistically authentic differences in ET-1 contents in blood serum of workers who were exposed to occupational noise (the 1st group) and workers exposed to industrial aerosols (the 2nd group) against those who were not exposed to adverse factors at their workplaces (the 3rd group) ($p_{1\text{-}3} = 0.003$, $Z = 2.9$; $p_{2\text{-}3} = 0.0008$, $Z = 2.6$; Mann – Whitney U-test). ET-1 contents in blood serum of people from the 3rd group were 2 times lower than its contents in the first two groups. We didn't detect any differences in ET-1 contents between the 1st and the 2nd group ($p_{1\text{-}2} = 0.831$, $Z = –0.2$; Mann – Whitney U-test). Having analyzed frequency of different ET-1 contents, we revealed that elevated ET-1 contents in blood serum (higher than 3.5 pg/ml) were detected in more than 30.0 % of people in the 1st and the 2nd group against only 12.0 % in the 3rd group. And we should note that high ET-1 contents (more than 12 pg/l) were not detected at all in the 3rd group of workers whereas such high ET-1 contents were detected in 14.2 % and 12.0 % accordingly among workers form the 1st and the 2nd group.

We detected that normal and elevated BP prevailed in all three groups and one third of the examined people turned out to have AH ($\chi^2 = 12.42$, $p = 0.015$). Differences were detected regarding frequency of optimal BP since it was most frequently detected among workers from the 2nd group (14.5 %) and least

Table 1

ET-1 concentrations (*Med* ± *IQR* (25–75 %)) and frequency of detecting different concentrations (%) in workers

Parameters	The 1st group (*n* = 32)	The 2nd group (*n* = 55)	The 3rd group (*n* = 31)
ET-1 concentration (pg/ml)	3.00 (2.36–7.20)	3.21 (2.57–6.78)	1.50 (1.04–1.80)
p	$p_{1\text{-}2} = 0.831$; $p_{1\text{-}3} = 0.003$; $p_{2\text{-}3} = 0.0008$		
ET-1 concentrations ranges (pg/ml)	Frequency of detecting ET-1 in different concentrations (%)		
3.50 and lower	64.2	69.0	88.0
3.51–12.0	21.6	19.0	12.0
Higher than 12.0	14.2	12.0	0

N o t e : *p* is validity of differences in ET-1 concentrations between workers' groups (Mann – Whitney U-test).

Table 2

Frequency of detecting different BP levels among workers, (%)

Parameter	The 1st group (n = 32)	The 2nd group (n = 55)	The 3rd group (n = 31)	χ^2 test	p
BP levels (mm Hg)	Frequency of different BP levels (%)				
Lower than 120 / 80	3.2	14.5	6.5	8.367	0.012
120–139 / 80–89	68.7	54.6	54.8	2.201	0.205
140 / 90 and higher	28.1	30.9	38.7	1.853	0.173

Table 3

ET-1 concentrations (*Med* ± *IQR* (25–75 %)) and frequency of its different concentrations detected in blood serum (%) depending on workers' BP

Parameters	BP (mm Hg)					
	Lower than 120 / 80 (n = 11)		120–139 / 80–89 (n = 69)		140 / 90 and higher (n = 38)	
ET-1 concentrations (pg/ml)	2.88 (2.18–3.6)		3.24 (2.64–6.6)		4.8 (3.02–15.21)	
p	p_{1-2} = 0.054; p_{1-3} = 0.021; p_{2-3} = 0.093					
Examined groups	Frequency of detecting different ET-1 concentrations (%)					
	Higher than 3.5 pg/ml	3.5 pg/ml and lower	Higher than 3.5 pg/ml	3.5 pg/ml and lower	Higher than 3.5 pg/ml	3.5 pg/ml and lower
1st (n = 32)	0	100.0	40.9	59.1	53.3	46.7
2nd (n = 55)	0	100.0	27.6	72.4	58.8	41.2
3rd (n = 31)	0	100.0	11.8	88.2	16.7	83.3

Note: p is validity of differences in ET-1 concentrations depending on BP (Mann – Whitney U-test).

frequently, among workers from the 1st group (3.2 %). These data are given in Table 2.

We examined a correlation between ET-1 concentration in blood serum and BP in the examined groups; the results are given in Table 3.

We didn't detect any statistically significant differences between the groups after comparing ET-1 concentrations in workers' groups distributed as per BP levels (p = 0.19, H = 3.29, Kruskal – Wallis test). Pair analysis revealed that in case BP was 140/90 mm Hg and higher, there was a trend (taking Bonferroni correction into account when p value was estimated) for growing ET-1 concentration in blood serum. ET-1 concentration in blood serum was the lowest among people with optimal BP and differed from ET-1 concentrations detected in people with higher BP levels (p_{1-2} = 0.054, Z = -0.14; p_{1-3} = 0.021, Z = -0.10, Mann – Whitney U-test).

We detected differences in frequency of elevated ET-1 contents in blood serum depending on BP levels in workers from different groups. Thus, there were no elevated ET-1 contents (higher than 3.5 pg/ml) among people with optimal BP in all three groups. Attention should be paid to people with normal and elevated BP since ET-1 contents were higher than reference values in 40.9 % examined people with such BP levels in the 1st group and in 27.6 % people in the 2nd group whereas elevated ET-1 contents were detected only in 11.8 % examined people with such BP from the 3rd group. A share of people with elevated ET-1 contents in blood serum grew by 2 times in the 2nd group (workers exposed to industrial aerosols) as BP levels increased, from 27.6 % to 58.8 % whereas ET-1 concentration grew by 12.4 % among those who were exposed only to occupational noise (the 1st group). The same trend was revealed in the reference group; however, an increase in frequency of detecting elevated ET-1 levels with a growth in BP was insignificant and amounted to 4.9 %. However, we should note that ET-1 contents were within the reference range in almost half of people with AH from the first two groups.

A share of people with AH who had normal ET-1 contents in their blood serum was the highest in the reference group and amounted to 83.3 %.

Our research revealed that almost half of the examined people in all three groups had dyslipidemia and were no differences in lipid profiles detected between the examined groups. A significant share of people (40.6–50.0 %) had elevated CS and LDLP-CS levels; almost one third had decreased HDLP-CS levels; elevated TG levels were detected in 13.7–18.7 % of the examined people. Having analyzed a correlation between ET-1 contents in blood serum and CS contents, we revealed that in case CS contents were more than 5.2 mmol/l, ET-1 concentration was authentically higher against the same parameter when CS contents were lower than 5.2 mmol/l ($p = 0.03$). Table 4 contains the results obtained via examining correlations between ET-1 concentrations in blood serum and CS concentrations in the examined groups.

Having analyzed relations between ET-1 and CS contents in three groups, we revealed certain trends for the parameters to differ. Thus, elevated CS levels in blood serum were accompanied with elevated ET-1 concentrations in more than half of workers exposed to permanent occupational noise (58.3 %) whereas in case CS levels were normal, elevated ET-1 contents were detected only in 20.0 % of the examined people. ET-1 contents in workers from this group was authentically higher in case CS was higher than 5.2 mmol/l against its values in case CS was lower than 5.2 mmol/l: 7.24 (2.88–12.6) against 2.64 (2.36–2.88) ($p = 0.012$). We didn't detect similar dependence among workers exposed to industrial aerosols and those who were not exposed to any adverse factors at their workplaces; and elevated ET-1 contents in blood serum with CS being higher than 5.2 mmol/l was detected in fewer people. We didn't detect any dependence between ET-1 contents in blood serum and TG, LDLP-CS and HDLP-CS concentrations.

Our analysis revealed two thirds of all the examined people had overweight or obesity and a greater number of people with obesity was detected among workers exposed to occupational noise than among those exposed to industrial aerosols or people with no exposure to adverse factors at their workplaces: 31.2 % against 14.0 % and 12.9 % accordingly. Table 5 contains data on a correlation between ET-1 contents and BMI of workers from three examined groups.

Having analyzed a correlation between ET-1 contents in blood serum and BMI, we revealed that in case BMI was 25 kg/m^2 and higher, ET-1 concentration was authentically higher than in people with BMI being lower than 25 kg/m^2 ($p = 0.03$). We revealed an ascending trend for ET-1 concentration almost in half of people with overweight and obesity who were exposed to adverse occupational factors at their workplaces and only in 17.1 % of workers who were not exposed to them. Elevated ET-1 concentration (higher than 3.5 pg/ml) was determined in a small number

Table 4

ET-1 concentrations (*Med* ± *IQR* (25–75 %)) and frequency of different concentrations (%) depending on CS levels among workers from the examined groups

Parameters	CS (mmol/l)			
	Lower than 5.2 (*n* = 58)		Higher than 5.2 (*n* = 60)	
ET-1 concentrations (pg/ml)	2.72 (1.84–3.44)		3.12 (2.24–7.8)	
p	*p* = 0.03			
Examined groups	Frequency of detecting different ET-1 concentrations (%)			
	Higher than 3.5 pg/ml	3.5 pg/ml and lower	Higher than 3.5 pg/ml	3.5 pg/ml and lower
1st (*n* = 32)	20.0	80.0	58.3	41.7
2nd (*n* = 55)	31.8	68.2	27.2	72.8
3rd (*n* = 31)	16.0	84.0	16.0	84.0

Note: *p* is validity of differences in ET-1 concentrations depending on CS levels as per Mann – Whitney U-test.

Table 5

ET-1 concentrations (*Med* ± *IQR* (25–75 %)) and frequency of detecting different concentrations (%) depending on workers' BMI

Parameters	BMI (kg/m^2)			
	below 25.0 (n = 40)		25.0 and above (n = 78)	
ET-1 concentrations (pg/ml)	2.64 (2.36–3.24)		3.24 (2.64–10.36)	
p	p = 0.03			
Examined groups	Frequency of detecting different ET-1 concentrations (%)			
	Higher than 3.5 pg/ml	3.5 pg/ml and lower	Higher than 3.5 pg/ml	3.5 pg/ml and lower
1st (n = 32)	24.5	75.5	42.1	57.9
2nd (n = 55)	14.2	85.8	54.1	45.9
3rd (n = 31)	16.6	83.4	17.1	82.9

Note: p is validity of differences in ET-1 concentrations depending on BMI as per Mann – Whitney U-test.

of workers with normal BMI in all three groups (24.5 %, 14.2 %, and 16.6 %). We should note that ET-1 contents were within the reference range in half of people from the 1st and 2nd group with overweight and obesity, and the highest share of people with ET-1 being 3.5 pg/ml and lower and overweight and obesity was detected in the 3rd group and amounted to 82.9 %.

Therefore, our research revealed that 50 % of workers exposed to adverse occupational factors at their workplaces had BP, CS, and BMI deviating from proper values. AH was detected in 20 % workers, one third of the examined people had elevated BP (according to JNC7 recommendations, these people can be considered pre-hypertensive) [19]. Optimal BP was detected only in 10.0 % of the examined people. Two thirds of workers had BMI equal to 25 kg/m^2 and higher. Half of the examined people had hypercholesterolemia.

The research results revealed a more apparent correlation between ET-1 concentrations in blood serum and BP, BMI, and CS contents among workers exposed to occupational noise. Thus, optimal BP was detected 4 times less frequently, and normal BP by 12 % more frequently among people with elevated ET-1 contents in blood serum who were exposed to occupational noise at their workplaces against those exposed to industrial aerosols. Elevated ET-1 levels together with CS contents being higher than 5.2 mmol/l were detected in more than half of workers exposed to occupational noise whereas ET-1 contents were higher than reference values only in 27.3 % of workers with such CS contents who were exposed to industrial aerosols. We should note that there were more people with obesity among workers exposed to occupational noise than among those exposed to industrial aerosols and workers without any exposure at their workplaces. Analysis of correlations between ET-1 contents in blood serum and BMI revealed that elevated ET-1 contents were detected 2 times more frequently even among workers with normal body weight who were exposed to occupational noise than among those exposed to industrial aerosols.

Special attention should be paid to workers with elevated ET-1 contents in blood serum and normal BP, CS, and BMI. Having analyzed such people, we revealed that elevated ET-1 contents were more frequently detected among those exposed to occupational noise. We can assume that endothelial dysfunction and ET-1 introduction into blood serum have occurred prior to AH development under exposure to occupational noise. On the other hand, ET-1 produces its effects on ET-B receptors in endothelial and smooth muscle cells thus stimulating formation of nitrogen oxide that helps resist vasoconstriction. There is a contribution by other factors that prevent vasoconstriction from developing such as prostacyclin and atrial natriuretic peptide that are produced by endothelium as a response to ET-1 release. In this case, elevated ET-1 levels in blood serum even if BP is normal and there is no dyslipidemia or obesity indicate that endothelium cells are activated and ET-1 has entered intracellular space and blood. That is, ET-1 as an endothelium dysfunction marker can be an independent risk factor of cardiovascular pathology. People with elevated ET-1 contents in blood serum and normal BP, CS, and BMI can be recommended to perform dynamic monitoring over their health with special attention paid to the cardiovascular system.

We should note that it is necessary to apply a personified approach when assessing elevated ET-1 contents and a probability to use it as a risk factor of cardiovascular pathology among young and middle-aged people working under adverse working conditions (especially under exposure to occupational noise). It is extremely vital given that personified activities aimed at reducing health risks are being actively developed at the moment [20, 21].

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Research article

METAL-CONTAINING NANOPARTICLES AS RISK FACTORS CAUSING PATHOMORPHOLOGICAL CHANGES IN INTERNAL ORGANS TISSUES IN AN EXPERIMENT

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Given wide spread of nanomaterials, it seems vital to estimate and predict changes in internal organs tissues under exposure to metal-containing nanoparticles that are risk factors causing negative effects occurring in critical organs and systems. It requires revealing objective procedures that can be used to quantitatively assess risks of pathologic changes in tissues that at present have only qualitative properties.

Our research goal was to quantitatively assess risks of lung diseases occurrence in rats exposed to metal-containing nanoparticles (exemplified by nano-sized CuO) using image analyzing procedures.

We examined toxic effects produced by nano-disperse CuO (45.86 nm) under inhalation (a single and 14-day multiple) exposure and oral exposure (for 20 days); the experiment was performed on male Wistar rats (60 animals). Exposed animals were divided into 5 groups, 12 animals in each (group 1, a single inhalation exposure; group 2, multiple inhalation exposure; group 3, oral exposure; groups 4 and 5 were exposed to bi-distilled water in a similar way, via inhalation and orally). When analyzing tissue images, we estimated first-, second- and third-order elements. Statistical significance of differences was estimated with Mann – Whitney U-test. Quantitative risk assessment (R) was performed taking into account probability (p) and severity (q) of pathomorphological changes in tissues.

We established that pathomorphological disorders might occur in lung tissue taking into account identification of all elements in all images for all experimental groups; the probability varied from 0.16 to 1.2. The total risk of lung diseases amounted to $1.0 \cdot 10^{-3}$ (average risk) under single inhalation exposure to a concentration equal to 0.001CL50; multiple inhalation exposure, $8.1 \cdot 10^{-3}$ (high risk, oral exposure to a dose equal to $0.1LD_{50}$, $2.5 \cdot 10^{-2}$(high risk).

Therefore, image analysis allows quantitatively assessing risks of diseases in critical organs and systems caused by exposure to metal-containing nanoparticles.

Key words: *metal-containing nanoparticles, health risk factors, copper oxide, inhalation exposure, target organs, alveolar pattern, dendrite geometry, damage to lungs, microscopy, image analysis.*

Nanomaterials are widely used in multiple technologies and many industrial branches on the international and national levels; their use exerts significant influence on various spheres of economic activity and makes for their development [1]. Nanomaterials, including metal-containing ones, are in high demand due to unique physical and chemical properties of nanoparticles related to their small size, big surface area, shape, surface charge, etc. At the same time these properties that are typical for nanomaterials also result in their great pene-

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trability and it, in its turn, can lead to their greater toxicity when they are introduced into a human body at any stage in production and consumption [2]. Volumes of metal-containing nanoparticles consumption are only growing and it causes their active introduction into environmental objects and, consequently, results in elevated health risks.

Nano-sized copper oxide (nano-CuO) is a widespread metal-containing nanomaterial; it is used in various production spheres as a component in sensors (49 %), catalysts (20 %), surfactants (6 %), anti-microbial substances (4 %), specific dyes (21 %), and other products [3–8]. The research work [9] revealed that copper oxide nanoparticles penetrated a human body predominantly via inhalation or oral introduction (with drinking water). Negative effects produced on critical organs and systems by exposure to ultra small copper oxide nanoparticles were described in the papers [10–14]. Available data indicate that exposure to copper oxide nanoparticles produces toxic and genotoxic effects, both under acute single exposure and multiple one. Significant changes occur in lung tissues both under inhalation and oral exposure [15]. Micro-sized copper oxide particles belong to moderately toxic substances (the 3rd hazard degree) regarding their hazards for human health [13] and it provides some understanding on maximum permissible no-effect concentrations; still, it is not enough for predicting risks of morphofucntional disorders in critical organs and systems, primarily the lungs.

Risks of morphofucntional changes in critical organs under exposure to metal-containing nano-particles are estimated via experiments performed on laboratory animals that are used as biological models. Changes in tissues are estimated in such experiments as per conventional procedures using histological preparations and these estimations are rather subjective and lack quantitative estimation parameters; it makes predicting and ranking risks of pathomorphological changes more difficult. «Image analysis» is a set of procedures that allows the most objective quantitative assessment of changes in tissues using computer vision.

Given that, it seems vital to develop approaches to quantitative assessment of risks that negative effects might be produced on tissues in target organs, notably the lungs, for different introduction ways and multiplicity of exposure to nanoparticles; the most efficient analysis techniques are to be well-grounded.

Our research goal was to reveal and quantitatively assess risks of the lung diseases in rats under exposure to metal-containing nanoparticles (on the example of nano-sized copper oxide CuO) using image analysis procedure.

Data and methods. Nanodispersed copper oxide (nano CuO) was used in the studies on revealing and quantitatively assessing risks of morphofucntional changes in lung tissues under inhalation and oral exposure to metal-containing nanoparticles. We used powder nanodispersed copper oxide II (CAS 1317-38-0) with average particle size being 45.86 nanometers and particle sphericity coefficient being 0.59 (Sigma-Aldrich, USA). Particles composure and morphometric properties were determined with scanning electronic microscopy performed on S-3400N high resolution scanning microscope («HITACHI», Japan) and with x-ray spectral microprobe analysis («Bruker», Germany).

Toxic effects produced by nano-sized copper oxide were examined in experiments that involved inhalation (single and multiple, during 14 days) and oral (20-day) exposure according to methodical guidelines and guides[1, 2]. Water suspensions based on bi-distilled water (TU 6-09-2502-77) were used for introduction. Prior to exposure, suspensions were preliminarily homogenized using SonopulsHd 3200 (Bandelin, Germany) ultrasound device under room temperature; the procedure was performed for

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2 minutes in uninterrupted pulsation mode with 20 kHz frequency.

Experimental exposure was performed on male Wistar rats (60 animals overall), aged 8 weeks and with body weight being 180–250 g; all the experiments were performed in conformity with the requirements fixed by the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (ETS No. 123) and the Ethical Committee of the federal scientific Center for Medical and Preventive Health Risk Management Technologies. Animals were kept in between the exposure sessions in accordance with the requirements SR 2.2.1.3218-14[3] in an vivarium in polyethylene cages under 22 °C and relative air humidity being 55 %, light/dark cycle was 12/12. During the whole experiment rats were given conventional feedstuff (solid extruded granules) and pure water.

Experimental research involved dividing animals into 5 groups, 12 animals in each; the test group 1 underwent single inhalation exposure to nano-sized copper oxide; the test group 2, multiple inhalation exposure to nano-sized copper oxide; the test group 3, multiple oral exposure to nano-sized copper oxide; the reference groups 4 and 5 were exposed to bi-distilled water via inhalation and orally accordingly.

Single and multiple inhalation exposure to the examined nanomaterial was performed in a full-body chamber (TSE Systems GmbH, Germany) according to the state standard GOST 32646-2014[4]. Chamber volume amounted to 0.1 m^3. Suspension was fed into the chamber in concentration equal to 1.25 mg/m^3 as an aerosol via mechanical injection with a spay nozzle. Air inflow was continuous during each exposure session and air was fed at a speed equal to 10 dm^3/min (oxygen concentration was not lower than 19 %, and carbon dioxide, 1 %); water suspension of nano-CuO was fed at a speed equal to 0.4 cm^3/min; air outflow speed was 10 dm^3/min; pressure fluctuation inside the chamber were equal to 0.4 millibar; temperature inside the chamber was 22–25 °C. Actual nano-CuO concentration in the chamber amounted to 1.17 ± 0.18 mg/m^3 (0.001 CL50). Single inhalation exposure lasted for 4 hours. Multiple inhalation exposure was performed via daily sessions, 6 hours each, for 14 days altogether. Multiple oral exposure was performed with cumulation examination procedure as per Lim [16] (once a day and every day for 20 days). Initial introduction dose according to the procedure amounted to 250 mg/kg of body weight (0.1 LD_{50}). Every 5 days subsequent doses were increased by 1.5 times. Total oral exposure dose introduced over 20 days amounted to 1,275 mg/kg of body weight a day (0.5 LD_{50}). Animals were not given and feedstuff or water during exposure sessions.

After the experiments were completed, the lungs were taken out via total evisceration as per Shore and then fixated in 10 % water neutral formalin solution; after that, the samples were dehydrated in spirits with upward concentration and then saturated with chloroform and paraffin and soaked in «Histomix» homogenized paraffin medium. Slices that were 4 µm thick were obtained with JUNG SM 2000R sliding microtome (Leica, Germany), dyed with Ehrlich’s hematoxylin and eosin. Samples were examined and their images were taken with Axiostar transmitted-light microscope (Carl Zeiss, Germany).

To reveal and quantitatively assess morphological changes in tissues, we applied image analysis based on computer vision using Image J-FiJi universal software (open-code software developed by Wayne Rasband, National Institutes of Health, USA).

Frequency of pathomorphological changes that didn’t have any apparent specific size parameters or calculated parameters was assessed quantitatively using mathematical analysis

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procedures. To do that, we determined whether there were basic components of histological images in lung tissues:

– first-order elements: negative space, that is, space that is not filled with tissue component; it allows estimating sizes and morphology of alveolar spaces; morphological parameters of alveolar spaces might not change in great details, and at initial stages in pathomorphological changes alveolar spaces only decrease in size while geometric patterns parameters remain unchanged [17, 18];

– second-order elements: tissue mass that was described with plane figures that created alveolar patterns and were estimated with dendritic geometry procedures using the following parameters: a ratio between an average length of a branch and a length of the longest branch, a ratio between a number of intersections and a number of branches and per cent of triple and quaternary intersections in the overall number of intersections. Images were preliminarily processed with binarization and skeletonization techniques [19, 20];

– third-order elements: cell nucleuses with their positions against each other allowing making a judgment on whether cells were evenly located in tissue structure, that is, the more pathologic changes occur, the more fluctuations are detected where cell nucleuses are located the closest to each other.

Statistical significance of differences between group parameters was estimated with Mann – Whitney U-test with preset significance being 0.05 since data obtained via using the above-listed image analysis procedures were not distributed evenly and could be interpreted only using non-parametric statistics. Statistical estimation was performed with BioStat 7.0 (Analyst Soft Inc.).

Quantitative risk assessment (R) was performed taking into account probability (p) and severity (q) of pathomorphological disorders occurring in tissues as per the following formula: $R = p \cdot q$. Severity of disorders was estimated as per weighted average parameter ranging from 0 to 1. Obtained risk values being lower than $1 \cdot 10^{-6}$ meant risk was negligible; from $1 \cdot 10^{-6}$ to $1 \cdot 10^{-4}$, low risk; from $1 \cdot 10^{-4}$ to $1 \cdot 10^{-3}$, average risk; higher than $1 \cdot 10^{-3}$, high risk[5]. Assessment was performed as per elements of all the above-mentioned orders and for all the groups. Risk was characterized as per the highest parameter detected for each experimental group as per analyzed first-order, second-order and third-order elements.

Results and discussion. Accomplished experimental research on inhalation and oral exposure to nano-CuO allowed obtaining histological images of rats' lung tissues. Figure 1 shows lung tissues taken from rats from the test and reference groups.

According to classic pathomorphological assessment (Table 1) there are no pathological changes in lung tissues taken from animals from reference groups 4 and 5. Pathomorphological changes in lung tissues were detected in animals from groups that underwent single and multiple inhalation exposure (Groups 1 and 2) and oral exposure (Group No. 3). Lung tissues taken from animals from all the test groups excluding reference ones (Groups 4 and 5) have signs of lymphoid tissue hyperplasia associated with bronchial walls with admixture of multiple eosinophils. There was also additional pigment accumulation in macrophages and vascular inflammation detected in Groups 2 and 3. Besides, we revealed certain peculiarities in lung tissues changes in Group 2 (focal interstitial inflammation and alveolitis) and in Group 3 (abscess).

Table 2 contains the results obtained via analyzing images of lung tissues when assessing first-order image elements.

Studies on first-order elements occurring in lung tissues allowed revealing that parameters obtained for Groups 2 and 3, that is, multiple inhalation and oral exposure, we statistically authentically different from reference Groups 4 and 5. Parameters obtained for Group 1 were not different from that contained for reference groups.

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[5] R 2.1.10.-1920-04. The Guide on assessing health risks caused by exposure to chemicals that pollute the environment. Moscow, The RF Public Healthcare Ministry Centre for State Sanitary and Epidemiologic Surveillance Publ., 2004, 143 p. (in Russian).

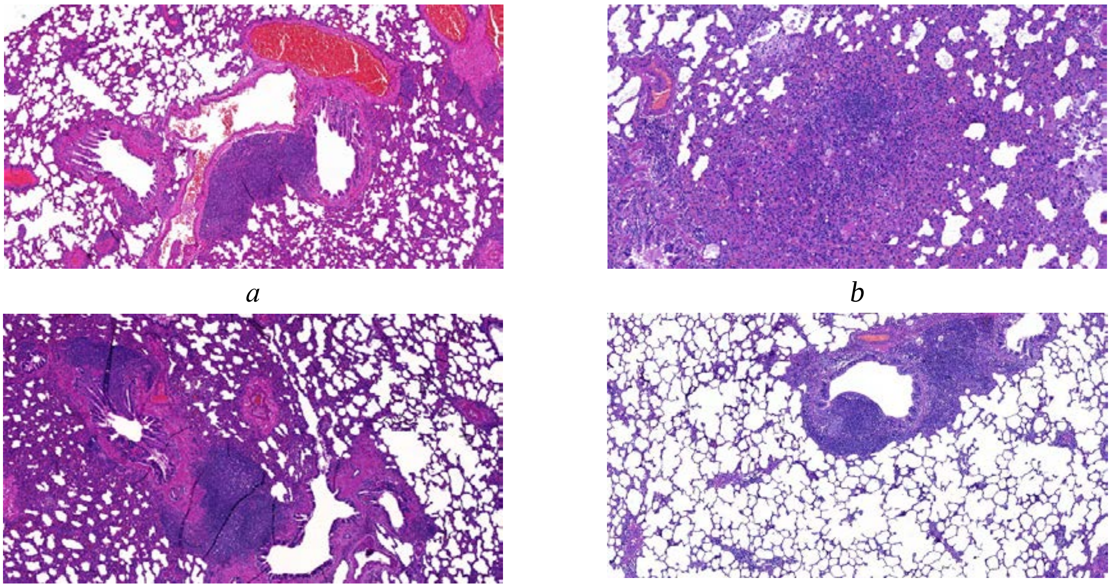

Figure 1. Rats' lung tissues under exposure to nano-sized copper oxide particles, x100: a is Group 1 (single inhalation exposure); b is Group 2 (multiple inhalation exposure); c is Group 3 (multiple oral exposure), d are Groups 4 and 5 (reference)

Table 1

Results obtained via pathomorphological analysis of lung tissues taken from Wistar rats in experiments on impacts exerted by exposure to nano-CuO

Group	Lung tissues
Group 1 (single inhalation)	Lymphoid tissue hyperplasia associated with bronchial walls with admixture of multiple eosinophils
Group 2 (multiple inhalation)	Lymphoid tissue hyperplasia associated with bronchial walls with admixture of multiple eosinophils. Disseminated vasculitis. Accumulated brown pigment in cytoplasm of multiple macrophages. Focal interstitial inflammation, alveolitis
Group 3 (multiple oral)	Lymphoid tissue hyperplasia associated with bronchial walls with admixture of multiple eosinophils. Disseminated vasculitis. Accumulated brown pigment in cytoplasm of multiple macrophages. Focal suppurative-destructive process
Groups 4 and 5 (reference)	Without visible morphological changes

Table 2

Results obtained via using computer vision for analyzing images of Wistar rats' lung tissues under exposure to nano-CuO as per first-order elements (significance is 0.05, comparison as per Mann – Whitney, $U_{cr} \leq 9$)

Estimated parameter	Group			
	1	2	3	4 and 5
Negative space square (S_{NS}), %	49.97 ± 7.55 $U = 12.5$; $p = 0.001$ ***$U = 4$; $p = 0.01$	27.62 ± 7.86 *$U = 3$; $p = 0.007$ ****$U = 6$; $p = 0.02$	15.54 ± 2.48 *$U = 1$; $p = 0.009$ **$U = 1$; $p = 0.011$	56 ± 5.33
Tissue component square ($100 - S_{NS}$), %	50.03 ± 12.3	72.38 ± 5.59	85.46 ± 5.55	63.06 ± 10.93
Total coefficient of first-order elements $S_{NS} / (100 - S_{NS})$	1.39 ± 0.22	*0.47 ± 0.04 $p = 0.02$	*0.17 ± 0.08 $p = 0.009$	1.55 ± 0.13
Probability of pathomorphological changes in tissue (p)	0.08	0.25	0.50	–
Risk of a disease occurrence (R)	$8 \cdot 10^{-5}$	$2.5 \cdot 10^{-4}$	$5 \cdot 10^{-4}$	–

Note: * means authentic difference from reference groups; ** means authentic difference from Group 1; *** means authentic difference from Group 2; **** means authentic difference from Group 3.

Table 3

Results obtained via using computer vision for analyzing images of Wistar rats' lung tissues under exposure to nano-CuO as per second-order elements (significance is 0.05, comparison as per Mann – Whitney, $U_{cr} \leq 9$)

Estimated parameter	Group			
	1	2	3	4 and 5
Ratio of a total number of intersection to a total number of brunches	0.49 ± 0.09 *U = 7; p = 0.002	0.48 ± 0.05 *U = 7; p = 0.003	0.54 ± 0.03 *U = 8; p = 0.006	0.38 ± 0.08
Ratio of an average length of a brunch to the maximum length	0.19 ± 0.08 *U = 1; p = 0.003	0.25 ± 0.09 *U = 2; p = 0.001	0.16 ± 0.04 *U = 1; p = 0.001	0.54 ± 0.01
A share of triple intersections, %	25.56 ± 5.23 *U = 5; p = 0.009	23.42 ± 6.27 *U = 5; p = 0.004	61.60 ± 5.74	48.92 ± 3.47
A share of quadrupole intersections, %	8.56 ± 6.11 *U = 4; p = 0.003	10.5 ± 7.43 *U = 4; p = 0.006	18.08 ± 4.26	14.00 ± 5.86
Probability of pathomorphological changes developing in tissue (p)	0.08	0.66	–	–
Risk of a disease occurrence (R)	$8.0 \cdot 10^{-4}$	$6.6 \cdot 10^{-3}$	–	–

Note: * means authentic difference from reference groups; ** means authentic difference from Group 1; *** means authentic difference from Group 2; **** means authentic difference from Group 3.

Total coefficient of first-order elements (integral parameter) amounted to 0.47 ± 0.04 and 0.17 ± 0.08 in Groups that underwent multiple inhalation and oral exposure accordingly and it was by 3.3–9.2 times lower than the reference value. The detected trend indicates that frequency and intensity of damage to lung tissues is by 2.0 and 2.8 times higher accordingly under oral exposure than under inhalation one. Risk of diseases occurrence caused by disorders in lung tissues detected via image analysis amounted to $8 \cdot 10^{-5}$ and $2.5 \cdot 10^{-4}$ under inhalation exposure and it meant low and average risk accordingly; it amounted to $5 \cdot 10^{-4}$ under oral exposure (average risk).

Table 3 contains the results obtained via analyzing images of lung tissues when second-order elements were assessed.

Computer vision used for analyzing lung tissues and detecting second-order elements provided an opportunity to establish that ratios between the total number of intersections and total number of brunches and between an average brunch length and the maximum brunch length differed in Groups 1, 2, and 3 from groups 4 and 5, but there were no difference between the three former groups. Shares of triple and quadrupole intersections were 1.8 times lower than the reference parameter only in Groups 1 and 2 (inhalation exposure). Values were not different between these two groups but changes parameters were registered 2 times more frequently under multiple inhalation exposure than under single one. Risk of diseases that might occur in lung tissues was determined via image analysis procedure and varied from $8.0 \cdot 10^{-4}$ to $6.6 \cdot 10^{-3}$ in Groups 1 and 2, or under inhalation exposure, and it indicated there was an average and high risk accordingly.

Table 4 contains the results obtained via analyzing images of lung tissue when third-order elements were analyzed.

Computer vision used for identifying third-order elements in lung tissue allowed establishing that a number of neighboring cells were authentically different in Groups 2 and 3 from the reference Groups 4 and 5. This parameter was 1.5 times higher in Group 3 (multiple oral exposure) than in the reference groups, and 1.7 times higher in Group 2 (multiple inhalation exposure). Disorders in lung tissues were registered 2 times more frequently after multiple oral exposure (Group 3) than after multiple inhalation exposure (Group 2).

Table 4

Results obtained via using computer vision for analyzing images of Wistar rats' lung tissues under exposure to nano-CuO as per third-order elements (significance is 0.05, comparison as per Mann – Whitney, $U_{cr} \leq 9$)

Estimated parameter	Group			
	1	2	3	4 and 5
Average number of neighboring cells, units/cell	9.6 ± 1.43 $U = 368; p = 0.11$	19.0 ± 2.75 $*U = 117; p = 0.099$	17.0 ± 2.98 $*U = 107.5; p = 0.087$ $*** U = 128; p = 0.088$	11.66 ± 2.18
Probability of pathomorphological changes developing in tissue (p)	–	0.25	0.5	–
Risk of a disease occurrence (R)	–	$1.2 \cdot 10^{-2}$	$2.5 \cdot 10^{-2}$	–

Note: * means authentic difference from reference groups; ** means authentic difference from Group 1; *** means authentic difference from Group 2; **** means authentic difference from Group 3.

Use of image analysis procedure to identify first-, second- and third-order elements revealed there was a possibility that pathomorphological disorders might occur in lung tissues in all three test groups but frequency of detected disorders was different under inhalation and oral exposure. Thus, damage to lung tissue was registered 1.2 times more frequently under oral exposure to nano-CuO than under multiple inhalation exposure to it. Overall, disorders in lung tissues were registered 7.2 times more frequently under multiple inhalation exposure than under single one. As a result, identification of all elements in images taken into account, probability of disorders occurrence varied from 0.16 to 1.2. The total risk of lung diseases, taking into account severity of identified elements, amounted to $1.0 \cdot 10^{-3}$ under single inhalation exposure (average risk); $8.1 \cdot 10^{-3}$, under multiple inhalation exposure (high risk); $2.5 \cdot 10^{-2}$, under multiple oral exposure (high risk).

We comparatively analyzed results obtained via image analysis procedure and classic pathomorphological assessment of lung tissues that showed morphofunctional changes in lung tissue and risk of diseases caused by exposure to nano-CuO. The analysis revealed that single inhalation exposure resulted in average risk of lung diseases and it corresponded to such pathomorphological changes in lung tissue as lymphoid tissue hyperplasia in the bronchial wall combined with eosinophilia. Multiple inhalation and oral exposure caused high risks of disease occurrence and this risk was 3 times higher under oral exposure than under inhalation one. It corresponded to the following pathomorphological changes in lung tissue: focal interstitial inflammation and alveolitis under multiple inhalation exposure and focal suppurative-destructive processes under multiple oral exposure.

Conclusion. Use of image analysis procedure for examining consequences caused by exposure to metal-containing nanoparticles allows identifying elements of morphofunctional changes in lung tissues that belong to different orders. This identification provides an opportunity to quantitatively assess risks of diseases in critical organs and systems. Quantitative assessment of risks related to disease occurrence was accomplished in the present research with image analysis procedure for exposure that was different either as per duration or a way of metal-containing particles introduction into a body (on the example of nano-CuO). This assessment allowed establishing that single inhalation exposure to the examined nanomaterial in concentration equal to 1.2 mg/m^3

(0.001CL50) caused average risk of lung diseases occurrence; multiple inhalation exposure in the same concentration that lasted for 14 days resulted in high risk. Oral exposure to a dose equal to 250 mg/kg of a body weight (0.1 LD_{50}) that lasted for 20 days also caused high risk of lung diseases occurrence and this risk was 3.1 times higher than that caused by multiple inhalation exposure.

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Research article

RISK OF SENSITIZATION TO ECOPOLLUTANTS IN TEENAGERS WITH INHERITED CHEMICAL BURDEN

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At present allergic diseases are detected in 30 % people and their frequency is only growing. A significant role in allergic pathology occurrence belongs to ambient air contamination and chemicals being introduced not only into children's bodies, but their parents' ones as well since pollutants can act as allergens and sensitizing agents.

Our research goal was to examine influence exerted by parents' pre-gestation exposure to chemicals on sensitization among teenagers living in an area where ambient air was contaminated.

We examined overall immunoglobulin E contents and leukocytes migration inhibition test with formaldehyde and sodium nitrite in 115 teenagers whose parents worked under adverse working conditions at chemical and petrochemical enterprises and in 244 schoolchildren whose parents didn't have any occupational contacts with chemicals. Each group was divided into sub-groups depending on inhalation chemical burden on schoolchildren's bodies caused by ambient air contamination and contaminated air indoors (with hazard index (HI) for immune disorders being lower than 2 and HI≥ 2).

The research allowed establishing that teenagers whose parents had worked at chemical and petrochemical enterprises during a pre-gestation period had elevated IgE contents more frequently as well as changes in leukocytes migration inhibition test with formaldehyde; it indicated there was sensitization to this chemical. Parents' occupational contacts with chemicals led to an increase in relative risks of elevated igE contents and 2.5 times higher sensitization among schoolchildren with HI < 2. Risk that sensitization to formaldehyde might occur was equal to 2.3 among senior schoolchildren with HI ≥ 2 whose parents worked at chemical enterprises.

Key words: *pre-gestation chemical exposure, teenagers, parents, sensitization, immunoglobulin E, leukocytes migration inhibition test, ambient air contamination.*

Over the last decades a number of allergic pathology cases has been growing actively all over the world and now this pathology is diagnosed in each third person. It deteriorates life quality and becomes a heavy burden for a society [1, 2]. Ambient air contamination makes a significant contribution into a risk of health disorders among population and ecopollutants can act as allergens and sensitizing agents and cause allergic diseases [3, 4]. It has been proven that ambient air contamination with formaldehyde, benzpyrene, phenol, and nitrogen dioxide produces effects on immune system functioning via inducing synthesis of anti-inflammatory cytokines, reducing IgA contents, increasing contents of specific auto-antibodies, inhibiting cell death via apoptosis and activating it via necrosis. It is also associated with allergic pathology among adults and children [5–8].

Sanitary-hygienic assessment of working area air at chemical productions revealed certain chemicals including butanol, dimethylamine, cobalt tetracarbonyle hydride, methyl tributyl ether, carbon oxide, and saturated hydrocarbons [9]. Chemicals in work-

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ing area air, even when they occur in concentrations not exceeding hygienic standards, can exert negative impacts on reproductive health of workers employed at chemical productions [10].

There are a lot of data in literature on influence exerted by alcohol, smoking, and other negative factors on future generation's health during pregnancy [11–15]. In recent years some data have been published on transgenerational epigenetic inheritance and its role in adaptation and occurrence of diseases in children [16–18]. It was revealed that chemotherapy applied in treating fathers for cancer modified sperm epigenome and entailed probable transgenerational transfer [19]. It was also established that when male and female rats were poisoned with combustion products prior to coupling, it led to changes in offspring's behavior and development [20]; when parents, either mothers or fathers or both, worked under adverse conditions, it was associated with an increase in primary morbidity, chronic pathology of the upper respiratory tracts, and frequent positive tests for allergens in children [21]. It was also shown that threats of miscarriage, gestosis in the first half of pregnancy, intrauterine hypoxia, and delayed fetus development in women employed at petroleum processing enterprises were to a great extent occupationally induced [10, 21].

Our research goal was to examine influence exerted by parents' pre-gestation exposure to chemicals on sensitization among teenagers living in an area where ambient air was contaminated.

Data and methods. Our research was performed in two industrial cities located in Irkutsk region with big chemical and petrochemical enterprises operating there. Schoolchildren were examined in spring prior to blooming season; prior to any examination parents (legal representatives) were questioned and then gave their written informed consent to let teenagers take part in the research. We took the following criteria for including children into the research: they permanently lived and attended schools on the examined territory; they were 14–17 years old; they didn't have any signs of an acute respiratory disease at the moment of the research.

To assess influence exerted by parents' exposure to chemicals in pre-gestation period, we took data on occupational conditions at workplaces and pollutants contents in working area air. Data on chemicals contents in working area air were taken from databases belonging to Rospotrebnadzor Regional Office in Irkutsk region, Rosgidromet, and also from research works performed by the East Siberian Institute for Medical and Ecologic Research [5, 9, 22, 23]. Longitude research performed by N.M. Meshchakova et al. [22] revealed that in 1988–1994 concentrations of certain chemicals in working area air at vinyl chloride production were substantially higher than maximum permissible concentrations. Thus, vinyl chloride contents amounted to 21.1–217 mg/m^3 and dichloroethane contents amounted to 140.7–156.0 mg/m^3; then production equipment was modernized (1995–2000) and single concentrations of these chemicals didn't exceed 1.8 maximum permissible concentration (MPC) after that [22]. Over a period starting from 2001 concentrations of dimethylamine, methanol, butanol, and carbon oxide varied from 0.20 to 0.55 mg/m^3, 1.0–11.0 mg/m^3, 1.0–4.0 mg/m^3, 4.4–10.0 mg/m^3 accordingly and didn't exceed MPC at enterprises that produced methanol, methylamines and butanol via oxo-synthesis and methyl-tributyl ether [9]. Ambient air contamination was estimated as high in the examined cities in 1990–1995. Hazard index (*HI*) for health disorders among population, taken without benzpyrene, varied from 8 to 10.2; priority pollutants included nitrogen dioxide, hydrogen sulfate, and formaldehyde. In 2015–2017 *HI* reached 15.9 [23].

When assessing chemical inhalation exposure on teenagers' bodies we took into account ambient air quality and pollutants contents in indoor air since the questionnaire revealed that teenagers spent most their time at home or at school (20–23 hours a day). To calculate personified *HI* of immune disorders among teenagers, we took data on contents of immune-tropic pollutants in ambient air, in air inside homes and classrooms, as well as schoolchildren's anthropometric and spirometric data and data on their daily routines [24]. The greatest contribution into individual *HI* of immune disorders was made by formaldehyde; its maximum concentrations reached 0.005 mg/m^3 inside classrooms; homes, 0.006 mg/m^3; ambient air, 0.006 mg/m^3 (reference concentrations is 0.003 mg/m^3) [5].

We spotted teenagers among the examined school children whose parents hadn't contacted chemicals in their occupational activity; they were included into the group I (244 schoolchildren). Teenagers whose parents had worked under adverse conditions at chemical and petrochemical enterprises were included into the group II (115 schoolchildren). Shares of smoking teenagers and those exposed to passive smoking were comparable in Groups I and II (62.4 and 60.0 % accordingly). *HI* values for immune disorders among schoolchildren varied from 1.34 to 2.7 and allowed us to divide both groups into subgroups *a* and *b*. Subgroups I_a and II_a were made up of teenagers with $HI < 2$ (114 and 56 people accordingly); subgroups I_b and II_b, teenagers with $HI \geq 2$ (130 and 59 people accordingly) (Figure).

Allergic proneness and sensitization of schoolchildren's bodies to chemicals were estimated as per total immunoglobulin E (IgE) and migration index (MI) in leukocytes migration inhibition (LMI) with formaldehyde and sodium nitrite. IgE was determined in blood serum via solid phase ELISA test with Total IgE reagents kit ("Xema", Germany). Contents equal to 1.3–70.0 IU/ml were taken as referent ones. Leukocytes extracted from whole blood were used in LMI. Formaldehyde or sodium nitrite was used as a chemokinetic factor in the reaction; mitogen phytohaemagglutinin was taken as positive control; cultural medium without chemo-attractant was taken as intact control [5]. MI varying from 0.80 to 1.20 was considered referent.

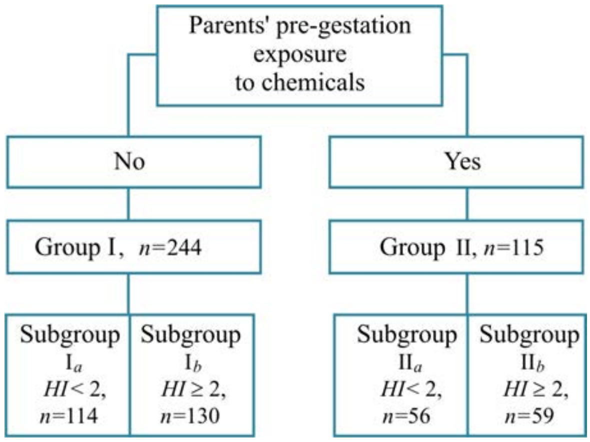

Figure. Research design

To compare quantitative parameters between groups, we took Mann – Whitney U-test (results are given as median (*Me*) and 25–75 quartiles (LQ–UQ)); and chi-square (χ^2) with Yates correction. Frequency of a parameter occurrence in the sampling was calculated as per 100 examined people and given with 95 % confidence interval (*CI*). Relative risk was assessed as per odds ratio (*OR*) with 95 % *CI*. Critical statistical significance of differences (*p*) was taken at 0.05. All the results were statistically processed with Statistica 6.0 applied software.

Results and discussion. Having compared average IgE contents in different groups, we revealed that it tended to grow in Group II. Analysis of migration indexes of LMI with formaldehyde and sodium nitrite (MI_f and MI_s accordingly) didn't reveal any significant differences depending on parents' occupational contacts with chemicals prior to a child birth, both in groups taken as whole and in subgroups with different *HI* (Table 1).

We assessed how frequently the examined parameters deviated from reference levels; the assessment revealed that elevated IgE levels were more frequent among teenagers with inherited chemical burden than among their counterparts whose parents hadn't contacted chemicals at their workplaces (Table 2). These differences were also significant when frequency of elevated IgE levels was compared in subgroups made up of schoolchildren exposed to different inhalation burden.

Table 1

Allergic proneness revealed among teenagers with inherited chemical burden who lived on a territory where ambient air was contaminated, *Me* (LQ–UQ)

Parameter	Subgroups	Group I	Group II	*p*
IgE, IU/ml	all	26.17 (4.11–66.03)	36.21 (7.37–93.58)	0.065
	$HI < 2$	24.11 (8.33–53.76)	33.76 (11.40–105.01)	0.610
	$HI \geq 2$	27.04 (2.08–83.73)	36.78 (3.04–93.58)	0.489
MI_f	all	0.97 (0.84–1.06)	0.92 (0.82–1.11)	0.508
	$HI < 2$	0.96 (0.76–1.10)	0.89 (0.54–0.96)	0.276
	$HI \geq 2$	0.98 (0.85–1.05)	1.00 (0.82–1.13)	0.918
MI_s	all	0.97 (0.85–1.09)	0.93 (0.71–1.21)	0.661
	$HI < 2$	0.92 (0.74–0.98)	0.77 (0.58–0.97)	0.227
	$HI \geq 2$	1.00 (0.86–1.14)	0.96 (0.82–1.29)	0.736

Note: *p* is statistical significance of differences between Groups I and II;
MI_f, MI_s are migration indexes for leukocytes in leukocytes migration inhibition with formaldehyde and sodium nitrite accordingly.

Table 2

Frequency of allergic proneness parameters deviating from reference levels in teenagers with inherited chemical burden and exposed to ambient air contamination

Parameter	Subgroups	Deviation frequency, per 100 examined [*CI*]		*p*
		Group I	Group II	
IgE, IU/ml	all	22.22 [16.79–27.65]	39.13 [30.21–48.05]	0.001
	$HI < 2$	17.12 [10.11–24.12]	33.96 [25.27–42.66]	0.015
	$HI \geq 2$	27.19 [15.21–39.17]	43.55 [31.21–55.89]	0.022
MI_f	all	34.97 [27.15–42.78]	56.36 [43.26–69.47]	0.007
	$HI < 2$	37.14 [21.13–53.15]	62.50 [38.78–86.22]	0.083
	$HI \geq 2$	34.26 [25.31–43.21]	53.85 [38.20–69.49]	0.028
MI_s	all	34.58 [25.57–43.59]	32.00 [19.07–44.93]	0.712
	$HI < 2$	40.00 [23.77–56.23]	37.50 [13.78–61.22]	0.892
	$HI \geq 2$	24.73 [15.96–33.50]	29.41 [14.10–44.73]	0.649

Note: *p* is statistical significance of differences between Groups I and II;
CI is 95 % confidence interval;
MI_f, MI_s are migration indexes for leukocytes in leukocytes migration inhibition with formaldehyde and sodium nitrite accordingly.

We also revealed difference in frequency of sensitization to formaldehyde in LMI between Groups I and II. MI values deviating from reference levels were more frequent in case there was inherited chemical burden. As for teenagers with $HI < 2$, we detected only a trend for a growth in a share of people with MI_f value being beyond the reference range (subgroup II_a against subgroup I_a). Frequency of deviations in these parameters was statistically significantly higher among teenagers with $HI \geq 2$ and inherited chemical burden (subgroup II_b) than among their counterparts without it (subgroup I_b). We should note that MI deviations from the reference range could be both elevated and decreased inhibition

(MI being lower than 0.8 or higher than 1.2 accordingly). There were 3.2–4 times more people with elevated inhibition with formaldehyde in both subgroups at *HI* < 2 (28.57 [13.60–43.54] % and 50.00 [40.57–59.43] % for subgroups I_a and II_a accordingly) than with decreased one (8.57 [0.00–17.85] % and 12.50 [6.26–18.74] %). As *HI* grew, a share of people with elevated leukocytes migration in a reaction with formaldehyde went down, both among schoolchildren without inherited chemical burden and with it (15.74 [0.00–33.59] % and 23.08 [9.85–36.30] % for subgroups I_b and II_b accordingly) and, on the contrary, a share of people with decreased migration grew (18.52 [0.00–37.55] % and 30.77 [16.28–45.25] % accordingly).

There were no differences in frequency of MI_s deviations from reference values in subgroups with different *HI* calculated for immune disorders among teenagers depending on their parents' contacts with chemicals. MI_s deviations from the reference range were detected in each third teenager in groups with inherited chemical burden and among their counterparts without it and there were no differences in their frequency between the groups.

Elevated IgE levels and changed MI in a reaction with formaldehyde were more frequent among teenagers whose parents had contacted chemicals at their workplaces in pre-gestation period. It indicates that there is sensitization to formaldehyde as well as a higher risk that allergic diseases might occur. Relative risk of an increase in IgE contents among teenagers with inherited chemical burden was higher than 1 in the subgroup with *HI* < 2 and was equal to 2.5 where as it was only 1.7 in the subgroup with *HI* ≥ 2 and this increase was not statistically significant (Table 3).

Parents' occupational contacts with chemicals in pre-gestation period didn't exert any influence on a risk of sensitization to formaldehyde among teenagers with *HI* < 2. But still, higher inhalation exposure to immune-tropic compounds together with inherited chemical burden caused elevated risk of sensitization to formaldehyde among teenagers. We didn't establish any influence exerted by parents' occupational contacts on a risk of sensitization to sodium nitrite.

Table 3

Relative risk of sensitization and allergic proneness among teenagers whose parents had contacted chemicals

Parameter	Subgroups	*OR* (*CI*)	χ^2	*p*
IgE	all	1.78 (1.07–2.95)	5.07	0.025
	HI < 2	2.49 (1.17–5.29)	5.83	0.016
	HI ≥ 2	1.37 (0.69–2.72)	0.79	0.375
MI_f	all	2.43 (1.28–4.58)	7.72	0.006
	HI < 2	2.82 (0.83–9.58)	2.85	0.166
	HI ≥ 2	2.27 (1.08–4.77)	4.77	0.029
MI_s	all	1.14 (0.59–2.23)	0.15	0.695
	HI < 2	0.90 (0.27–3.04)	0.03	0.866

Note: χ^2 are chi-square values;
p is statistical significance as per χ^2 test;
OR (*CI*) is odds ratio with 95 % confidence interval;
MI_f, MI_s are migration indexes for leukocytes in leukocytes migration inhibition with formaldehyde and sodium nitrite accordingly.

Our data indicate that contacts with chemicals by parents (fathers included) in a period before the examined children were born result in elevated risks of teenagers becoming allergic. It is in line with results obtained via research performed with participating workers employed at industrial rubber production as well as at hothouses where chemical compounds were used as fertilizers [25, 26]. There are data in these works on a decrease in non-specific resistance and protective-adaptive capabilities of children's bodies as well as on an increase in morbidity including allergic diseases. Besides, S.H. Arshad et al. revealed that inhalation exposure of mothers or grandmothers to chemical compounds caused by smoking prior to pregnancy was associated with allergic diseases in children [27]. It is well-known that most allergic diseases have IgE-dependent development mechanism and are accompanied with an increase in contents of this immunoglobulin in blood serum. It is diagnostically important to determine total IgE in case of allergic pathology since its contents correlate with concentrations of allergen-specific IgE in most cases [28, 29]. When there are only initial signs of sensitization to allergens and there are no apparent symptoms of an allergic disease, specific IgE can already start to occur [28]. Therefore, elevated IgE contents indicate there is sensitization, regardless of allergic pathology being apparent or not. Relative risk of this immunoglobulin occurring in a body in elevated contents that is higher than 1 indicates that parents' occupational contacts with chemicals play a significant role in sensitization developing in their children's bodies. We should note that relative risk of elevated IgE contents caused by parents' contacts with chemicals during pre-gestation period was higher among teenagers with $HI < 2$ than among those with $HI \geq 2$. It is due to differences in growth in a share of people with elevated IgE contents depending on inhalation exposure to immune-tropic compounds among teenagers with inherited chemical burden and without it. Effects produced by contaminated ambient air were stronger among teenagers without inherited chemical burden. Thus, as *HI* grew, frequency of elevated IgE increased by 1.6 times in Group I (from 17 to 27 %, $p = 0.126$ when subgroups I_a and I_b were compared); and by 1.3 times in Group II (from 34 to 43 %, $p = 0.187$ when subgroups II_a and II_b were compared). We should note that both risk factors combined (parents' pre-gestation contact with chemicals and *HI* calculated for immune disorders being equal to 2 or higher) caused a significant increase in OR (2.54 (1.19–5.40), $\chi^2 = 6.03$, $p = 0.015$).

It is well known, that both biologic allergens (animal dandruff and hair, house-dust ticks, plant and mushroom pollen) and chemical contaminants (ozone, sulfur dioxide, nitrogen dioxide, diesel fuel combustion products, tobacco smoke, etc.) can act as sensitizing agents [30]. Therefore, a contribution into occurring sensitization to formaldehyde can be made both by inherited chemical burden and elevated ambient air contamination with immune-tropic chemicals. It was established that an increase in inhalation exposure for teenagers didn't result in growing OR of changing MI in LMI with formaldehyde in Groups I and II (0.88 (0.40–1.95) and 0.75 (0.24–2.4) accordingly) but a risk of sensitization to formaldehyde increased only under elevated inhalation exposure to immune-tropic chemicals ($HI \leq 2$). This detected increase in a risk of sensitization to formaldehyde is in line with research results that revealed more frequent positive skin tests to household, epidermal and pollen allergens among teenagers living in cities with heavily contaminated ambient air whose parents contacted adverse chemicals at their workplaces [22]. Chemical pre-gestation exposure is an epigenetic factor and it can become apparent via changes in methylation of certain DNA section in genes associated with allergic diseases development. Thus, it was established that DNA methylation in promoter of the neuropeptide S-receptor 1 that was linked to asthma and allergy occurrence was associated not only with parents and their children suffering from allergy but also with environmental exposure [27]. These results indicate that epigenetic factors exert certain influence on occurring sensitization to formaldehyde among teenagers living under adverse exposure to ambient air being contaminated with immune-tropic chemicals.

Conclusion. Our research allowed establishing that teenagers whose parents had worked at chemical and petrochemical enterprises during pre-gestation period more frequently had elevated IgE contents in blood serum as well as changes in LMI with formaldehyde indicating there was sensitization to this chemical. Parents' occupational contacts with chemicals resulted in 2.5 times higher relative risk of elevated IgE contents, sensitization, and allergic pathology development among schoolchildren living under moderate exposure to ambient air being contaminated with immune-tropic chemicals ($HI < 2$). Risk of sensitization to formaldehyde amounted to 2.3 for teenagers living under inhalation exposure with $HI \geq 2$ and with parents who had worked at chemical enterprises. Therefore, inhalation exposure to immune-tropic chemicals and parents' occupational contacts with chemicals during pre-gestation period cause elevated risks of sensitization and allergic diseases among teenagers.

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Research article

SUICIDES DURING THE COVID-19 PANDEMIC: COMPARING FREQUENCIES IN THREE POPULATION GROUPS, 9.2 MILLION PEOPLE OVERALL

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There are observations that right after total quarantine measures were introduced, there was no growth in number of suicides, but a situation remains unclear when it comes down to new waves in the pandemic development.

Our research goal was to estimate risks of suicide in heterogeneous population groups in 2020, that is, from the pandemic start and up to the second wave rise.

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We analyzed data on completed suicides in Saint Petersburg, Udmurtia Republic (Russia), and Odessa region (Ukraine), 6375 cases overall among population groups with total number of people being equal to 9,216 thousand starting from January 01, 2016 to December 31, 2020. Confidence intervals for frequencies as per months (per 100,000 people) in 2020 were calculated as per Wilson and compared with average ones calculated for 2016–2019.

There was a decrease in frequency of completed suicides in all three population groups during a period when the strictest quarantine measures were valid; by the mid-summer the trend normalized or there was even a slight increase. When the second pandemic wave came, changes were multidirectional; in particular, in Saint Petersburg there was another decrease by the end of the year, the most apparent and statistically significant among men whereas there were short-term rises in Udmurtia and Odessa.

Our comparison performed for population groups with initially different levels of suicides confirms that right after a crisis starts, suicidal behavior becomes less frequent among people; however, as a response to the second pandemic wave, we can expect both falls and rises in number of suicides and it requires more intense preventive activities.

Key words: *suicides, suicidal behavior, pandemic, large population groups, males and females, frequency estimate, confidence intervals calculation, different stages in an epidemic process.*

On March 11, 2020 the WHO Director-General declared that an outbreak of a new coronavirus infection (caused by 2019-nCoV more widely known as COVID-19) was "an international emergency in public healthcare", that is, a pandemic [1]; more than a year has passed since then. Over this period 128 million people have caught this infection worldwide and 2.79 million out of them have died (as per data on April 01, 2021) [2]. Over the same year, according to the WHO estimates, approximately 0.8 million people have committed suicide [3]. At the same time many suicidologists in different countries are of the same opinion that the figure is rather underestimated, by 30 percent or even more (here opinions are different); therefore, this number is likely to be close to one million [4–6]. In Russian experts in demography believe that in some regions even higher per cent of unaccounted suicides may be among death cases accounted as "self-mutilations with uncertain intentions" or among causes that are stated inaccurately [7, 8]. Moreover, according to the WHO estimates, approximately 10 times more people have tried to commit suicide over the last year and it means 10 or more million potential suicides worldwide [3]. All this indicates that suicide is a complicated issue that is wider and more significant than it is usually seen by public (and even by professionals) if we rely solely on mortality figures.

Issues related to suicides have acquired some new aspects during the pandemic that has aggravated multiple economic and political problems as well as problems in public healthcare all over the world. This pandemic has certain peculiarities but the most outstanding ones are not ultrahigh mortality (approximately 2.81 % worldwide and it is much lower than in case of some other infections) and even not significantly high incidence but extremely intensive media and information campaigns that accompany the epidemic process and everything related to it including measures aimed at fighting the disease. Global nature of the disease, information about it being easily available and obtrusive, everyday reports on a number of people who have caught it or died from it, reports on insufficient capabilities of public healthcare systems, and extreme measures taken by governments, stories on TV showing patients in reanimations being in grave condition have become a part of our everyday life. All this combined with rather strict limitations introduced in most countries was justly considered to be a serious threat to mental health of wide population groups and also a potential danger that a number of suicides would grow [9–11].

Indeed, studies performed instantly in many countries (basically, they were online polls) indicated that stress, anxiety, and depression tended to be high among public at large as well as among medical personnel, students, and some other categories, in particular among people who already had mental issues directly during strict isolation [12–14]. There was no unified methodology developed for such studies, and prevalence figures differed significantly (from 10–15 % to 45–50 %) depending on a country, context, a methodology for involving respondents, etc. even despite standardized questioning instruments were applied [12–14]. More objective longitude studies that allowed tracing dynamics prior to and during pandemic waves on the same continent revealed that actual depression levels changed only slightly whereas anxiety among population indeed grew by almost two times (from 13 % to 24 %) especially among women, young people, and people with low socioeconomic status [15].

At the same time, analysis of the existing situation in 21 counties revealed that a number of suicides either didn't grow during the strictest quarantine (April–May 2020) and the 1st wave (up to September 2020) or even went down in a significant number of cases [16]. Our observations also showed that there was a short-time decrease in suicidal behavior in urban population directly after an external global stressor as an existential threat was "introduced" [17]. It can be considered an effect of a society uniting in the face of danger and a subsequent activation of adaptive (vital) trends versus non-adaptive (anti-vital) ones [16, 17].

However, it is not the reason for complacency; moreover, as the pandemic has been developing in several waves, there are changes in lifestyle and stress levels people have to face, there is growth not only in anxiety or depression, but also aggression (it can be seen in countries where long-term and strict quarantine was introduced and it led to protests and demonstrations). Given that, concerns regarding growth in suicides are becoming more intense and more and more people are included into risk groups. On one hand, it is the overall population that faces problems and frustration due to changes in lifestyle, ruined plans, family complications, children's distant studies etc. On the other hand, there are people who have had the infection; this number is growing all the time, and this group causes the greatest alarm. Many recovered patients may still have chronic consequences such as neurologic, psychiatric, and psychological disorders including PTSD, depression, sleeping disorders, lower working capacities, and psychosomatic symptoms caused by a stress they survived, or by biological factors, for example, chronic inflammation in nerve tissues [18, 19]. All these consequences may enhance suicidal risks. Patients who already have mental disorders are another additional risk group since this situation involves not only aggravating symptoms for them but also impossibility to get all the necessary help. Observations indicate that a number of applications for aid to psychiatric clinics dropped directly after the pandemic started; it may be due to people believing their mental issues "are no longer important now", and it is also an alarming signal that a considerable number of patients are left alone with their issues and these issues are only accumulating and aggravating [20].

All this requires more attention to be paid to suicidal behavior among population, and it is necessary to assess risks basing on profound and wide-scale analysis of mortality, taking into account morbidity dynamics and limitations. These considerations gave grounds for the present research where we have tried to cover as wide heterogeneous population groups as it was only possible since it is easier to detect nonrandom trends when "big data" are analyzed; or, at least, it is possible to assess whether all concerns that are being discussed in expert society are real or not.

Data and methods. We were provided with data on a number of completed suicides for the following population groups: Saint Petersburg (the Russian Federation), overall population amounted to 5,368 thousand people on January 01, 2021; Udmurtia Republic (the Russian Federation), overall population amounted to 1,493 thousand people; and Odessa region (Ukraine) overall population mounted to 2,355 thousand people; the overall sampling was equal to 9,216 thousand people. Geographically these three regions are three vertexes of a equilateral triangle since Odessa and Saint Petersburg are located practically on the same meridian (30° east longitude) but the latter lies much farther to the north, and Izhevsk, the center of Udmurtia, is located much farther to the east and lies somewhere in between Odessa and Saint Petersburg as per latitude. Population density in Saint Petersburg amounted to 3,730 people per 1 square km taking into account geographical boundaries of the city; Odessa region, 71 people per 1 square km; Udmurtia, 35 people per 1 square km. As for national structure, Russians prevailed overwhelmingly in Saint Petersburg (92.5 %), Ukrainians took the second place (1.5 %) some other nationalities accounted for shares not exceeding 1 %. In Udmurtia Russians accounted for 62.2 %; Udmurts, 28.0 %; Tatars, 6.7 %; the other nationalities, less than 1 %. According to the latest available data, Ukrainians prevailed in Odessa region (62.8 %), followed by Russians (20.7 %), Bulgarians (10.1 %), Moldavians, (5 %), Gagauz, (1.1 %), all the other nationalities accounted for less than 1 %. Climate was moderately continental in Saint Petersburg and partially moderately marine. In Odessa region climate was humid and moderately continental combined with warm marine; Udmurtia is located in a zone with intra-continental climate with typically hot summers and cold winters with a lot of snow.

Criminal data on suicides given as “a date of death, sex, age, and suicidal style” were provided by the Saint Petersburg City Office for Forensic Medical Examination and Odessa Regional Office for Forensic Medical Examination; data on Udmurtia Republic were provided by the administration of the Republican Clinical Psychiatric Hospital, Udmurtia Public Healthcare Ministry. Data on population number were taken from official sources (Rosstat, The Central Statistic Office in Odessa Region). Initial data on completed suicides as per years are given for a period 1995–2020 for Udmurtia; 2001–2020, for Odessa region; 2016–2020, for Saint Petersburg. Criminal data (as per months and with a date of death) were obtained for all three population groups for a period of time from January 01, 2016 to December 31, 2020.

Frequencies were calculated per 100,000 people a year or a month, depending on goals that were to be achieved via comparative analysis; Wilson score method was applied to calculate confidence intervals for relative frequencies [21]. Changes that occurred during the pandemic were analyzed with a simplified procedure called “excess mortality” that involves comparing frequency in the index year to average frequencies over 4 previous years [22]. Effects produced by the pandemic were given on graphs as a difference between monthly frequencies obtained via averaging data collected over 2016–2019 and monthly frequencies in 2020. Confidence intervals for differences in frequencies were also calculated as per Wilson score method. Significant differences were those for which a confidence interval for a difference in frequencies didn’t cross a reference line for 2016–2019. Over the examined period, 2,316 suicides were registered in databases in Udmurtia; 2,282 suicides, in Odessa region; 1,777 suicides, in Saint Petersburg; 6,375 suicides overall. Men/women ratio for three population groups over the examined period amounted to 5.00 in Udmurtia; 4.50, in Odessa region; 2.87, in Saint Petersburg. Data on dynamics of morbidity with COVID-19 were taken from the sources [23, 24].

Results and discussion. At a preliminary stage in our research we traced changes in relative frequencies of suicides a year over the last 10 years (from 2011 to 2020) in Udmurtia and Odessa region, as well as over the last 5 years (from 2016 to 2020) in Saint Petersburg (Figure 1). The graphs show that, in spite of apparent differences in absolute values, there was a descending trend in a number of suicides in all three examined population groups. In Udmurtia it went down from 47.1 in 2011 to 28.4 in 2020; in Odessa region, from 25.9 to 18.3 accordingly; in Saint Petersburg, from 7.2 to 6.1 over the last 5 years. And it is interesting to note that curves showing data on Udmurtia and Odessa region are very much alike, the correlation is equal to 0.963 at $p = 0.00001$ (Spearman’s rank

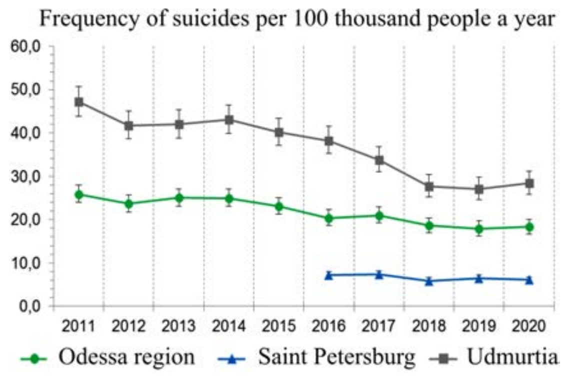

Figure 1. Average annual number of suicides in the examined population groups taken in dynamics over a period of time from 2011 to 2020

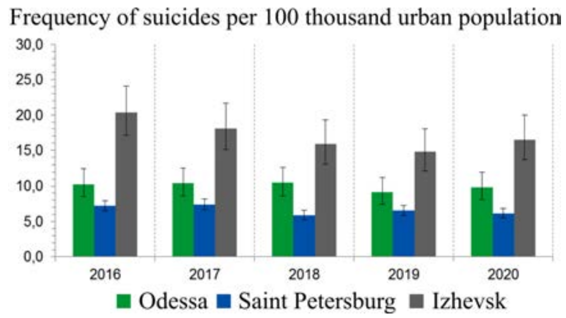

Figure 2. Average annual number of suicides among urban population in three examined cities from 2016 to 2020

correlation coefficient). At the same time, there was a small rise in the trend for these two groups in 2020 and there were no such changes in Saint Petersburg.

Since it seems advisable to make any comparison between urban population groups only, these parameters were calculated separately for Izhevsk, Odessa, and Saint Petersburg within comparable time periods (Figure 2). As we can see, from 2016 to 2020 frequencies were the lowest in Saint Petersburg (7.2–5.9 per 100,000 people a year); they were approximately 1.5 times higher in Odessa and 2.5 times higher in Udmurtia. Differences in frequencies between all three cities were statistically significant in each year.

Figures 3–5 show differences in relative monthly frequencies in 2020 and average monthly ones in 2016–2019 together with confidence intervals for these differences. In Saint Petersburg there was a decrease in frequency of suicides against its average value just after strict quarantine was introduced (March – April); it was especially apparent in April (by 24.4 % from 0.6376, *CI* 95 % 0.5391–0.7542 to 0.4821, *CI* 95 % 0.3290–0.7064). Then there was a rise in June (by 13.5 %) and then in July – September frequencies remained lower than average (by 21.6 % in September). After a rise in October frequencies went on declining reaching their minimum in December (fall by 37.7 %, from 0.5954, *CI* 95 % 0.5005–0.7084 to 0.3708, *CI* 95 % 0.2401–0.5758).

Figure 3 shows that there was a fall in frequency of suicides in Saint Petersburg both among men and women after the pandemic had been declared; then there were slight rises in May (men) and in June (women). However, certain differences occurred in October-December: values fluctuated near the reference line for women but there was a significant drop in the trend for men after a rise in October, by 45.1 % in November and by 44.1 % in December, and in the latter case it can be considered to be significant (fall from 1.0260 to 0.5731, the difference is –0.4529 (*CI* 95 % –0.7745–0.0230)).

Suicidal activity among population in Udmurtia and Odessa region was quite similar to that in Saint Petersburg during the 1st pandemic wave but there were still certain differences (Figures 4 and 5). Thus, frequencies for the total population were lower than usual in the 1st half of the year; the greatest decrease was detected in Udmurtia in May, by 27.8 % (from 3.0432, *CI* 95 % 2.6341–3.5158 to 2.1968; *CI* 95 % 1.5656–3.0875) and in Odessa region also in May, by 22.2 %. There was a slight rise in Udmurtia in June and July (by 12.2 % maximum) whereas in Odessa region the trend just returned to average values detected in previous years. Then the trend went down again in autumn in Udmurtia (the greatest decrease was in September, by 19.9 %) and in Odessa region in August (by 19.2 %). In Udmurtia the second peak occurred in December (the trend rose by 29.1 %) and in Odessa it was in October (by 28.3 %). Therefore, at the end of the year the situation in Odessa region was similar to that in Saint

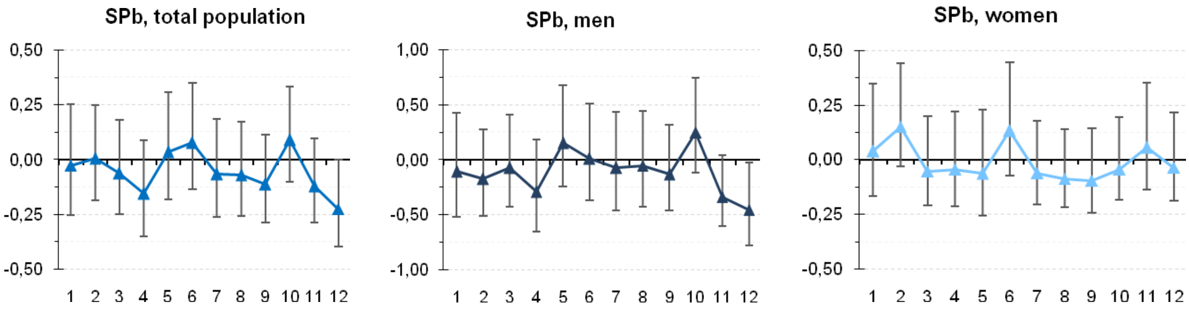

Figure 3. Deviations in frequencies of monthly suicides in Saint Petersburg (total population, men, women) in 2020 from average values over 2016–2019 and their confidence intervals

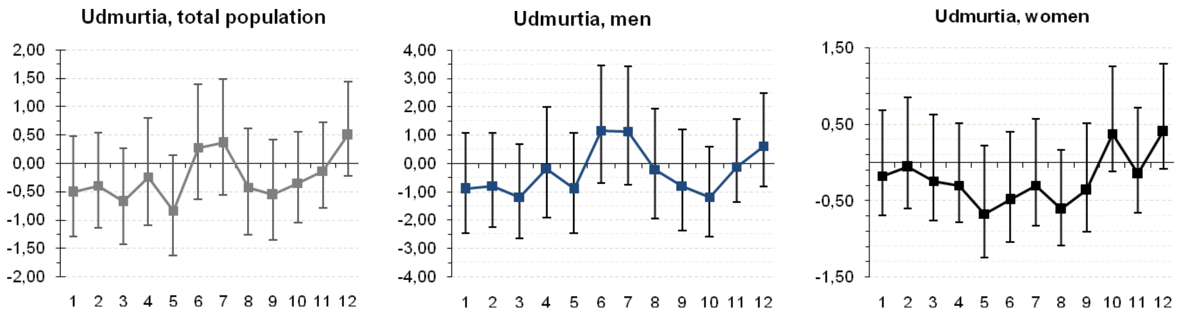

Figure 4. Deviations in frequencies of monthly suicides Udmurtia (total population, men, women) in 2020 from average values over 2016–2019 and their confidence intervals

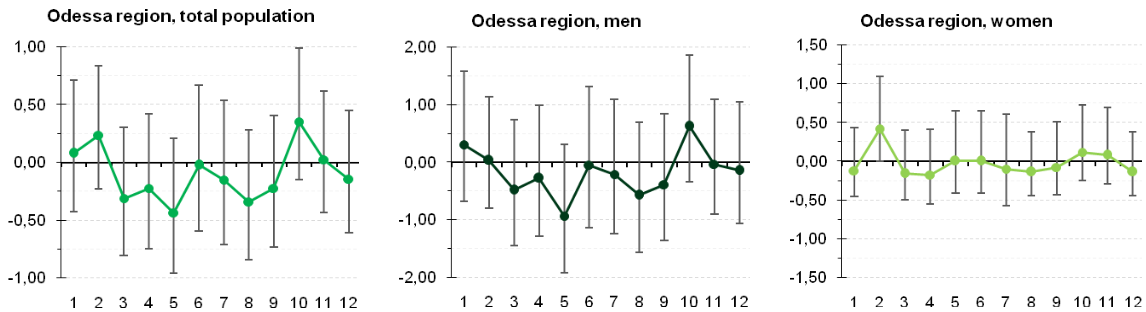

Figure 5. Deviations in frequencies of monthly suicides in Odessa region (total population, men, women) in 2020 from average values over 2016–2019 and their confidence intervals

Petersburg whereas it was rather different in Udmurtia since the peak was delayed and there was no decrease at the end of the year (Figures 4 and 5).

Curves that show changes in frequencies of suicides are similar to those showing these changes for men in all three population groups; it is due to suicides among men prevailing significantly over suicides among women if we consider absolute values. In other words, any changes in the trends occur predominantly due to suicides among men and women make a much smaller quantitative contribution. And curves showing frequencies of suicides among women are rather peculiar and apparently tend to fluctuate less[1]. However, if

[1] Graphs in Figures 3–5 are given with different axis scales for men and women to make them easier for perception.

Maximum fluctuation range for changes in frequencies of suicides among men and women in the examined population groups (in %)

Region	Men			Women		
	minimum	maximum	range	minimum	maximum	range
Saint Petersburg	–45.1	+35.6	80.7	–39.2	+79.7	118.9
Odessa region	–26.9	+28.4	55.3	–30.1	+111.5	141.6
Udmurtia	–27.4	+22.8	50.2	–62.2	+101.5	163.7

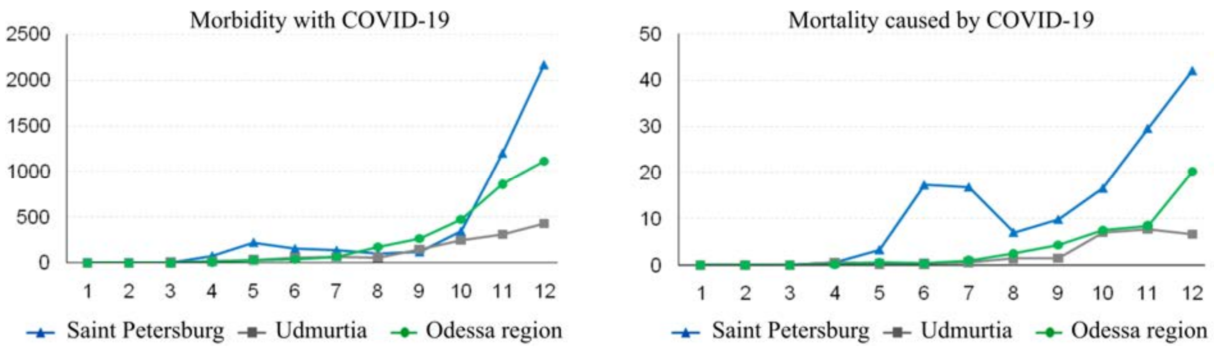

Figure 6. Morbidity and mortality caused by COVID-19 among the examined population groups per 100,000 people a month in 2020

we estimate maximum and minimum deviations in parameters in 2020 from averaged values in 2016–2019 in per cent, we can see that fluctuation range is more apparent for women (1.5–3 times). It occurs in all three population groups with certain differences between them; the higher is suicide-related mortality as a whole, the smaller is fluctuation range for men and the greater for women (Table 1). We should also note that rises in frequencies among women were much greater than falls whereas these changes in the trends were quite similar among men.

If we consider COVID-19-related incidence and mortality in all three regions (Figure 6), we can see that the curves had more apparent 1st wave in Saint Petersburg and parameters per 100,000 people as a whole were much higher there. The situation in Udmurtia could be considered the most favorable. Odessa region was somewhere in between in this respect.

Our basic research result is that frequency of suicides didn't grow in either of three examined groups during the first months after the pandemic had started, that is, when strict quarantine was introduced. Such a growth had been predicted quite often; instead, we detected that there was a descending trend in the parameter. After that, in summer when incidence started to fall and the situation seemed to be stabilizing, there was a slight rise or return from the expected level. These changes were quite similar in all three groups. Then, at the end of 2020, that is, when the 2nd pandemic wave was developing and it was much more apparent than the 1st one, the trends fluctuated in different directions. Thus, in Saint Petersburg and Odessa region (where incidence was high) there was a decrease in December whereas in Udmurtia where incidence was lower, there was a rise. We should note that fluctuations in frequencies calculated for the whole population were within 30–40 % and didn't reach statistical validity.

The same drop in suicidal activity among population was detected during the 1st pandemic wave in some other countries and regions, in particular, in New South Wales (Australia); Alberta and British Columbia (Canada); Chile; Leipzig (Germany); Japan; New Zealand; South Korea; California, Massachusetts, Illinois, and Texas (the USA); and Ecuador. This drop varied from 6 to 50 % and it was not statistically confirmed for some specific territories, but still it was proven to be statistically authentic when pooled estimates were performed for all population groups and time series analysis was applied [16]. Falls in Norway, Peru, Austria (Tirol) and Japan were reported separately [25–28]. We should also note that as it was stated in the work [16] the fall occurred only in 12 out of 21 examined population groups, there were no marked changes in some countries and cities, and there was even a slight rise (by 10–20 %) in some European regions (Carinthia in Austria and Cologne administrative district in Germany), as well as in Brazil (Botucatu), New-Jersey, and Puerto-Rico [16].

We should point out that the research we have already cited and which is the most comprehensive one on the subject at the moment focuses on analyzing the situation only over a rather short period of time, starting from the moment when the first world lockdown was introduced, that is, March 2020, and to June 2020 [16]. We should also mention a short study in Russia that was based on data collected in 5 RF regions (Krasnodar region, Transbaikalia, Bashkortostan, Udmurtia, and Belgorod region); the authors compared a number of suicides in April 2019 and April 2020 and there was a drop in it everywhere [29]. At the same time, in Japan there was a fall by 14 % during the first 6 months in 2020; but the number grew by 16 % already in October during the 2nd pandemic wave, and this growth was higher among women (by 37 %) and teenagers (by 49 %) [30, 31]. Our observations cover a longer period of time since we took data for the whole 2020; they indicate that changes could take different directions during the 2nd pandemic wave. In particular, rises in the trend in Saint Petersburg and Odessa region occurred simultaneously with the beginning of the 2nd pandemic wave and then there was a fall; in Udmurtia a rise in number of suicides occurred later than a growth in incidence.

Therefore, our research revealed rather similar trends in three populations that were hardly interrelated. These trends are close to those revealed in wider-scale studies and it confirms their basic conclusions regarding a drop in a number of suicides during the 1st pandemic wave and simultaneously allows noticing how people responded to the 2nd pandemic wave. We should note that previously we described the situation in Odessa and the region in greater detail covering long periods of time and it turned out to be quite typical (more suicides among rural population than among urban one, and suicides among men were 4–5 times more frequent than among women) [32–34]. Suicides in Udmurtia were also considered; frequencies tended to be higher in this region than on average in Russia, especially in rural areas where native Udmurt people accounted for the greatest share of population, and also among women living in urban areas [35–37]. Suicides in Saint Petersburg have not been analyzed recently within any statistic studies when it comes to population as a whole; there was only a profound analysis regarding suicides among young people[2].

So, we have revealed similar trends, especially during the 1st month after the pandemic was officially declared, in a highly urbanized megacity in the north-western region in the country; in the southern region that was historically close to Saint Petersburg (Black Sea steppes were actively populated after Ismail fortress was taken, and Odessa as a city was founded as a part of imperial projects developed by Ekaterina II at the end of the 18th century); as well as in an eastern region that was historically more traditional with its history being closely connected with the Kazan Khanate and its developing having started as far back as in the 16th century. These revealed trends indicate that there are the same factors that influence heterogeneous population in case of a pandemic. These factors are

[2] Shamkova S.V. Social parameters of suicides among young people in Saint Petersburg: Abstract of the thesis … for the Candidate of Social sciences degree. – Saint Petersburg, 2006. – 24 p.

most likely related to a sense of a danger and a crisis and they tend to produce unified effects despite all cultural, national and economic differences, different degree of urbanization, population density, geographic and climatic conditions. And there is a certain relation with pandemic waves since their occurrence results in changes in suicidal activity by population, basically, short-term drops in the beginning with subsequent return to expected values or a rise depending on a region. As for a degree of urbanization, a recent study performed in Japan has revealed that suicidal thoughts that occurred during the pandemic (August–September, 2020, an online poll) were to a greater extent associated with it as well as with low quality of living conditions than with incidence in a given region [38]. Our data contradict this conclusions and it may be due to different approaches to assessing quality of living conditions and Japan cultural peculiarities.

Some studies performed in other countries and regions also indicate there are similar trends in changes of population's suicidal behavior at early stages in the pandemic. Thus, in the USA in 2020 number of suicides fell by 5.6 % simultaneously with an overall rise in mortality by 17.7 % [39]. And there was a drop not only in a number of completed suicides but also suicide attempts and other self-mutilations. Thus, experts analyzed data on applications to emergency departments in 23 hospitals in 10 countries (Great Britain, Scotland, Ireland, Italy, Hungary, Serbia, Turkey, Oman, and the UAE) covering 31.2 million people and approximately 200 thousand application per year; the analysis revealed that there was a 33 % drop in a number of applications by children and teenagers caused by any self-mutilations and mental disorders during the strict lockdown (March–April 2020) [40]. However, an increase was detected in a number of grave self-mutilations (when a potentially lethal suicidal style was chosen or there were medical outcomes that required staying in a hospital for not less than 72 hours) [40].

It is interesting to compare intensity of fluctuations in suicidal behavior by men and women, especially taking into account degree of urbanization and national and cultural differences between population groups. In our research, we revealed a single statistically significant event and it was a 45 % drop in frequency of suicides among men in Saint Petersburg against the 2nd pandemic wave. At the same time, fluctuations were much more intense among women, both rising and falling ones, and reached 100 % but remained statistically insignificant. Many authors mention higher quantities of mental disorders among women during the pandemic [12–15], and also note that the greatest rise in frequency of suicides occurred exactly among women after a slight fall in it during the first months of it [17, 30]. Women are traditionally considered to be home-keepers, both in our culture and in many others, and it is a factor that prevents them from committing suicide [41]; nevertheless, more profound research is required if we want to clarify to what extent this factor preserves its influence under such uncommon circumstances as a pandemic.

This pandemic, being a true world crisis, has created a unique situation that allows assessing not only dynamics of incidence and efficiency of vaccination but also psychological state and suicidal behavior among broad masses of population given this global external threat. All these parameters as well as related risks should be assessed taking into account limitations, mortality caused by the infection, as well as activities aimed at compensating for a fall in economy and growth in unemployment. It seems vital to get a better insight into trends in suicidal behavior in different countries, among different population groups with variable ethnic structure, with geographic and other peculiarities, both for monitoring and for working out relevant guidelines on how to prevent suicides during such global crises. It is still too early to make any conclusions on a relation between suicidal behavior and pandemic ways basing solely on the results obtained via the present study; more targeted research is requires that involves using analysis of dynamic series and it also attracts our attention. Although there are no clear perceptions of these relations, we still believe that it is advisable to rely on available guidelines that have been published recently [42–44] and focus on how to adapt prevention activities during the pandemic. In our opinion, the most relevant ones are educational activities that are aimed at raising awareness about suicide-related issues among people and medical personnel responsible for rendering first aid to population as well as organizational activities that help improve communications within a system for medical aid provision; achieve more qualitative accounting of completed suicides and non-fatal self-mutilations; and implement more efficient procedures for providing psychosocial help to people who have tried to commit suicide.

Limitations. The present study is based on an approach that doesn't allow assessing influence exerted by a prevailing trend or seasonal fluctuations; it was performed on only three population groups that were relatively weakly interrelated.

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

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Research article

RESTRICTED ACTIVITY AND NEGATIVE SELF-ASSESSMENT OF HEALTH AS RISK INDICATORS FOR LATENT DISABILITY ANALYSIS PERFORMED ON POPULATION GROUPS DIFFERENT AS PER SEX AND AGE

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A necessity to detect and assess probable latent disability makes the present research vital; it can be done using available parameters that characterize population health.

Our research object was adult population living in the Russian Federation.

Our research goal was to reveal a relation between self-assessment of health and health-related restrictions among respondents form different sex and age groups in order to determine latent disability among overall RF population.

Previously Russian researchers revealed certain relations between disability and low self-assessment of one's health. However, there was no profound study on an issue related to using such criteria as «negative self-assessment of health» and «restricted activities» used to reveal latent disability. This aspect has not been examined in great detail in domestic research and it makes the present work truly vital. We took data collected via the Russian sociologic study performed within the European sociological study (ESS) in 2018–2019 as well as data from sampling studies on population in the RF performed by the Federal Statistics Service in 2018 and 2019. To analyze a relation between self-assessment of health and existing restricted activity, we calculated Kramer's coefficients for different sex and age groups of respondents who took part in the Russian sociologic study.

Calculated Kramer's coefficient values indicate there is an average relation between such parameters as «self-assessment of health» and «existing restricted activity». We established that 7 % of respondents who were not disabled still had health characteristics implying there was a disability risk. It was shown that use of such criteria as «self-assessment of health» and «existing restricted activities» allowed more authentic assessment of latent disability among males aged 50–59 and women aged 20–29, 30–39, and 40–49. In future we plan to obtain more accurate results using data from other representative sociologic studies on population including regional ones.

Key words: *population health, disability, restricted activity, self-assessment of health, sociologic study, measuring disability levels.*

The WHO experts believe that disability among population is inseparably linked to demographic ageing and a growth in chronic diseases burden. In 2015 there were more than 1 billion disabled people all over the world and the number was expected to grow [1]. In the Russian Federation there were 11.875 million disabled people registered on January 1, 2020 and it was approximately 8 % of the total country population. Researchers often mention that a system applied for statistic register of disability is rather imperfect since it contains data only on those people who have applied for being registered as disabled [2]. This underestimation creates a distorted picture of the current situation in public health since it doesn't take into account hidden risks of demographic losses caused by latent disability; it also results in incorrect predictions for a scope of public expenditure on healthcare and social support provided for population. Certain positive experience was gained in some countries in applying a specific questionnaire developed by the WHO and the World Bank for revealing actual numbers of disabled people [3]; unfortunately, this experience is still neglected in Russia. The outlined issues are rarely given any attention in domestic scien-

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tific literature. A.O. Makarentseva et al. [4] discuss a methodical approach to revealing "latent" disability using data obtained via representative sociological studies. This approach is based on disability criteria determined as per "procedures by the Washington Group on Disability Statistics"; however, the authors point out that they obtained rather ambiguous results for women from older age groups. Samplings that are surveyed in sociological studies (including those aimed at studying disabled people's opinions), as a rule, include negligibly small number of people who are officially registered as "disabled". At the same time, disability means that a person has to face some restrictions in his or her life activities; according to data obtained via sociological studies, disability is more often accompanied with low self-assessment of health [5]. Indirect signs of disability (restricted life activity) are mentioned by notably greater number of respondents and it allows considering them as people who have failed to exercise their rights to be registered as "disabled".

In the present work we plan to examine how those people who think their life activities are restricted assess their health. We assume that restricted life activity combined with negative self-assessment of health leads to greater probability that a person is already registered as disabled or plans to do it in the nearest future. On the other hand, a significant share of people who are not registered as disabled but still state that their life activities are restricted and their health is rather poor may indicate that such people face substantial difficulties in registering as disabled, or they do not wish to do it since disabled people are seen as a discriminated group.

While accomplishing our research, we took into account methodological limitations of applied instruments. Thus, there are certain difficulties in achieving uniform interpretations of reasons for self-assessment of health. For example, not every questionnaire contains not only a direct question on how a person assesses his or her health but also a clarifying question on reasons that make a respondent assess his or her health as good or poor. These reasons can be overall health, chronic diseases, injuries, psychological state, etc. On the other hand, self-assessment of health can be influenced indirectly by social and economic factors [6, 7]. M.A. Kaneva and V.M. Baidin [8] highlight that it is important to take heterogeneity into account when self-assessment of health is analyzed. Foreign researchers took data obtained via a longitude survey and showed that social capital exerted significant impacts on self-assessment of health [9]. Higher self-assessment of health is typical for people who tend to have higher social trust, are able to enter intense informal interactions, have variable friendly relations and are involved in activities performed by social organizations [10]. Similar conclusions were made by researchers who examined data obtained via sociological questionings performed in Russia [11]. Several research works published abroad concentrated on a complicated relation between self-assessment of health, life quality, existing restrictions in life activities and objective parameters of people's health and lifestyle. Thus, a lower self-assessment of health may result from loss of a job and people with objectively poorer health run greater risk of such an event [12]. At the same time, objective characteristics that indicate poor health may exert smaller influence on respondents' assessment of their life quality than existing restricted life activities. Thus, Whitley et al. showed in the research [13] that absence of any restrictions in life activities was seen as a significant condition of proper ageing by elderly people whereas absence of a chronic disease was not considered to have the same significance. Self-assessment of health by employed population is significantly influenced by microclimate and other conditions at a workplace (noise and air contamination) [14]. A lot of foreign and domestic authors have mentioned a relation between subjective assessments of health made by respondents and their social and demographic characteristics [15–17]. Gender-related peculiarities typical for self-assessment of health have also been studied in detail as well as gender-related specificity of factors that influenced distributions of these self-assessments[1] [18]. Given all the above mentioned, we should note that results obtained in our present research require more detailed validation in future research.

Data and methods. We took adult population in the Russian Federation as our research object. Our research subject was a correlation between self-assessments of health and restricted life activities as per different age and sex groups in adult population.

Our research goal was to reveal correlations between self-assessments of health and restricted life activities among respondents from different age and sex groups in order to determine latent disability among population in Russia. To achieve this goal, we had to solve the following tasks:

1) to analyze prevalence of restricted life activities among respondents;

2) to examine a correlation between such variables as "self-assessment of health" and "restricted life activities" in different age and sex groups;

3) to analyze a correlation between a structure of a population group determined as per such parameters as negative self-assessment of health and restricted life activities and a population group that includes "disabled people".

Information basis of the research was made up of data obtained via *Russian Social Survey* accomplished as per a program developed by European Social Survey (ESS). The questioning was performed by CESSI (Institute for Comparative Social Research) in November 2018 – February 2019 via personal interviews conducted at respondents' homes on a random probability sampling of the country population with respondents being not younger than 15. Overall, 2,416 people were questioned. The research methodology is described in detail in the project technical documentation[2].

Apart from data obtained via the European Social Survey, we also took data obtained via *the sampling observation over population health* (VN SZN–2019) and *sampling observation over behavioral factors that influence population health* (VN PFZN–2018) performed by Rosstat in 2019 and 2018 accordingly. A unit in observation was a household (household members) with only one member in each household being included into the observation (respondents were 15 years or older). 60 thousand households took part in the sampling observation SZN–2019; 15 thousand households, in VN PFZN–2018.

Respondents' belonging to this or that sex and age group can exert significant influence on examined health parameters such as self-assessment, existing restrictions in life activities, and disability. Respondents included into the sampling examined within Russian Social Survey (RSS) were distributed as per sex and 10-year age groups (plus groups made up of people aged 15–19 and people aged 70 and older). Number of respondents in groups aged 15–19 and 70 and older turned out to be substantially lower in comparison with other age group in the total RSS sampling (68 and 72 people accordingly). These groups were not examined in the present research and we didn't calculate correlations between self-assessment of health and existing restricted life activities for them. Calculation of Cramer's V-coefficient was applied as a procedure that allowed determining whether there was a significant correlation between such variables as "self-assessment of health" and "existing restrictions of life activities"[3]. The procedure was selected due to an essence of examined variables (they are nominal values).

The next step was to check any coincidence in structure of groups made up of respondents with disability and respondents who assessed their health as poor and had certain restrictions of their life activities. To do that we created an additional variable that was called "negative self-assessment of health" and

[1] Nazarova I.B. Employed population's health: a monograph. Moscow, MAKS Press, 2007, 526 p.

[2] Russian Social Survey as per a program developed by European Social Survey. European Social Survey. Available at: www.ess-ru.ru (April 20, 2020).

[3] This coefficient is applied for nominal values and its values vary from 0 to 1. The closer a value is to 1 the higher is a probability that there is a statistical correlation between examined parameters.

existing restrictions in life activities" in our research database. Then we created a combination table on "disability" and "negative self-assessment of health" and existing restrictions in life activities" variables.

Results and discussion. *Prevalence of restricted life activities among adult population in Russia.* According to data provided by Rosstat[4] a number of disabled people aged 18 and older amounted to 11.28 million people on January 1, 2018; 4.8 million were men and 6.48 million were women. Overall number of disabled per 1,000 people amounted to 81.4 (or 8 % of the overall country population). These data cover only people who are officially registered as disabled. In order to obtain more precise number of disabled people, we suggest examining data obtained via representative sampling observation over population health in Russia.

A questioning used in the sampling observation over population health (VN SZN–2019) contained a block of questions called "health" where respondents were offered, among other things, to give self-assessment of their health; another block was called "Life activities of an adult person" and included questions aimed at detecting possible restricted life activities. According to data obtained via this research approximately 8 % of the adult population in Russia stated that their health was "poor" and it was quite similar to the registered overall number of disabled people. At the same time, according to data obtained via the sampling observation over behavioral factors that influence population health (PFSZ–2018), a share of respondents who thought their health to be poor or very poor was substantially higher as it amounted to 13 % (Table 1). However, this substantial change in distribution of health assessments could be caused by different reasons for giving an answer to this question[5].

Overall, these distributions of health assessment indicate that from 8 to 13 % of the adult population in the country have more or less serious health problems that prevent them from assessing their health as satisfactory or good.

Let us analyze data obtained via Russian Social Survey performed as per ESS program (RSS) and data obtained due to the 9th wave in European Social Survey (ESS). In both surveys, respondents were asked to assess their health (answer variants were comparable). And it was in Russia where a share of respondents who assessed their health as "poor" and "very poor" (11 % altogether) was high together with a small share of people who assessed their health as "good" (42 %). The highest shares of positive answers were given in Switzerland (84 %) and Ireland (81 %) (Table 2).

Table 1

Self-assessments of health by Russian population as per data obtained via two sampling observations

Self-assessment of health	Sampling observation data	
	VN SZN–2019	VN PFSZ–2018
Good and very good	56.3	39.6
Satisfactory	35.7	47.1
Poor and very poor	7.8	13.1

Source: data obtained via sampling observations over population health and behavioral factors that influence population health[3].

[4] The situation with disabled people. *The Federal State Statistic Service*. Available at: https://www.gks.ru/folder/13964 (April 20, 2020).

[5] A clarifying question on reasons that made a respondent give this or that assessment of his or her health was included into the VN PFSZ–2018; however, a distribution of answers to it was not given in the ultimate observation results. Data obtained via VN SZN–2019 could allow assessing prevalence of restricted life activities among population but answers to relevant questions were not published.

Table 2

Distribution of health assessments in European countries (% of the overall population)

Self-assessment of health	Ireland	Cyprus	Switzerland	Norway	Hungary	Bulgaria	Estonia	Russia
Very good	40	41	37	33	17	16	11	7
Good	41	34	47	44	45	42	41	35
Satisfactory	15	20	13	18	28	31	37	46
Poor	3	4	2	4	7	9	9	10
Very poor	1	1	0	1	2	3	2	1

Source: data obtained via Russian Social Survey as per ESS program and data obtained within the 9th wave of European Social Survey (ESS).

Table 3

Respondents' distribution as per restricted life activities in European countries (% of the total number of respondents)

Self-assessment of health	Ireland	Cyprus	Switzerland	Norway	Hungary	Bulgaria	Estonia	Russia
Grave restrictions	5	4	4	6	4	4	8	6
Certain restrictions	14	17	16	22	17	14	23	29
No restrictions	81	79	80	73	78	83	68	64

Source: data obtained via Russian Social Survey as per ESS program and data obtained within the 9th wave of European Social Survey (ESS).

Table 4

Distribution of respondents' health assessment depending on restricted life activities (% of the overall number of respondents)

Restricted life activities / health self-assessment	Very good	Good	Satisfactory	Poor	Very poor	All respondents
Grave restrictions	0	10	20	**49.3**	**20.7**	6.2
Certain restrictions	0.1	9.3	67.3	**22.2**	1.1	30.9
No restrictions	10.1	48.2	39.7	1.9	0.0	62.8
All respondents	6.4	33.8	47.0	11.1	1.6	100

Source: data obtained via Russian Social Survey as per ESS program; results obtained for 2,404 observations.

In both surveys, respondents were also asked whether they had any restrictions in life due to physical handicaps or disability. Russia also turned out to be among the most unfavorable countries as per a share of people who didn't have any restrictions in life. At the same time, a share of people who have grave restrictions in our country is close to values obtained for other European countries. Basic differences were detected regarding those respondents who, in their own opinion, had certain restrictions in life. An overall picture of respondents' distributions as per existing restrictions of life activities is the most favorable in Bulgaria, Ireland, and Switzerland (Table 3).

Self-assessment of health and restricted life activities (analysis of correlation based on data obtained via social surveys). Data obtained via European and Russian Social Surveys allow comparing respondents' self-assessments of health and existing restrictions of their life activities. Table 4 contains data on distribution of health assessments among respondents from three groups: without any restrictions, with certain restrictions, and with grave restrictions. We can see a correlation between the examined parameters. Thus, only 10 % respondents with grave restrictions assessed their health as good and the biggest share in this group stated it was poor (49 %) or very poor (21 %). Positive assessments were much more frequent among respondents without any restrictions (58 %) and low assessments were quite rare (2 %) (Table 4). The questionnaire used in 2018 didn't contain a question on reasons that made respondents give this or that assessment of their health. At the same time, this distribution given in Table 4 allows assuming that existing restrictions in life activities are among such reasons.

At the same time, as it was mentioned above, the same factor can be significant regarding its influence on respondents' self-assessments of health in some demographic groups and insignificant in others. To clarify this correlation between self-assessment of health and existing restrictions of life activities, let us examine the data as per different social and demographic groups. To do that, we should divide the sampling into certain groups as per sex and 10-year age groups.

There were substantial variations in prevalence of restricted life activities in specific age and sex groups of respondents. The greatest share of people with any restrictions was detected among respondents aged 60–69; the lowest share, among respondents aged 20–29 (Figure).

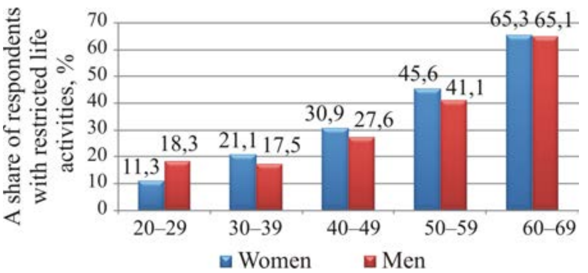

Figure. Prevalence of any restricted life activities among respondents from different age and sex groups (% of a number of respondents in a relevant group)
Source: calculated as per data obtained via Russian Social Survey as per ESS program

We calculated Cramer's V-coefficient values to reveal correlations between respondents' self-assessments of health and existing restricted life activities (Table 5).

The obtained data indicate that there is an average correlation between such criteria as "self-assessment of health" and "existing restrictions in life activities". And coefficient values are a bit lower for men aged 30–39 and women aged 40–49 than for other groups. The maximum Cramer's V value for women was obtained for people aged 60–69 (0.455); the maximum value for men (0.570) was obtained for people aged 20–29. Overall, Cramer's V values calculated for men (excluding group aged 30–39) were higher than values calculated for women. It allows us to assume that men took into account any life restrictions to a greater extent than women when assessing their health. At the same time, as we will show a bit later, women who don't have any restrictions in their life activities tend to assess their health lower than men and it explains the obtained coefficient values. It was especially apparent for women aged 40–49 who didn't have any restrictions in their life activities (Table 6).

Restricted life activities make people believe their health is poor thus resulting in low self-assessments of it. Thus, a longitude survey that was performed in Great Britain revealed that elderly people with poorer hearing and eyesight tended to assess their health lower than their counterparts without such disorders [19]. Some surveys performed in Russia showed that there was a correlation between disability and self-assessment of health and these assessments tended to be negative more frequently among disabled people [5]. In our research more frequent negative self-assessments of health were detected among respondents who had restricted life activities, regardless of their belonging to a specific sex and age group, against respondents without any restrictions[6]. It allows assuming that restricted life activities make for lower self-assessment of health. A share of negative health assessments grew among men with restricted life activities in each next age group. The only exclusion was a group made up of men aged 30–39. As for women who had restricted life activities, the highest share of negative health assessments was detected among those aged 60–69 (34 %). But when it

[6] As we have already mentioned, a number of respondents aged 15–19 and 70 and older was substantially lower than in other age groups; therefore Table 6 doesn't contain any data on these age groups.

Table 5

Cramer's V-coefficient values for "self-assessment of health" and "existing restrictions in life activities" in different sex and age groups of respondents

Age groups	Men			Women		
	Cramer's V	Feasible observations, number	Significance	Cramer's V	Feasible observations, number	Significance
20–29	**0.529**	225	0.000	0.390	189	0.000
30–39	0.376	275	0.000	0.438	205	0.000
40–49	0.501	194	0.000	0.366	186	0.000
50–59	0.482	143	0.000	0.452	252	0.000
60–69	0.476	115	0.000	**0.455**	248	0.000

Source: calculated as per data obtained via Russian Social Survey using IBM SPSS Statistic software (ver.22.0). Data were preliminarily weighted in order to provide representativeness as per created age and sex groups.

Table 6

A share of respondents who assessed their health as "very poor" and "poor" in different sex and age groups (in % of the total number of respondents)

Sex and age groups	20–29	30–39	40–49	50–59	60–69
Women					
Have restrictions of life activities	18.2	20.9	22.8	21.1	34
No restrictions	1.8	1.9	4.7	0.7	1.2
Men					
Have restrictions of life activities	17.5	10.5	20.4	20.6	30.7
No restrictions	0.0	0.9	0.7	1.2	0.0

Source: calculated as per data obtained via Russian Social Survey with IBM SPSS Statistic software (ver.22.0).

comes down to women without any restrictions, we should note that the highest share of negative health assessments was detected among those aged 40–49. This might be due to women in this age group paying special attention to feeling bad and having malaise when they assessed their health; these disorders didn't result in any restrictions but created certain discomfort (Table 6).

Since we have managed to reveal a certain correlation between self-assessment of health and existing restricted life activities, let us now consider whether we can use these parameters for estimating latent disability among population. 2 % (45 people) among respondents aged 60–69 who took part in the examined survey were registered as disabled; another 7 % (138 people) had restricted life activities and assessed their health as poor or very poor. Disability among women, apart from restricted life activities, was more often accompanied with negative assessment of health (72.7 %) whereas a considerable share of men (26.1 %) stated they didn't have any restrictions of life activities and assessed their health quite positively. It is probably due to these respondents having failed to adapt to their condition. Negative self-assessment of health is not detected among disabled people without any restrictions in life activities whereas it is still possible to assess one's health positively even if there are restricted life activities. 5.4 % of men who were not registered as disabled simultaneously stated that they had restrictions in life activities and gave negative assessments of their health. As for women, a share of those who were not disabled but still had restricted life activities amounted to 8.4 % (Table 7).

We calculated Cramer's V-coefficients for the examined variables to determine to what extent officially registered disability was

Table 7

Combination table: "negative self-assessment of health and restricted life activities" and "disability' variables (in % of the overall number of respondents)

Health parameters	Respondents not officially registered as "disabled"		Respondents officially registered as disabled	
Sex	men	women	men	women
Negative self-assessment of health and restricted life activities	5.4	8.4	43.5	72.7
Positive self-assessment of health and restricted life activities	22.5	27.2	30.4	27.3
Negative self-assessment of health and absence of restricted life activities	0.4	1.3	0.0	0.0
Positive self-assessment of health and absence of restricted life activities	71.7	63.1	26.1	0.0

N o t e : 100 % as per columns
Source: calculated as per data obtained via Russian Social Survey with IBM SPSS Statistic software (ver.22.0).

related to a combination of negative health assessment and restricted life activities in different sex and age groups. According to the obtained results, the strongest correlations between "disability" and "negative self-assessment of health and restricted life activities" variables were detected for women aged 20–29 and 30–39; the weakest ones, for men and women aged 60–69. That is, if young women have restrictions in life activities and assess their health negatively, it is quite probable that they are simultaneously disabled. Low values of the calculated coefficient in older age groups indicate there is greater probability that a number of disabled people is underestimated in these age groups in spite of poorer health (in comparison with younger age groups). This situation may be due to, on one hand, elderly people having weaker motivation to register officially as disabled after retirement; on the other hand, due to a share of negative assessments of health being naturally higher in older age groups regardless of disability. Calculated values of the coefficient indicate that a number of disabled people is more likely to be underestimated for men than for women, the only exception being an age group 50–59 (Table 8). A weak correlation between the examined variables for men may indicate that disability is not always combined with restricted life abilities and negative self-assessment of health among them. If we correlate this result with previously mentioned assumption about greater correlation between self-assessment of health and restricted life activities among men (in comparison with women), we can come to the following: men to a greater extent tend to take restricted life activities into account when assessing their health, but combined restrictions and poor health are less likely to indicate there is officially registered disability.

Let us analyze a number of respondents with a combination of "negative self-assessment of health" and "restricted life activities" who are not officially registered as disabled in the examined age and sex groups. The highest share of respondents with these two parameters was detected among women and men aged 60–69 (20.3 and 19.5 % accordingly). Bearing in mind that there is a weak correlation between disability and restricted life activities and negative self-assessment of health in these groups of respondents, we can assume that a number of disabled people is the most likely to be underestimated in them. 3 % among men aged 20–29 had restricted life activities and assessed their health as poor or very poor. Bearing in mind, that the examined parameters are relatively weakly correlated with officially registered disability, we can assume that these 3 % men can also make a contribution into latent disability. The same is true for 4.8 % respondents with such parameters among men aged 40–49. As it has already been shown, men aged 30–39 tend to have the least apparent

Table 8

Cramer's V coefficient values "negative self-assessment of health and restricted life activities" and "disability" variables in different sex and age groups

Sex	Age groups				
	20–29	30–39	40–49	50–59	60–69
Men	0.263	0.309	0.228	0.368	0.119
Women	0.496	0.493	0.401	0.338	0.198

Source: calculated as per data obtained via Russian Social Survey with IBM SPSS Statistic software (ver.22.0).

correlation between self-assessment of health and restricted life activities. At the same time, a combination of these parameters is even more weakly correlated with officially registered disability. It indicates that men from this age group are to the smallest extent prone to try and register themselves as disabled officially even when they have restrictions in life activities; it also means that these men tend to probably overestimate their health. This age group among men is the most difficult for revealing scales of latent disability via social survey techniques. The strongest correlation between officially registered disability and restricted life activities and negative assessment of health is detected among men aged 50–59 (in comparison with other age groups among men). There is also an average correlation between negative self-assessment of health and existing restricted life activities detected for this group of respondents. 5.9 % men in this age group had the above mentioned parameters but were not officially registered as disabled. These respondents can be considered people who in future may apply for being officially registered as disabled.

A share of women with restricted life activities and negative self-assessments of health varied from 1.6 % among those aged 20–29 to 8.5 % among those aged 50–59. We have already shown that a correlation between self-assessment of health and existing restricted life activities was weaker among women aged 20–29 and 40–49 and a correlation between these parameters and officially registered disability was stronger in these age groups than in older ones. At the same time, women who don't have any restrictions of their life activities still tend to underestimate their health. These facts indicate that women from the above mentioned age groups are less likely to be latent disabled since they are rather alert regarding their health and readily apply for being officially registered as disabled in case it is necessary. As it has already been shown, there is an average correlation between restricted life activities and negative self-assessments of health detected among women aged 50–59. A correlation between self-assessments of health and existing restricted life activities is just a bit weaker among women from this age group than among those aged 60–69. These facts indicate that when women retire, they have weaker motivation to be officially registered as disabled even if there are restricted life activities. Therefore, 8.5 % female respondents from this age group can also be conditionally considered to be latent disabled (Table 9).

Table 9

Number of respondents with restricted life activities and negative self-assessment of health in different age and sex groups

Sex	Age groups				
	20–29	30–39	40–49	50–59	60–69
Men, people	7	4	9	8	22
% of the overall number of people in an age group	3.1	1.5	4.8	5.9	19.5
Women, people	3	6	10	21	48
% of the overall number of people in an age group	1.6	3	5.5	8.5	20.3

Source: calculated as per data obtained via Russian Social Survey with IBM SPSS Statistic software (ver.22.0).

Conclusion. In our research we tested an assumption that people who were not officially registered as disabled still had a risk that they might have to do so in future in case they already had restricted life activities and assessed their health as poor or very poor. In its turn, a considerable share of such people among overall population may indicate that they either don't want to apply for being officially registered as disabled or they face objective difficulties in trying to get this official "disabled" status.

This research allows concluding that a combination of such criteria as "negative self-assessment of health" and "existing restricted life activities" can be considered risk indicators showing a risk of latent disability among adult population. It has been shown that a combination of these parameters to a greater extent correlated with official disability among men aged 50–59 and women aged 20–29, 30–39 and 40–49. Respondents from these groups who have restricted life activities and assess their health as poor or very poor are more likely to be officially registered as disabled in future. The situation is a bit more difficult when it comes down to men and women aged 60–69: restricted life activities combined with negative self-assessment of health are more frequent in these groups but these parameters to a smaller extent correlate with official disability than in other age groups. These facts may indicate that elderly people either don't want to apply for being officially registered as disabled or they face certain difficulties in doing so. Given that, elderly men and women are more likely to be latent disabled.

The least exact results in revealing latent disability via applying these indicators were obtained for men aged 30–39. There is a weak correlation between self-assessment of health and restricted life activities detected for this group of respondents, on one hand, and also a weak correlation between these parameters and officially registered disability, on the other hand.

To determine latent disability is a task with great practical significance since, on one hand, it allows revealing population groups with elevated risks of underestimated number of disabled people in them; on the other hand, it helps make timely managerial decisions regarding disability prevention and providing support for risk groups. Revealing latent disability also allows reducing a probability of mistakes in predicting expenditure on social support for population and public healthcare. Bearing in mind that the issues discussed in the present work are rather complicated, it is necessary to accomplish further examinations using data obtained via other representative social questionings (including regional ones); it will allow solving methodological issues when the examined criteria are used to estimate latent disability (including estimations performed as per different age and sex population groups).

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Review

ANALYTICAL REVIEW OF APPROACHES TO PROVIDING SAFETY WHEN SUBSTANTIATING HYGIENIC STANDARDS FOR CHEMICALS CONTENTS IN AMBIENT AIR

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A necessity to harmonize Russian sanitary-epidemiologic approaches with international standards is fixed in the federal legislation in the RF; given that, it seems vital to harmonize standards for ambient air quality taking into account a period of their averaging. To do that, previously methodical approaches were suggested to substantiating average annual MPC of chemicals in ambient air as per health risk criteria.

The research goal here was to make a review of previously applied and newly created methodical approaches to establishing average annual MPC taking into account an extent to which they were harmonized with international approaches and their capacity to provide safety for population.

As per results obtained via the performed literature review, we spotted out key elements in methodical approaches applied in the RF and abroad when substantiating standards for ambient air quality taking into account chronic inhalation exposure; the further analysis was performed in accordance with them.

It was detected that approaches applied to establish average annual MPC were partially harmonized since they didn't involve using threshold levels (BMC, BMCL); use of results obtained in previous studies to establish starting points in developing hygienic standards does not allow taking all the existing uncertainties into account. It seems impossible to estimate their safety as per health risk criteria due to absence of relevant parameters. Methodical approaches to substantiating average annual MPC as per health risk criteria are fully harmonized. Thus, they involve using BMC and BMCL for determining starting points when standards are being developed; values for such starting points can be established, among other things, as per data obtained via analyzing results of previous studies and are also supplemented when it comes down to taking uncertainty factors into account. Safety of developed average annual MPC is provided, among other things, due to obtained standards being verified as per acceptable (permissible) risk criteria. Given that, they can be used for developing harmonized average annual MPC.

Key words: *average annual MPC, average daily MPC, hygienic standards, risk criteria, harmonization, ambient air, safety, methodical approaches.*

The RF Government Order issued on September 28, 2009 No. 761 "On providing harmonization of Russian sanitary-epidemiologic requirements, veterinary-sanitary and phytosanitary measures with international standards" (last edited on September 04, 2012) stipulates the necessity to modernize regulatory and legal documents applied for control over ambient air quality[1,2] [1]. To do that, a domestic list of hygienic standards is

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[1] On providing harmonization of Russian sanitary-epidemiologic requirements, veterinary-sanitary and phytosanitary measures with international standards: The RF Government Order issued on September 28, 2009 No. 761 (last edited on September 04, 2012). *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_91969/ (April 01, 2021).

[2] On approving the procedure for accomplishing examination of legal documents that stipulate sanitary-epidemiologic requirement in order to determine their conformity with international standards: The Order by the RF Ministry for Public Healthcare and Social Development issued on July 30, 2010 No. 581. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_104442/ (March 25, 2021).

being extended via including average annual maximum permissible concentrations ($MPC_{av.an.}$) of chemicals in ambient air. This activity is essentially vital since in the RF only average daily maximum permissible concentrations ($MPC_{av.d.}$) were applied until recently for providing safety for population health under unlimited long-term exposure to chemicals[3]. But in foreign countries average daily values are applied only to assess exposure to chemicals over 24 hours and are taken for a period not longer than 2 weeks; and average annual concentrations are usually applied to assess chronic exposure [1, 2]. Thus, control over ambient air quality in foreign countries involves using, among other things, quality standards with values applied to assess risks of negative outcomes for health caused by chronic exposure to chemicals [3]. Such values include reference concentrations (RfCs) and minimal risk levels (MRL); chronic periods for such values correspond to those used for annual averaging [4, 5].

Public management in the sphere of providing sanitary-epidemiologic welfare for the country population is developing via updating public mechanisms that involves implementation of risk analysis elements. Given that, each element in the management system [6–8] should be added with a list of hygienic standards for ambient air quality that are averaged over a year ($MPC_{av.an.}$) and are substantiated as per permissible (acceptable) health risks for population; it will allow using these standards as a criteria for assessing health risks under chronic inhalation exposure [9–11]. Adherence to these standards will allow providing safety (absence of impermissible risks for people's life and health) under chronic exposure to contaminants contained in ambient air.

Given the necessity to substantiate average annual hygienic standards as per risk criteria, it is advisable to develop harmonized methodical approaches based on existing domestic ones together with approaches applied for determining parameters that are used in risk assessment [12]. To do that, experts suggested certain methodical approaches to substantiating $MPC_{av.an.}$ for chemicals in ambient air as per health risk criteria [2]. They include an algorithm for fixing $MPC_{av.an.}$ that consists of some starting points (LOAEL, NOAEL, BMC, and BMCL, determined due to analyzing results obtained via previous research or as per experimental results); establishing relevant uncertainty factors (from 1 to 10); substantiating and validating all obtained standards as per permissible (acceptable) risks and assessing safety given life-long exposure to $MPC_{av.an.}$ These approaches can be used for establishing and substantiating harmonized $MPC_{av.an.}$ and it will allow using them as criteria for risk assessment under chronic inhalation exposure. To do that, we should assess methodical approaches to establishing $MPC_{av.d.}$ that were applied previously and newly developed approaches to establishing $MPC_{av.an.}$ taking into account an extent to which they are harmonized with international approaches and whether standards developed on their basis can truly provide safety for population.

Our research goal was to review domestic methodical approaches to substantiating standards for chemicals contents in ambient air under chronic exposure ($MPC_{av.d.}$ and $MPC_{av.an.}$) taking into account an extent to which they were harmonized with international approaches and could provide safety for population.

To achieve this goal, we had to fulfill the following tasks:

1) to spot out key elements in domestic and foreign methodical approaches used for

[3] Temporary methodical guidelines on substantiating maximum permissible concentrations (MPC) of contaminants in ambient air in settlements. Moscow, USSR Public Healthcare Ministry; The Chief Sanitary-Epidemiologic Office / Approved by the USSR Public Healthcare Ministry on June 15, 1988, No. 4681-88, 1989, 110 p.

establishing standards for chemicals contents in ambient air under chronic exposure ($MPC_{av.d.}$ in the Russian Federation and average annual concentrations in foreign countries) basing on our review of scientific literature;

2) to assess an extent to which domestic approaches to establishing $MPC_{av.d.}$ for adverse chemicals in ambient air spotted out at the previous stage were harmonized with international ones and could provide safety for population;

3) to assess methodical approaches to substantiating $MPC_{av.an.}$ for chemicals in ambient air as per health risk criteria according to the obtained results taking into account an extent to which they were harmonized with international approaches and could provide safety for population.

Data and methods. To achieve our goal, we analyzed approaches applied in Russia and abroad for establishing ambient air quality standards. These approaches were determined basing on reviewing regulatory and methodical documents on the subject as well as previously performed surveys that were available in such databases as Research Gate, Scopus, Web of Science, Cyber Leninka, eLibrary, Google Scholar, NCBI PubMed, Elsevier.

Approaches applied for fixing $MPC_{av.d.}$ for adverse chemicals in ambient air in the Russian Federation were stipulated in the Temporary methodical guidelines substantiating maximum permissible concentrations (MPC) of contaminants in ambient air in settlements No. 4681-88 issued on July 15, 1988[3] and principles fixed within hygienic standardization paradigm. To analyze approaches to substantiating $MPC_{av.an.}$, we used methodical approaches to substantiating average annual maximum permissible concentrations of adverse chemicals in ambient air in settlements as per permissible health risks [2]. To analyze worldwide experience in the sphere, we reviewed regulatory documents on ambient air quality issued by the US Environmental Protection Agency (USEPA), European Union (EU), US Agency for Toxic Substances and Disease Registry (ATSDR), and the World Health Organization (WHO) [4, 5][4, 5, 6].

Results and discussion. Basing on the review and analysis of data taken from available scientific literature, we spotted out the following key elements in domestic and foreign methodical approaches applied for establishing standards for chemicals contents under chronic exposure:

1) a period for averaging a standard;

2) use of safety criteria (absence of impermissible risk) when standards are substantiated;

3) use of results obtained via previously performed research for fixing initial parameters when developing new standards;

4) choice on exposure levels used as initial ones when hygienic standards are fixed;

5) a procedure for taking uncertainties into account.

$MPC_{av.d.}$ were used in the Russian Federation for a long period of time for assessing chronic effects produced by chemicals under unlimited long-term inhalation exposure. Average annual concentrations were established only for particulate matter PM_{10} and $PM_{2.5}$ and tarry matter (peck sublime) in electrolysis dusts emitted from aluminum productions[7]. But in world practice only average annual concentrations are used for providing safety under chronic inhalation exposure to chemicals in ambient air [2]

[4] Air Quality Guidelines for Europe. Second Edition. World Health Organization, Regional Office for Europe, Copenhagen, 2000, 288 p.

[5] Technical Guidance Document on Risk Assessment. European Communities, 2003, 337 p.

[6] Guidelines for Human Exposure Assessment (EPA/100/B-19/001)// Risk Assessment Forum. Washington, DC, U.S. Environmental Protection Agency, 2019, 223 p.

[7] HS 2.1.6.3492-17. Maximum permissible concentrations (MPC) of contaminants in ambient air in urban and rural settlements. Available at: https://docs.cntd.ru/document/556185926 (April 03, 2021).

since it provides greater safety for people during the whole life span. Given that, we can use them as criteria for health risk assessment which is an essential part of public management at every level at the contemporary stage in society development in Russia; health risk assessment is also considered a basic mechanism in developing policies aimed at reducing negative effects produced on population health in most countries and international organizations [6–8, 11, 13, 14]. Use of this methodology is fixed in the RF sanitary legislation; however, it is limited due to absence of sufficient number of average annual standards and use of permissible risks for people's life or health as criteria that show safety of environmental factors [7].

Having reviewed all the available data and assessed an extent to which a period of time for averaging standards used in assessing chronic inhalation exposure to chemicals was harmonized with international approaches, we established that domestic approaches applied for establishing $MPC_{av.d.}$ were not harmonized with international ones. The reason is that only average annual concentrations are applied in world practice to assess chronic exposure to adverse chemicals [2].

The next key element was assessing an extent to which use of safety criteria (absence of impermissible risk) was harmonized in domestic and foreign practices when substantiating standards for chemicals contents in ambient air under chronic exposure.

The health risk assessment methodology used for assessing risks under exposure to chemicals that pollute the environment contains carcinogenic and non-carcinogenic risk criteria. HQ ≥ 1 is fixed as permissible non-carcinogenic risk; permissible carcinogenic risks can be higher than $1 \cdot 10^{-6}$ but lower than $1 \cdot 10^{-4}$. This level is commonly used in most foreign hygienic standards and those recommended by international organizations when assessing risks for overall population (for example, the WHO stipulates $1 \cdot 10^{-4}$ as permissible risk for ambient air)[8]. Domestic methodology for establishing $MPC_{av.d.}$ doesn't apply permissible risk criteria.

Having assessed harmonization, we established that this element was not harmonized due to the methodology for establishing $MPC_{av.d.}$ not using criteria of permissible health risks; however, these criteria are used when most foreign standards are developed.

Having reviewed exposure levels used as initial ones for establishing hygienic standards, we revealed that foreign practices mostly relied on NOAEL (non-effective level), LOAEL (lowest observed effect level), BMC (benchmark concentration) and BMCL (lower limit of BMC CI)[4,5,9] [15–17].

It is assumed that there is a concentration for most chemicals that produce toxic effects below which no side effects can be observed (that is, a threshold); such a concentration can be taken as a threshold one in the first approximation. NOAEL is a value often used for assessing exposure threshold. In an experiment NOAEL is determined as the highest experimentally detected exposure level that does not cause statistically or biologically significant increase in frequency or gravity of side effects[9]. In case NOAEL can't be estimated, LOAEL is used in assessment with extrapolation onto NOAEL via using a modifying factor [15, 17]. In an experiment, LOAEL is the lowest dose that can produce unfavorable effects. Use of NOAEL has certain limitations [16, 18–20]. Thus, NOAEL is essentially an experimental dose and takes into account changeability in determining its statistical significance against a reference group. Given that, we can't exclude unfavorable effects occurring under exposure to NOAEL as per statistical

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

[9] Guidelines for Exposure Assessment (EPA/600/Z-92/001). Risk Assessment Forum. Washington, DC, U.S. Environmental Protection Agency, 1992, 139 p.

and analytical reasons. Besides, NOAEL value is influenced by a sampling size since a response to a certain concentrations is compared with a response given by a reference group [21]. Given that, an opportunity to observe statistical difference will decrease as a number of animals under exposure goes down and, consequently, there will be a growth in NOAEL [20]. Therefore, NOAEL value depends on a number of experimental concentrations and an interval between them [22]. These and some other limitations of this approach encouraged searching for alternatives; a procedure that applies a benchmark concentration (BMC) has become one of them. BMC is a statistical lower confidence limit of exposure that causes an established negative effect [16, 23–26]. BMC can be used both in experiments on animals and for establishing reference health parameters basing on epidemiological data[10] [27, 28]. BMCL is the lower limit of PMC CI that is determined as a point on a curve showing "dose – response" dependence; this point is usually determined basing on experimental data and usually corresponds to low exposure level (from 1 to 10 %). Abroad BMC is applied by USEPA for determining reference concentrations[5] [18]. This approach that applies benchmark doses is also used as an alternative for the traditional NOAEL-based one within OECD activities and when technical regulatory principles are revised in the EU for new and existing chemicals [29].

When standards are being developed and there are data on several starting points, it is advisable to select such parameters that require applying as few uncertainty factors as it is only possible. And use of BMC and BMCL seems to be the most optimal in this respect since these parameters are developed basing on mathematical modeling of "dose – response" dependence and using available relevant data obtained via other experiments [25–28].

Hygienic standardization in Russia applies several initial parameters for establishing $MPC_{av.d.}$; they are threshold and maximum non-effective concentrations similar to NOAEL (no effect level) and LOAEL (lowest observed effect level) that are applied abroad[4] [30, 31]. But we should mention that reference parameters, such as BMC and BMCL, are not applied in Russia though they are quite widely used by international organizations. Therefore, the performed review allowed establishing that domestic approaches used for determining $MPC_{av.d.}$ were partially harmonized regarding applied exposure levels.

Use of results obtained via previously performed research for establishing initial parameters when standards were developed was analyzed as the next key element. This approach is widely used in international practice due to its capability to provide wide opportunities for using data on effects produced by toxicants on health accumulated both in foreign and domestic literature. These data have been obtained via previous toxicological and epidemiologic research and it allows avoiding duplication of results and to a certain extent makes the process less labor-consuming and expensive. This stage involves analyzing all the available data on results obtained via previously performed research on negative effects produced by a chemical in order to assess their sufficiency for establishing initial parameters required for developing a certain standard [2]. To do that, a database is created that covers all previously performed research works on negative effects produced by an examined chemical that correspond to relevance criteria. Such databases use conventional information sources such as domestic and international databases (including Scopus, Web of Science, CyberLeninka, eLibrary, Google Scholar, NCBI PubMed, Elsevier, Research

[10] Benchmark Dose Technical Guidance (EPA/100/R-12/001). Risk Assessment Forum. Washington, DC, U.S. Environmental Protection Agency, 2012, 99 p.

Gate) and reviewed scientific editions. Then, it is necessary to qualitatively assess this created database; basing on its results key research papers are selected and they are estimated in accordance with minimal criteria for database completeness. In case they correspond to these criteria, qualitative and integral assessment of selected research papers is performed in order to estimate whether there are enough data for establishing initial parameters required to substantiate a hygienic standard. In case data are sufficient, then a standard is fixed as per results obtained via previous research. Should data be insufficient, then conventional experimental toxicological and/or epidemiologic research is required or new data should be analyzed again after some new research papers have been published. Within these approaches it is also possible to revise all obtained values when new experimental data have been published after accomplished experiments that concentrated on effects produced by an examined chemical; these new data can be used in developing and substantiating new hygienic standards.

When $MPC_{av.d.}$ are determined in Russia, literature data are analyzed for characterizing physical-chemical and toxicological properties of a standardized chemical. And initial parameters that are used as grounds for establishing a standard are determined only as per results obtained via performed experimental research.

Having assessed to what extent this element in Russia was harmonized with international practices we established that harmonization was only partial since the procedure for establishing $MPC_{av.d.}$ didn't involve using results obtained via previous research when a new standard was established; however, they are applied when a chemical is described at a stage that involves creating an experiment design.

Having reviewed domestic and foreign regulatory and methodical documents, we concluded that standards for chemicals contents in ambient air under chronic exposure were fixed basing on starting points with their adjustment as per uncertainty factors in foreign practices regarding ambient air quality standards and with assurance factors in domestic hygienic standardization, including $MPC_{av.d.}$ establishment [4, 5, 32–34].

Assurance factor is determined depending on an overall idea of a hazard caused by a chemical both as per toxicometric parameters and qualitative parameters of effects it produces; variability of species sensitivity; conditions and factors that influence precision of threshold values substantiated during an experiment, a coefficient used for extrapolating data obtained via using a limited number of experimental animals onto human population[3]. That is, they take into account, how many times $MPC_{av.d.}$ for a specific chemical that is established for people is less than a chronic exposure threshold determined in experiments on animals.

International organizations and EU countries apply uncertainty factors (UF) when developing ambient air quality standards and taking uncertainties into account. These uncertainty factors have been developed for most spheres where uncertainties may occur [35, 36]. Thus, there are factors that take into account intra-species uncertainty (the most sensitive groups), inter-species uncertainty (when results obtained via laboratory experiments on animals are extrapolated on people), extrapolation of data obtained in acute, sub-chronic and chronic examinations for the whole life span, using threshold levels instead of non-effective ones, using incomplete data arrays[4,6][32, 34, 37, 38]. Therefore, an approach that involves using UF allows taking more uncertainties into account than an approach based on applying assurance factors; the formed allows developing standards that correspond to lower exposure levels than those that, according to available data, may cause negative outcomes for health among the most sensitive population groups.

Recommendations on harmonizing domestic methodical approaches to establishing $MPC_{av.d.}$ for chemicals contents in ambient air

Harmonization point	Current situation		Recommendations on domestic approaches harmonization
	The Russian Federation	Foreign countries and international organizations	
1. Standards averaging under chronic inhalation exposure	Basically $MPC_{av.d.}$ and several $MPC_{av.an}$	Standards are average only for a year	To add a list of domestic standards with $MPC_{av.an}$
2. Use of safety criterion (no impermissible risk) when substantiating standards	Are not used	Permissible risk criteria are widely used	To provide for using permissible risk criteria when substantiating standards
3. Selecting levels of exposure used as initial ones for establishing hygienic standards	Minimal effective concentrations and maximum non-effective concentration	LOAEL (lowest observed effect level), NOAEL (maximum non-effective level), BMC, BMCL (threshold levels)	To develop a procedure for using NOAEL, LOAEL, BMC, BMCL when establishing hygienic standards
4. Use of results obtained via previous research for establishing initial parameters when standards are developed	Previously accomplished research works are used only to characterize a chemical and starting points are established as per experimental research results исследований	Starting points can be establishing via analyzing results obtained via previous research and no experiments are required in case they are sufficient	To develop methodical approaches to substantiating standards basing on results obtained via previous research
5. A procedure for taking uncertainties into account	Assurance factors	Uncertainty factors (allow taking a wider range of uncertainties into account)	To modify a domestic system for taking uncertainties into account when developing standards via including additional spheres

Basing on the performed review, we established that this element was partially harmonized since the procedure for establishing $MPC_{av.d.}$ based on using assurance factors didn't allow taking into account the whole range of uncertainties that occurred when standards were developed.

To sum up, we reviewed domestic methodical approaches to establishing $MPC_{av.d.}$ and assessed to what extent they were harmonized with international ones; it allowed us to reveal that all domestic approaches were partially harmonized since they didn't involve using criteria of permissible health risks, threshold levels (BMC, BMCL) and uncertainty factors as well as using results obtained via previous research to substantiate standards. It seems impossible to assess safety (absence of impermissible risk) of $MPC_{av.d.}$ determined within existing approaches due to parameters necessary for such assessment being unavailable.

Basing on the obtained results, we developed some recommendations that would allow providing full harmonization of domestic approaches with international ones as per the examined key elements (Table).

According to developed recommendations we assessed methodical approaches to substantiating $MPC_{av.an.}$ for chemicals in ambient air as per health risk criteria and taking into account to what extent they were harmonized with international ones and provided safety for population. We revealed that these domestic approaches were completely harmonized with international ones since they involved establishing $MPC_{av.an.}$ and permissible risk criteria when they were substantiated for assessing chronic inhalation exposure to chemicals. A procedure for using NOAEL, LOAEL, BMC, and BMCL for fixing hygienic standards is developed within these approaches; these values can be determined, among other things, as per analyzing results obtained via previous research. An extended list of spheres is applied for taking uncertainties into account; this list is supplemented with relevant data on obtaining more precise values in harmonized ranges. When it comes to safety assessment, average annual standards developed according to these methodical approaches provide absence of impermissible risk due to permissible risk criteria being used in their development; obtained $MPC_{av.an.}$ are also verified via applying evolution models for calculating whether health risk under life-long exposure conforms to permissible levels. All this allows establishing $MPC_{av.an.}$ that do not result in impermissible life-long health risks for population including the most sensitive groups.

Harmonized methodical approaches to substantiating $MPC_{av.an.}$ for chemicals in ambient air as per health risk criteria were used within the Sanitary-Epidemiologic Rules 1.2.3685-21 "Hygienic standards for providing safety and (or) harmlessness of environmental factors for people"[11]. However, some values there do not coincide numerically with reference concentrations (RfC) fixed in "The Guide on assessing health risks for population under exposure to chemicals that pollute the environment"[12] which is a fundamental document applied in risk assessment procedures. It is due to effects produced by so called principle of renewal when previously established values are revised after new data have been obtained that are relevant for establishing and substantiating them. Thus, $MPC_{av.an.}$ for mercury was fixed two orders lower than RfC since in 2008 OENNA approved a new, lower LOAEL value for effects produced by this element on the nervous system [39]; differences in values obtained for ethylbenzene are caused by new LOAEL approved for this element by ATSDR in 2010 and lower MLR was offered basing on it [40]; LOAEL for ethenylbenzene (styrene) were renewed by ATSDR in 2012 and it also led to difference in standards developed on this basis [41]. Differences in $MPC_{av.an.}$ established for such chemicals as tetrachrolomethane, chloroethane, and vinyl chloride are detected due to RfC values being fixed only as per non-carcinogenic risk criteria whereas $MPC_{av.an.}$ were calculated as per both non-carcinogenic and carcinogenic risks criteria. It provides greater safety under chronic exposure to these chemicals. Given all the above mentioned, differences in numeric values were caused by new data becoming available and it allowed calculating new values.

Therefore, methodical approaches to substantiating $MPC_{av.an.}$ for chemicals in ambient air as per health risk criteria are fully harmonized with international ones and allow establishing $MPC_{av.an.}$ that cannot cause unacceptable life-long health risks for population including the most sensitive groups.

Conclusion. Our analytical review of data available in scientific literature allowed us to spot out key elements in domestic and foreign methodical approaches applied for establishing standards for chemicals contents in ambient air under chronic exposure. These key elements included a period for a standard averaging, choice on starting points, use of results obtained via previous research for establishing initial parameters when developing standards, a procedure for taking uncertainties into account, and use of safety criterion (absence of impermissible risk). We revealed that approaches applied for developing $MPC_{av.d.}$ were only partially harmonized since they didn't involve using threshold levels (BMC, BMCL) and results obtained via previous research for establishing starting points when hygienic standards were developed; they also didn't allow taking into account the whole range of uncertainties that

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[11] SER 1.2.3685-21. Hygienic standards for providing safety and (or) harmlessness of environmental factors for people. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573500115 (April 03, 2021).

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occurred when a standard was developed. It doesn't seem possible to assess safety of average daily standards as per health risk criteria due to parameters necessary for risk assessment being not available for them. Basing on the obtained results, we developed some recommendations that would allow full harmonization of domestic approaches with world practices; these recommendations were taken into account within methodical approaches to substantiating $MPC_{av.an.}$ for chemicals in ambient air as per health risk criteria. These approaches are fully harmonized since they involve fixing $MPC_{av.an.}$ for assessing impacts exerted by chronic exposure to adverse chemicals; they suggest a procedure for using NOAEL, LOAEL, BMC, BMCL for establishing starting points when standards are developed and these values can be established, among other things, basing on data obtained via previous research; these approaches are also supplemented with new instruments regarding uncertainty factors. Safety of $MPC_{av.an.}$ values developed within these approaches is provided, among other things, due to using permissible risk criteria in their development. It allows developing average annual standards that do not cause unacceptable life-long health risks for population, including the most sensitive groups. Methodical approaches to substantiating $MPC_{av.an.}$ for chemicals in ambient air as per health risk criteria are fully harmonized with international ones and can be used for establishing harmonized $MPC_{av.an}$.

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Review

COVID-19: NEUROLOGICAL SEQUELAE

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COVID-19, the human primarily respiratory disease caused by the coronavirus SARS-CoV-2, commonly involves the nervous system, the effects of which may persist for many months. Post-acute sequelae of COVID-19 include relapsing and remitting neurological and neuropsychiatric symptoms that can affect children and adults, including those who had mild acute illness. Since longer-term adverse effects on the central and peripheral nervous system of COVID-19 cannot be excluded, patient and societal health trends should be monitored going forward. Urgent present needs include not only global immunization against SARS-CoV-2 but also the reestablishment of lapsed mass vaccination programs to prevent resurgence of other viral diseases (e.g., measles, polio) that can impact the nervous system.

Key words: *SARS-CoV-2, PASC: post-acute sequelae of SARS-CoV-2 (Long Covid), vaccines.*

COVID-19 Origins. The COVID-19 pandemic appears to have begun in China at the end of 2019 from the prior transfer of an enveloped single-strand RNA virus from a wild animal (probably the horseshoe bat) to humans, possibly via an intermediate host, with subsequent efficient human-to-human transmission that was first recognized in Hubei province in central China [1–7]. Given the country's recent experience with human and animal coronavirus diseases, including Severe Acute Respiratory Syndrome (SARS) and Swine Acute Diarrhea Syndrome, Chinese scientists predicted in March 2019 that coronaviruses acquired from bats would cause a future SARS-like outbreak of human disease, most probably in China [8]. In 2020, SARS-CoV-2 and mutants thereof had spread around the world and, by May 1, 2021, the World Health Organization reported >150 million confirmed cases of COVID-19, with an average fatality rate of 2.1 %.

Acute COVID-19. SARS-CoV-2 targets, enters and replicates in cells with angiotensin converting enzyme two (ACE2) receptors throughout the human body, including the nervous system [9–14]. Persons with relative ACE2 deficiency, including the elderly and those with preexisting non-communicable health disorders (hypertension, diabetes, cardiovascular disease or cancer), have a higher risk for severe COVID-19 [15–17]. The immune system targets the foreign SARS-CoV-2 spike protein resulting in local inflammation

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and generation of cytokines and chemokines. Infection of the vascular endothelium may disrupt the blood-brain barrier [18], promote a hypercoagulable state, and increase the risk for arterial and venous thrombosis. While pulmonary and cardiovascular dysfunction usually dominate the acute phase of the illness, many patients experience neurological symptoms (headache, dizziness, fatigue, reduction/loss of smell and taste, myalgia), signs (altered mental status), and unusual/rare disorders (seizures, meningitis, encephalitis, encephalopathy, transverse myelitis, and Guillain-Barre syndrome, among others) [19–28]. COVID-19 has not increased the incidence of epilepsy but has presented patient management and therapeutic challenges [29, 30]. The proportion of patients with COVID-19 reported to have acute new onset neurological disease or symptoms varies significantly depending on the study population, availability of assessment and many other factors; the proportion of these patients in the hospitalized population is also heterogeneous, but in most studies is reported to be 30–60 % [31].

SARS-CoV-2 Distribution. While SARS-CoV-2 is readily detected by reverse transcriptase quantitative polymerase chain reaction in bronchial fluid, sputum, nasal and pharyngeal swabs, detection of virus in serum has varied from 0–40 % [32]. The virus or corresponding antibodies have been only occasionally detected in cerebrospinal fluid and brain tissue [27, 32–35]. Unproven is whether the virus can enter the brain via axonal transfer from nerve terminals in the olfactory and pulmonary epithelium or via the glossopharyngeal, trigeminal and vagus nerves [10, 26]. Neuropathological studies conducted post-mortem have demonstrated multifocal microvascular injury with fibrinogen leakage, microthrombi and spontaneous hemorrhage, perivascular activated microglia, microglial nodules, macrophage infiltrates, and astrogliosis, with neuronophagia in the olfactory bulb, substantia nigra, dorsal vagal motor nucleus, and the medullary respiratory center [33, 36]. Thirty percent of cases in one study showed acute-hypoxic-ischemic changes [33]. Viral protein has been detected in the medulla oblongata and proximal regions of cranial nerves IX and X in association with marked brainstem inflammation attributed to localized immunological responses (cytokine storm) and/or to SARS-CoV-2 infection [37]. Nigrostriatal dopamine dysfunction was reported in three patients who developed parkinsonism 2–5 weeks after severe SARS-CoV-2 respiratory infection [38].

Post-Acute SARS-CoV-2 («Long-COVID»). Virus-associated CNS effects, whether anoxic/ischemic, hemorrhagic or encephalitic in origin, together with damage to other organs (notably, lungs, kidneys and heart) in those with severe COVID-19, compromise health post-hospitalization, especially for those with comorbidities, and result in increased use of medications and excess deaths after 6 months [16, 21, 39–44]. In addition, a significant percentage of adults and children, including those who had mild acute COVID-19, develop post-acute sequelae of SARS-CoV-2 (PASC) [45, 46] that may persist for at least 6 months following the original illness [47, 48] (Figure), with features similar to the pos-SARS syndrome and that overlap with Chronic Fatigue Syndrome and Functional Neurological Disorder [24, 28, 49].

PASC, also known as Long-COVID [50], which is more common in females than males, includes the following manifestations: neurological/neuropsychiatric symptoms (fogginess, headache, dizziness, loss of attention, confusion, mood disorders, sleep-wake disturbances, hyposmia/anosmia and dysgeusia/ageusia), as well as disorders of the gastrointestinal system (abdominal pain, diarrhea) and cardiorespiratory and musculoskeletal systems (fatigue, exercise intolerance, myalgias, dyspnea, cough, arthralgias) [46, 48]. Long-lasting symptoms consistent with autonomic function (breathlessness, chest pain, palpitations and orthostatic intolerance) are also reported [50]. In Moscow, a telephone

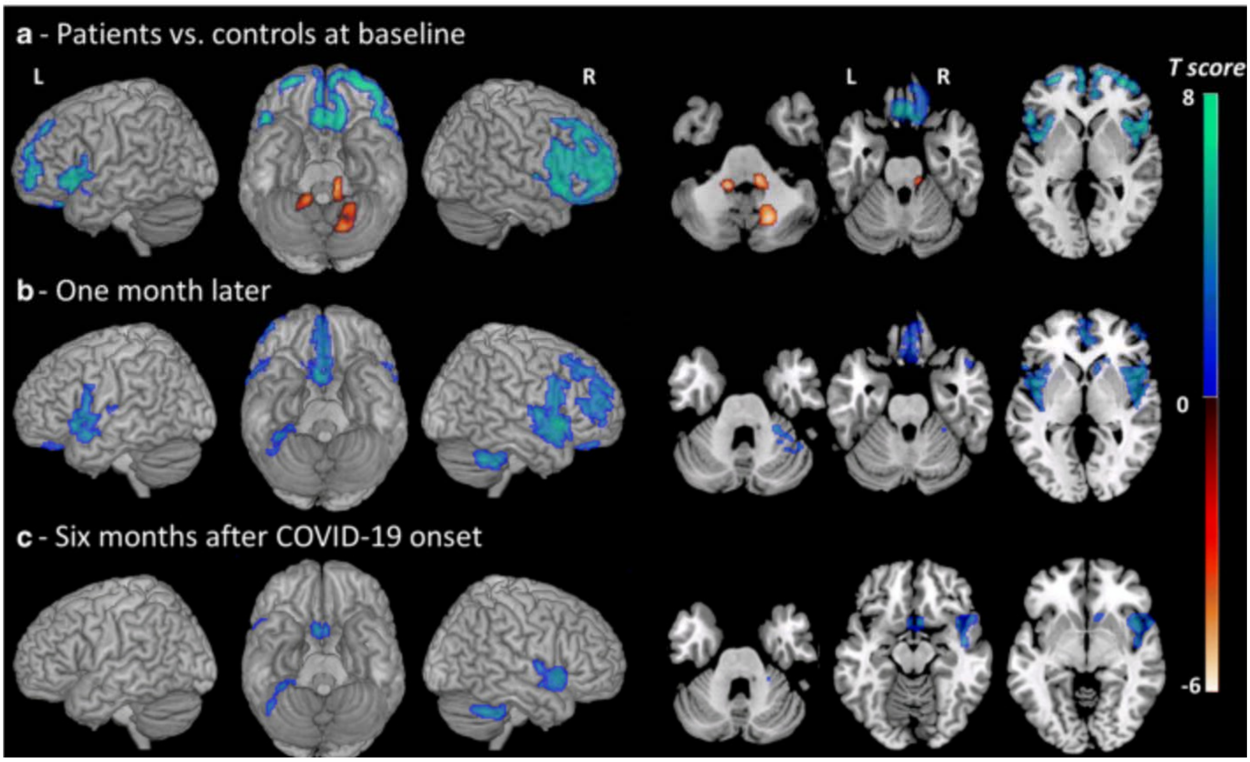

Figure. Brain metabolism changes in COVID-19

N o t e : Brain metabolism changes in COVID-19. Once in the acute phase, 1 month later and 6 months after COVID-19 onset, brain metabolism of seven patients ($n = 7$) with variable clinical presentations of COVID-19-related encephalopathy were examined with 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT). PET images were analyzed with voxel-wise and regions-of-interest approaches in comparison with 32 healthy controls. Hot and cool color scales show regions with hypermetabolism and hypometabolism in patients vs. controls, respectively. Statistical Parametric Maps (https: //www.fil.ion.ucl.ac.uk/spm/) are projected onto a surface rendering and onto axial views of the customized magnetic resonance imaging template. The axial slices are shown using neurological conventions (right is right). R, right; L, left. At baseline, hypometabolism was found in the bilateral prefrontal cortex with right predominance, insula, anterior cingulate and caudate ($p < 0.05$ corrected). Analysis showed a mild hypermetabolism in the cerebellar vermis, dentate nucleus and pons ($p < 0.05$). One month later, hypometabolism was limited to the mediofrontal, right dorsolateral areas, olfactory/rectus gyrus, bilateral insula, right caudate nucleus and cerebellum ($p < 0.001$). Six months after COVID-19 onset, decreased metabolism was observed in the same regions but they were less extended ($p < 0.001$). At this timepoint, the majority of patients had improved clinically but cognitive and emotional disorders of varying severity remained with attention/executive disabilities and anxio-depressive symptoms. Reproduced from Figure 1, legend, and extracted text of Kas A, Soret M, Pyatigoskaya N, Habert MO, Hesters A, Le Guennec L, Paccoud O, Bombois S, Delorme C; on the behalf of CoCo-Neurosciences study group and COVID SMIT PSL study group. The cerebral network of COVID-19-related encephalopathy: a longitudinal voxel-based 18F-FDG-PET study. Eur J Nucl Med Mol Imaging 2021 Jan 15: 1–15. doi: 10.1007/s00259-020-05178-y. [Authors own copyright under exclusive license to Springer-Verlag GmbH, DE part of Springer Nature 2021, with article available via the PubMed Central Open Access Subset for unrestricted research re-use and secondary analysis in any form or by any means with acknowledgement of the original source. These permissions granted for the duration of the World Health Organization (WHO) declaration of COVID-19 as a global pandemic.]

interview study of 2640 COVID-19 male and female patients 6–8 months after their hospital discharge recorded significant fatigue (~21 %), shortness of breath (~14 %) and forgetfulness (~9 %), mood disorders and behavioral changes [45]. In the USA, a large case-control study of non-hospitalized veterans 1–6 months after illness onset found an excess of nervous system, neurocognitive and mental health disorders, and metabolic, gastrointestinal and cardiovascular disorders, including anemia, malaise, fatigue, and musculoskeletal pain, increased use of opioid and non-opioid medication and excess deaths (8/1000) among COVID-19 survivors [39].

Longerterm Concerns. COVID-19 patients might have a higher risk for delayed/long-term neurological and neuropsychiatric sequelae [51, 52]. Persistent hyposmia following SARS-CoV-2 infection is of note because this symptom is an early but non-specific marker of Alzheimer disease, a prominent genetic risk factor (ApoE4) for which is associated with severe COVID-19 [23, 54, 55]. Unknown is whether reservoirs of SARS-CoV-2 remain in immunologically privileged sites (eye, testes, brain), comparable to the persistence of human coronavirus OC43 in mouse brain [27]. ACE2 receptors are present in the human eye [11] where other viruses (Ebola, Marburg or Rubella) can reside after clearance from the systemic circulation [56, 57, 58]. Measles Virus can develop hypermutated forms in vivo that establish latent neuronal infection which, in the event of subsequent immunosuppression, can reactivate and precipitate the fatal neurological illness Subacute Sclerosing Panencephalitis (SSPE) [59, 30]. Persistent or latent brain infection with SARS-CoV-2 is unlikely but has not been ruled out. However, COVID-19 has disrupted global vaccination campaigns, including those for measles, mumps and rubella (MMR) which, given the progressive loss of MMR immunity over time, may result in a resurgence of measles and even higher rates of SSPE in at-risk countries, such as those in southern Asia [60, 61, 62].

In conclusion, SARS-CoV-2 produces a systemic transmissible infection that often impacts the nervous system in the short- and longer-term [63]. In addition to cardiopulmonary and hematogenous disorders that secondarily precipitate brain hypoxic disease, coronaviruses can invade the nervous system and trigger neurological disorders arising from the host's immune response and/or viral propagation in the nervous system [63, 64]. There is an urgent need for global SARS-CoV-2 immunization not only to prevent COVID-19 but also to restore mass vaccination campaigns for common infectious diseases that existed prior to the present pandemic.

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Review

ASSESSING RISKS CAUSED BY NICKEL-BASED NANOMATERIALS: HAZARDOUS FACTOR IDENTIFICATION

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Nanoparticles of nickel (Ni) and its compounds attract a lot of attention bearing in mind their promising innovative properties allowing their use as catalysts, components in electrical appliances, electronic and photonic devices, and materials used in producing medications, diagnostic preparations, and pesticides. Production volumes of these materials in their nano-form are likely to grow rapidly in the nearest future and it involves greater loads created by these nanomaterials on a human body. And we should remember that Ni and its compounds are highly toxic for humans even in their traditional disperse forms. Their toxicity induces oxidative stress, cellular membranes and mitochondria dysfunction, expression of nuclear transcription factors that are responsible for apoptosis, caspases, as well as proto-oncogenes. Leading role in toxicity of Ni-containing nanomaterials obviously belongs to ions of heavy Ni++ being emitted from them since this heavy metal has pro-oxidant properties and influences enzyme activity and gene expression. Cytotoxic effects produced by Ni-containing nanomaterials were revealed in model experiments in vitro performed with suitable cellular cultures that were morphologically and functionally similar to epithelial cells of respiratory and gastrointestinal tract, liver, kidneys, and nervous system; these materials were able to stimulate oxidant stress, influence expression of apoptosis proteins and nuclear transcription factors, induce apoptosis and necrosis. There are data indicating that Ni-containing nanomaterials can produce malignant transforming effects in vitro. All the above mentioned proves that nickel compounds in their nanoform are a new hazardous factor that requires assessing related risks for workers, consumer, and population in general.

Our review focuses on analyzing literature sources on cytotoxicity of Ni-containing nanomaterials and their effects produced on molecular-genetic and cellular levels taken over a period starting from 2011.

Key words: *nickel, nickel oxide, nanoparticles, cytotoxicity, genotoxicity, transforming ability, apoptosis, gene expression, risk assessment.*

Nanoparticles (NPs) of nickel (Ni) and its compounds are given special attention since they seem promising for innovative use in engineering, consumer goods manufacturing, and in medicine. Starting from the beginning of the 20th century, metallic Ni has been used as a catalyst in food and technical fats hydrogenation [1]. A basic drawback of this technological process is that it involves side creation of unsaturated fatty acids trans-isomers in substantial quantities; it happens owing to hydrogenation process being far from thermodynamic equilibrium since substrate molecules diffusion to nickel catalyst surface is kinetically limited. It is possible to substantially reduce these effects via using a catalyst based on nickel NPs immobilized on inert carriers (silicon dioxide or carbon) [2]. A wide range of such catalysts is reported to be synthesized and they contain NPs with their size being both less than 10 nanometers (so called cluster particles) and significantly greater [3]. Nano-structured Ni-containing catalysts are also applied in technologies involving fine organic synthesis, pharmaceutical industry included [4].

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Ni NPs are applied in electronics, electrical engineering and optoelectronics due to their unique magnetic and electrochemical properties. Thus, there are data on creating memory elements based on nano-rings made of Ni NPs [5]. Heterostructures based on Ni-NPs, NiO-NPs, as well as carbon nanotubes and graphene are used to make electrodes in rechargeable batteries with high electric capacity [6], multilayer ceramic super-condensers [7] and solar batteries [8]. Highly sensitive magnetic and chemical sensors have been developed that are based on Ni-containing nanoparticles [2]; these sensors are applied in medical diagnostics to detect tumor cells [9]. Ni NPs can be deliberately used in cosmetic products including tonal creams and dye stuff or accidentally penetrate into them [10]. Therapeutic use of Ni NPs and NPs of its alloys with copper includes controlled magnetic hyperthermia and theranostics [11]. Finally, there are some developments on using NPs of Ni and its compounds produced via biotechnological procedures as insecticides aimed at controlling population of mosquitoes that are communicable diseases carriers [12, 13].

In 2019 annual production of nano-sized Ni and its compounds was estimated as being equal to 20 tons only in the USA and tended to grow in future [14].

All these data indicate that NPs of Ni and its compounds are nanotechnological products with great prospects for their production to grow in the nearest future and it will unavoidably result in greater exposure to these nanomaterials, both for people and ecosystems [15]. Health risks that are likely to occur due to it are caused by Ni and its compounds being highly toxic even in their traditional dispersion. Multiple experimental and epidemiologic research works have revealed that metallic nickel and its compounds are carcinogenic (see early papers reviewed in [16]). Basing on these data IARC ranked Ni (II) compounds into Group 1 (carcinogenic for people) whereas metallic Ni is classified as Group 2B (possibly carcinogenic for people). Ni compounds are also known to be highly allergic [17]. After the paper by Kornick and Zug on nickel dermatitis epidemiology was published in 2008 [18] nickel was chosen as “the allergen of the year” by the American Contact Dermatitis Society.

There are growing concerns that NPs of Ni and its compounds may penetrate a body much more easily through respiratory tracts, gastrointestinal tract, or skin than their macrodisperse analogues due to their very small size; it may result in all the above mentioned adverse effects being aggravated. Ni nanoforms are especially alerting as adverse occupational factors (in chemical industry, metallurgy, electrical engineering and other branches) where risks caused by workers’ exposure are the highest [15, 19].

All this indicates that it is necessary to assess potential health risks caused by Ni compounds in nanoform as independent adverse factors. According to the methodology applied in Russia[1] risk assessment includes several necessary preliminary stages such as hazard factor identification and assessment of “dose – response dependence, that is, qualitative characteristics of a hazard. The first element in risk assessment involves analyzing mechanisms of toxic effects, toxicity signs, and biomarkers that allow identifying adverse impacts exerted by an examined chemical on a body.

The goal of the present review was to analyze and generalize data on identifying Ni-containing nanomaterials as hazardous factors basing on results obtained via experiments *in vitro* and on assumed molecular-genetic, biochemical, and cytological mechanisms of their toxic effects. And the greatest attention is paid to data published over the last decade (starting from 2011) and available in sources that conform to conventional requirements regarding scientific validity and completeness and contained in international abstract databases PubMed, WoS and Scopus.

[1] R 2.1.10.1920-04. The guide on assessing health risks for population under exposure to chemicals that pollute the environment. The Guide. Moscow, The Federal Center for State Sanitary and Epidemiologic Surveillance of the RF Public Healthcare Ministry Publ., 2004, 143 p.

Cytotoxicity of Ni-containing nanomaterials. Cytotoxicity is understood in literature as an ability of substances to reduce cells viability and produce damaging effects on them at morphological and metabolic levels under incubation *in vitro*. As for NPs of Ni and its compounds, research on their cytotoxicity has been intensely accomplished starting from early 2000-ties [20]. Cytotoxicity studies do not give a direct answer to a question on a value of toxic doses for a body as a whole; however, they are useful, first of all, as a tool for screening potentially toxic nanomaterials and, secondly, they provide valuable data on molecular mechanisms and biomarkers of their effects produced on cells and, consequently, on a body as a whole.

Most toxicological studies *in vitro* are performed on unlimitedly dividing cells in a culture that, as a rule, are tumor ones. Nevertheless, all these cells have analogues among normal cells in organs and tissues and they are similar to these analogues as per morphofucntional, genome, and metabolome parameters. Therefore, it is quite relevant to consider available data in a sequence that reflects effects produced by Ni-containing NPs on cells in organs that are targets for effects produced by nanomaterials under actual exposure.

Respiratory organs cells. NPs of metallic Ni and NiO, but not Ni microparticles (MPs), were captured by epithelial cells in the human lungs belonging to H460 line and primary cells in bronchial epithelium; Ni++ ions were released from absorbed particles of both types [21]. Ni NPs, NiO NPs and $NiCl_2$ solution caused stabilization and nuclear translocation of transcription factor HIF-1α induced by hypoxia and it resulted in elevated contents of its target NRDG1 (Cap43). Ni microparticles (MPs) didn't produce such effects whereas HIF-1α activation caused by exposure to NPs was even more apparent than under exposure to a salt form. NiO NPs were equally toxic for cells from both lines, Ni microparticles were not toxic, and Ni NPs toxicity was intermediate. Caspases and poly- (ADP-ribose) polymerase were activated in all cases of toxicity that indicated apoptosis was developing.

NiO NPs turned out to be cytotoxic in experiments on human bronchial epithelial cells HEp-2 and breast cancer cells MCF-7 as they induced developing oxidation stress, glutathione quantity depletion, and lipid peroxides accumulation. There was caspases-3 activation, DNA fragmentation, and apoptosis markers expression. Effects produced by NPs on cells could be blocked by adding curcumin [22]. Micronucleuses appeared in lung epithelial cells of V79 hamster under exposure to NiO NPs sized 30 nm in concentrations equal to 250 and 2,500 µg/ml. DNA fragmentation was observed in a comet assay under exposure to NPs in concentration being equal to 62 µg/ml and higher [23].

NiO NPs toxicity was examined on two lines of human lung cells under exposure to doses varying from 20 to 100 µg/ml; the research revealed that concentration of reactive oxygen species (ROS) grew already 45 minutes after exposure started; after 24 hours a significant number of cells died due to both necrosis and apoptosis [24]. It was accompanied with interleukins IL-6 and IL-8 appearing in large quantities and the process was mediated with MAPK kinase signal pathway that induced activity of NF-kB transcription factor. There was also disrupted cell cycle, genotoxic effects, and damage to DNA. All the above mentioned effects were observed both in A549 cells that absorbed NPs actively and in BEAS-2B cells though endocytosis was not typical for them.

In the work [25] performed on cells from A549 line NPs of Ni and NiO and Ni MPs caused changes in mitochondrial activity and increased cells proliferation; the effects were dose-dependent. When A549 cells were exposed to Ni NPs, it resulted in lower viability and damage to DNA; and it should be noted that metallic NPs had greater genotoxicity than MPs even in doses that were similar as per Ni contents, and they also stimulated greater oncogenes activation [26]. A549 cells exposure to sub-lethal NiO NPs doses was accompanied with signs of epithelial-mesenchymal transitions mediated with activation of TGF-β1/Smads – signal pathway. It was supported by stronger expression of type 1 collagen, TGF-β1, p-Smad2, p-Smad3, α-actin, vimentin, E-cadherin and fibronectine, that is, changes that characterized fibrosis development at tissue level. SB431542 substance being an antagonist to TGF-β1 was able to block these changes [27]. When A549 cells were exposed to NiO NPs (20 nm in diameter), there was a growth in expression of hemoxigenase-1 (HO-1) and surfactant protein-D, that is, genes regulated by hypoxia-induced transcription factor HIF-1α [28]. These data coincided with those obtained on an alternative cell model in the work [21].

Oxidation stress induced by NiO NPs in A549 cells could be partially blocked by essential oil from *Pistacia lentiscus* that contained terpenoids [29].

BEAS-2B human bronchopulmonary epithelium cells were exposed to NiO NPs in concentrations equal to 5, 10 and 20 μg/ml; there was a decrease in expression of SIRT1 histone deacetylase and it resulted in gene p53 hyper-acetylation and Bax (Bcl-2 associated X protein) hyper-expression. An effect related in SIRT1 inhibition could be removed by resveratrol administration. These data indicate that SIRT1 can be a key molecule in developing cellular toxicity of Ni-containing nanomaterials [30]. When cells from this line were cultivated for 6 months with very low doses (0.5 μg/ml as per Ni) of Ni NPs, NiO NPs, or $NiCl_2$ salt, there were significant changes in trascriptome though cells viability was seemingly preserved [31]. The greatest number of genes (197) that responded via changes in their expression was detected for the salt form. There were changes in expression of *S100A14* и *S100A2 (*Ca-binding proteins) genes as well as *TIMP3*, *CCND2, EPCAM, IL4R* and *DDIT4* under exposure to all Ni forms. Bioinformatics analysis allowed revealing signal pathways of IL-1α, IL-1β and VEGF-A cytokines as targets for Ni nanoforms.

Ni and NiO NPs were effectively captured by BEAS-2B cells in a culture [32]. Unlike, Ni++ ions penetrated into cells rather poorly. Ni and NiO nanoforms and Ni salt induced chromosome aberrations, DNA breaks, and intracellular ROS accumulation in exposed cells. It was accompanied with a growth in intracellular Ca quantity, and adding up chelating agents resulted in lower genotoxicity signs. Genotoxicity and mutagenicity of Ni NPs (approximately 100 nm) and NiO (approximately 50 nm) in comparison with $NiCl_2$ salt was examined for HBEC human bronchial epithelial cells via a comet assay and dyeing against γ-H2AX (H2A histone family member X). Both NPs types aggregated intensely in a cultural medium. There was a growth in a number of DNA breaks under exposure to NiO NPs and to a lesser extent to Ni NPs; there were no such effects revealed under exposure to soluble Ni salt in comparable doses [33].

Cells of organs in the gastrointestinal tract. Intestine epithelium is among primary targets for NPs under oral exposure. In the work [34] toxicity of NiO NPs sized 15 nm was revealed in Caco-2 human cells culture that were similar to the small intestine enterocytes. NPs caused a 50 % drop in cell survivability in a concentration equal to 352 μg/ml; oxidation stress and damage to DNA, in a concentration equal to 30–150 μg/ml. Apoptosis was a primary mechanism of cell death.

Human HepG2 cells that were hepatocytes analogues were exposed to NiO NPs (44 nm in diameter) and it resulted in dose-dependent oxidation stress development and cells death, micronucleuses formation, chromatin condensation, Bax and caspases-3 expression, and Bcl-2 inhibition; it indicated that apoptosis was developing. All these processes were inhibited by ascorbic acid [35]. In the work [36] the same cell line was exposed to metallic Ni NPs that were 28 nm in diameter and in a concentration equal to 25–100 μg/ml; it resulted in dose-dependent oxidation stress. A great number of cells in subG1 phase in cellular cycle was revealed under exposure to sub-lethal NPs dose and it indicated that apoptosis was induced. There was also caspase-3 expression and apoptotic DNA fragmentation, an increase in p53 expression and Bax/Bcl-2 ratio with simultaneous loss of mitochondrial membrane potential that indicated cell apoptosis was developing as per “mitochondrial” way.

Damage to DNA was analyzed in HepG2 cells via a comet assay; the analysis revealed that there was a 26-time increase in DNA fragmentation under exposure to NiO NPs in a concentration equal to 0.1 μg/ml. Simultaneously flow cytometry revealed elevated ROS concentrations. There was also stronger expression of superoxide dismutase (SOD) as well as p53, Bax and Bcl2 [37]. Transcriptional analysis using total RNA-sequencing revealed [38] that changes in expression of HepG2 cells genes occurred when NiO NPs concentrations exceeded 5 μg/ml. Expression of hypoxia-related HIF-1α and micro-RNA(miR)-210 grew under exposure to 25–100 μg/ml of these NPs; and there were variable changes in trascriptome including activations of glycolysis metabolic pathways, glutathione synthesis, lysosome digestion and autophagy even under exposure to concentrations that didn't cause any apparent cytotoxic effects. There was a growth in intracellular NO and calcium contents, and greater esterase activity as well as disorders in mitochondria membrane potential. Cell cycle deregulation became apparent via appearing 30.5 % subG1 apoptotic peak. Therefore, cytotoxicity of NiO NPs for liver cells becomes apparent predominantly via hypoxia and oxidation stress that causes transcriptome changes, apoptosis, and DNA fragmentation.

Data in the work [39] indicate that NiO NPs may produce fibrogenic effects on liver cells; it was shown that HEPG2 cells exposure to these NPs in a concentration equal to 100 μg/ml resulted in elevated expression of TGF-β1, p-Smad2, p-Smad3, α-actin-smooth muscles, matrix metalloproteinase (MMP) of isoform 9, tissue inhibitor of metalloproteinase (TIMP)-1 and reduced E-cadherin and Smad7.

There was a single research work [40] that concentrated on comparing cytotoxicity of Ni NPs, NiO NPs, and $Ni(OH)_2$ NPs for bronchoalveolar A549 cells and hepatocytes-like HepG2 cells. Metallic Ni NPs turned out to be significantly more toxic for the first of these two lines, and there were no similar differences detected for oxide NPs. Basic cytotoxicity mechanisms were oxidation stress, disorder in mitochondrial membrane potential and caspase-3 synthesis induction that resulted in apoptosis development. Cytotoxicity of different NPs types given as per a nanomaterial mass correlated with their specific surface area and solubility in biological environment.

Kidney cells. An experiment on NRK-52E kidney tubule epithelial cells revealed that NiO NPs with average size being 10–20 nm and in a dose equal to 0–500 μg/ml were captured by cells and induced dose-dependent increase in contents of malonic dialdehyde, 8-oxo-2-deoxyguanosine (8-oxo-G) – DNA oxidation destruction product, and carbonylated protein, as well as glutathione reserves depletion. When concentrations of these NPs exceeded 290 μg/ml, it resulted in death of more than 50 % cells via both apoptosis and necrosis [41].

Skin cells. Metallic Ni NPs were cytotoxic and genotoxic for epidermal A431 human skin cells in concentrations varying from 2 to 20 μg/ml and exposure to them resulted in apoptosis and damage to DNA [42]. Cell death was accompanied with oxidation stress, glutathione reserves depletion, and caspase-3 activation; these effects were inhibited by N-acetylcysteine indicating that cell thiols, glutathione in particular, might probably have protective functions regarding toxic effects produced by NPs. There was an experiment when epidermal mice cells belonging to line JB6 were exposed to Ni NPs in a tetrazolium dye (MTT) assay; NPs turned out to be more cytotoxic in comparable concentrations than corresponding MPs. Both Ni forms caused apoptosis but NPs were more active [43]. Ni NPs induced expression of activator protein-1 (AP-1) and NF-κB in the same cells and these effects were inhibited by epigallocatechin-3-gallate (EGCG). EGCG was shown to weaken NPs cytotoxicity due to inhibiting a response by MAPK-signal pathway [44].

Immune cells. The work [45] concentrated on studying NiO cytotoxicity in lymphocytes extracted from human peripheral blood. Primary NPs size was 18 nm; they aggregated intensely in water media. IC50 amounted to 24 μg/ml after 24 hours of exposure. A comet assay and micronucleuses analysis revealed that NPs were highly genotoxic. Lymphocytes primarily died via apoptosis induced by ROS and lipid peroxides production.

Intact and oxide-passivated Ni NPs induced stronger expression of miR-21, MMP-2, MMP-9, as well as TIMP-1 and TIMP-2 in primary mice monocytes. These effects were not observed in mice cells with knocked-out gene miR-21 as well as in wild mice cells under exposure to Ni NPs covered with a carbon layer. These data indicate that miR-21 plays a significant role in inducing an inflammatory response to nickel NPs [46].

Reproductive system cells. An experiment performed on primary Sertolli cells of rat testis revealed that Ni NPs stimulated apoptosis with participating *Igfbp3* genes, non-coding RNA *LOC102551356* and mitochondrial mechanism. *Igfbp3* is seen as a target gene in p53-mediated apoptosis [47]. Effects produced by Ni NPS on Gc-1 line cells that were similar to mice stem sperm cells were accompanied with changes in ultra-structure, cell cycle delayed in phase G1, and activation of apoptosis as per inhibition of PI3K/AKT/mTOR signal pathway [48].

Embryonic cells. The work [33] concentrated on Ni NPs genotoxicity that became apparent via breaks in single-stranded DNA in mice embryonic stem cells belonging to line mES via using Hprt test based on reporter *HPRT* (Hypoxanthine Phosphoribosyltransferase) gene mutation; experiments were also performed on six lines of mice embryonic stem cells reconstructed in such a way so that they could respond with fluorescence to development of some genotoxicity and malignant transformation (so called “ToxTracker” assay). It is interesting that Ni NPs produced more apparent genotoxic effects in these systems in comparison with NiO NPs and Ni chloride solution.

Connective tissue cells. The work [49] dwelled on studying Ni NPs genotoxicity and mutagenicity for fibroblast cells of Chinese hamster lungs under exposure on the air-water interface. More than 50 % cells died after 48-hour exposure to NPs in quantities equal to 0.15 and 0.32 μg/cm^2 of the culture surface with a growth in a number of breaks in DNA chains and this growth was enhanced significantly after exposure to an inhibitor of single-stranded DNA reparation.

Neurons. NiO NPs with average diameter being 15.0 nm were captured in a dose-dependent way by neuron-like SH-SY5Y cells and caused death of 50 % cells in a dose equal to 229 μg/ml. There were morphological changes, a 3–11-time growth in DNA fragmentation and 80–99 % apoptosis together with oxidation stress [50]. The same NPs were shown in the work [51] to induce does-dependent apoptosis in cells from this line. To get an insight into effects produced by Ni-containing NPs on neurons, thermodynamic modeling was performed; it revealed how Ni NPs interacted with tau protein. As a result, there was expression of apoptosis gene Bax and in increase in Bax/Bcl-2 ratio, greater lactate dehydrogenase and caspases 3 and 9 activity. In further research [52] it was shown that exposure to NiO NPs in high doses induced oxidation stress and apoptosis of SH-SY5Y cells whereas in case doses were non-lethal, there was prevailing interaction between nanomaterial and tau-protein structures together with an increase in hydrophobic tau and formation of its amorphous aggregates.

Effects produced by NiO and Mn_3O_4 NPs with diameters varying from 12 to 24 nm on neuronal human cells were examined via comparative analysis in the work [53]. To analyze multiple data that characterized cytotoxicity, response surface methodology was applied and it, according to the authors' opinion, allowed extrapolating obtained results onto effects produced by NPs *in vivo*. It was shown that NiO NPs were less toxic for neuronal cells than Mn_3O_4 NPs; however, in case they were introduced together, NiO NPs made a prevailing contribution into cytotoxicity. The authors performed statistical analysis that revealed variable combined toxic effects depending on particles nature, size, and concentration. A primary factor that reduced cytotoxicity was NPs solubility in biological environment that decreased when fetal bovine serum was added to the examined cell cultures.

Transforming activity in vitro. Data obtained in some works discussed above indicate that exposure to NPs of Ni and Ni-containing compounds may induce processes similar to malignant transformation. Thus, the authors of the work [21] believe that persistent activation of HIF-1α signal pathway in cells induced by Ni and NiO NPs may result in malignant transformation with subsequent tumor development *in vivo*. An experiment performed on epidermal mice cells JB6 [54] revealed that exposure to Ni NPS sized 50 nm led to activated synthesis of tumor transformation promoter activator protein-1 and NF-κB as well as elevated expression of R-Ras, c-myc, C-Jun, p65 and p50 that was not compensated with significantly lower expression of pro-apoptotic factor p53. The authors applied cultivating on soft agar and revealed that cells treated with Ni NPs tended to form colonies and it was considered to be similar to malignant growth. It is interesting that expression of p53 turned out to be a prevailing outcome in case cells were exposed to Ni MPs (micron-sized). Multiple DNA breaks detected in human bronchial epithelial cells exposed to NPs of Ni and NiO are also seen as a precondition of malignant transformation [33]. It is difficult to interpret facts obtained within *in vitro* systems since it was noted in most works that pro-apoptotic factors, including Akt-kinase and p53 were expressed simultaneously with oncogenes activation under exposure to Ni-containing nanomaterials [43]. Probable differences in assessing genotoxicity and transforming ability of Ni nanoforms in different test-systems *in vitro* might be related to differences between cell lines used in experiments regarding NPs capture by cells. Presumably, macropinocytosis or clathrin-mediated endocytosis are mechanisms used by cells to capture Ni NPs [55]. Particles absorption can depend on Ca++ ions concentration in a cultivating medium as well as on particles sizes, charge and surface properties.

Besides, we should bear in mind that vast majority of data on genotoxicity and "carcinogenic" activity of Ni-containing nanomaterials were obtained via experiments on cell lines that were, to a greater or lesser degree, already transformed in comparison with their primary analogues. Therefore, it is obviously impossible to give an unambiguous answer to a question whether Ni and NiO NPs can produce carcinogenic effects if we rely solely on data obtained in experiments on cellular cultures.

Molecular and cellular cytotoxicity mechanisms. Data obtained via studies *in vitro* allow making well-substantiated conclusions on molecular and cellular cytotoxicity of Ni-containing NPs.

Oxidation stress. Oxidation stress develops due to imbalance between (predominantly fermentative) oxidation of organic substrates in metabolic processes and antioxidant system activity. The process is accompanied with ROS being synthesized in elevated quantities that exceed abilities of a body to eliminate them; it results in irreversible oxidative damage to proteins and membrane lipids. Excessive ROS can damage mitochondria which, due to that, can intensify ROS accumulation themselves; that is, oxidation stress can develop as per positive feedback mechanism with ultimate mitochondrial apoptosis activation [20].

Oxidation stress is seen as a basic nanotoxicity type and it occurs due to exposure to a great number of artificial nanomaterials. Some of them are relatively chemically inert and poorly soluble in biological media (for example, NPs of Si, Ti, Ce, Zr, and Al oxides) and exposure to them induces oxidation stress via non-fermentative catalytic ROS generation at an interphase surface between NPs and a medium [56]. In case of exposure to carbon nanotubes oxidation stress seems to develop due to hyperproduction of oxidants by cells (first of all, macrophages) that are primary targets for effects produced by this nanomaterial. Bearing in mind that Ni-containing NPs are highly soluble, we can assume that the latter of the above mentioned mechanisms is combined with influence exerted by Ni ions on fermentative systems that are responsible for balance between ROS synthesis and elimination [20].

Damage to cells and their membranes caused by effects produced by ROS can be a basic Ni NPs toxicity mechanism due to Ni++ being able to bind to amino acids, polypeptides, and enzymes thus inducing ROS synthesis [57]. A contribution made by oxidation stress into cytotoxicity of Ni-containing NPs is also confirmed by multiple facts of their effects being inhibited by antioxidants introduction [29, 35, 42, 44].

Apoptosis. Apoptosis is programmed cell death with a very complicated mechanism that includes actions performed by cysteine proteases family, proteins p53, Bcl-2, and others. There are two basic ways of apoptosis, namely death receptor way and mitochondrial way [20]. The first one basically involves apoptotic factor Fas (CD95) and Fas-associated death domain (FADD) protein creating a Fas-associated death-inducing signaling complex (DISC) with lamin A and β-actin disintegration that can bind and activate caspase-8 and the following caspase-3. Mitochondrial apoptosis includes caspase-dependent and caspase-independent pathway. The first of them involves Bax and Bak factors binding to mitochondria membranes thus releasing cytochrome C from them. It, in its turn, creates apoptotic complexes with adapter protein Apaf-1 and caspase-8 that activate caspase-3 and the latter induces apoptosis. Caspase-independent apoptosis flows as follows: a factor that induces apoptosis (AIF) is directly released by mitochondria into cytoplasm where it penetrates a nucleus and DNA is destroyed [16]. Apoptosis induced by NPs of Ni and its compounds includes both the death receptor way and those mediated by mitochondria. It follows from the data on an experiment on female rat ovaries exposed to Ni NPs where these particles simultaneously increased levels of such pro-apoptotic factors as caspase-3, caspase-8, caspase-9, Fas, Bax, Bid, cytochrome C and AIF and decreased levels of anti-apoptotic factor Bcl-2 [58]. As per data taken from the work [43], cytotoxicity of Ni NPs mostly develops due to apoptosis induced by a death receptor, namely, Fas activation. However, it was shown in the same work that Ni NPs activated Bcl-2 and, as a result, cytochrome C was not released from mitochondria into cytoplasm and this way of apoptosis didn't obviously occur.

Similar results were obtained in the works [54, 59], where it was shown that cytochrome C release was inhibited by Bcl-2 under exposure to Ni NPs. Bcl-2 is known to be a variety of proto-oncogene that can inhibit apoptosis [20]. Therefore, Ni NPs can paradoxically not only stimulate but also inhibit apoptosis due to Bcl-2 activation and thus they induce cellular "carcinogenesis". It was also revealed [54, 59] that Ni NPs inhibited expression of pro-apoptotic factor p53. If p53 activation is reduced, apoptosis medicated by caspase-3 and caspase-8 is inhibited and it can ultimately result in tumor occurrence.

Damage to DNA and genotoxicity. Cell cycle is known to consist of four phases; they are DNA synthesis prophase (gap phase G0/G1), DNA synthesis phase (phase S), DNA synthesis anaphase (gap phase G2) and mitosis phase (phase M). Gap phase G0/G1 is a key to a proper start of a cell cycle. In case phase G0/G1 is blocked, cells will not go to mitosis and proliferation and it will ultimately result in apoptosis. Phase G0/G1 in human epidermal cells is blocked by Ni NPs in concentrations equal to 2.5 and 5 μg/ml and it leads to apoptosis whereas phase G2/M is blocked by Ni NPs in concentrations equal to 7.5 and 10 μg/ml and it results in a great number of DNA breaks [44]. These results provide an insight into a reason why low Ni NPs concentrations promote apoptosis whereas Ni NPs in high concentrations damage cellular DNA and induce mutagenesis with probable further malignant transformation.

MAPK signal pathway. MAPK signal pathway also known as mitogen-activated protein-kinase pathway includes three parallel pathways, namely ERK pathway, JNK/SAPKK pathway, and P38MAPK pathway. Further on the MAPK pathways for signal transfer there are two transcription factors, activator protein-1 (AP-1) and nucleus factor-jB (NF-jB) that participate in regulating multiple important cell activities such as proliferation, cells differentiation and apoptosis. AP-1 is a dimer that consists of c-Fos and c-Jun subunits and NF-jB is a dimer that consists of p65 and p50s subunits. Three MAPK pathways play an important role in carcinogenesis. ERK1/2 is activated via phosphorilation that regulates with c-Fos, c-myc and C-Jun thus increasing activity of transcription factor AP-1. Ultimate kinases JNK can also be activated via phosphorilation; they phosphorilate C-Jun and then AP-1. P38MARK phosphorilation results in IjB and NF-jB depolymerization. Expression of R-Ras, c-myc, C-Jun, p65 and p50 proteins grows slowly under exposure to Ni NPs, moreover Ni NPs, in comparison with Ni MPs, are more likely to stimulate greater AP-1 and NF-jB activity [54]. Exposure to Ni NPs in concentrations being higher than 2.5 μg/ml resulted in a substantial increase in expression of phosphorilated ERK1/2 (p-ERK1/2), phosphorilated JNK (p-JNK) and phosphorilated P38 (p-P38) [44]. Therefore, Ni NPs turned out to be able to activate AP-1 and NF-jB in model *in vitro* systems via MAPK signal pathway and it could untimely result in malignant transformation.

HIF-1a signal pathway. Hypoxia-induced factor-1 (HIF-1) is a heterodimer that consists of HIF-1α and HIF-1β subunits [20]. HIF-1α is responsible for the complex activity and is initially localized in cytoplasm where as HIF-1β is expressed both in cytoplasm and nucleoplasm and its function is to stabilize the active complex. HIF-1α translocation into a nucleus under exposure to Ni-containing NPs is considered by some authors to be a key element in their fibrogenic, genotoxic, and transforming activity. As per data obtained in experiments on human monocytes exposure to Ni NPs in concentrations equal to 10 and 30 μg/ml resulted in an increase in contents of HIF-1α that participated in MMP-2 and MMP-9 and TIMP-1 activation [60]. HIF-1α pathway is assumed to participate in abnormal expression and changed activity of MMP induced by Ni NPs. Besides, HIF-1α pathway activation may lead to malignant transformation of cells and tumor occurrence. Ni NPs are known to activate HIF-1α pathway more intensely in comparison with Ni MPs or its soluble salt [21].

Figure shows a hypothetic chain of events occurring under exposure to Ni-containing nanomaterials at cellular level.

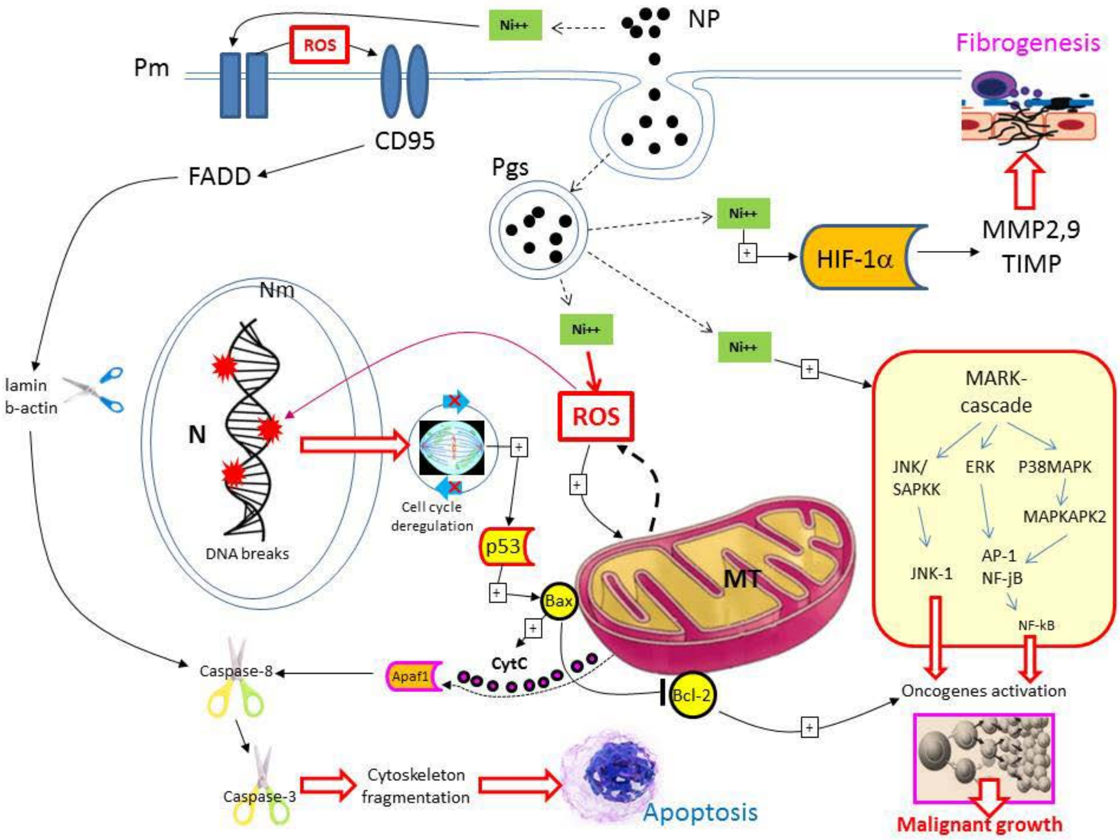

Figure. Basic outlines and targets of toxic effects produced by NPs of Ni and its compounds at cellular level

Note: NPs are nanoparticles; Ni++, nickel ions; Pm, plasmatic membrane, Nm, nuclear membrane; N, nucleus; MT, mitochondria; Pgs, phagosome/phagolysosome; ROS, reactive oxygen species; [+], stimulation; [⊥], inhibition.

Table 1

The most significant biomarkers showing cytotoxic effects produced by Ni-containing nanomaterials in vitro

No.	Biomarker	Abbreviation	Cell model (analogue)	Source
1	Hypoxia-induced factor	HIF-1α	Lung epithelium cells	[21]
2	A member of N-myc inhibited proteins family	NRDG1	The same	[21]
3	Nuclear transcription factor	NF-κB	The same	[24]
4	Interleukins	IL-1α, IL-1β, IL-2, IL-6, IL-8, INF-γ	The same	[24]
5	Transforming growth factor	TGF-β1	The same	[27]
6	Hemoxigenase 1	HO-1	The same	[28]
7	Apoptosis inhibitor	Bcl-2	Liver cells	[35, 43]
8	Bcl-2-associated X-protein	Bax	Lung epithelium cells	[30]
9	Matrix metalloproteinase	MMP 2, 9	Liver cells, leukocytes	[39]
10	Tissue inhibitors of metalloproteinase	TIMP 1,3	Lung epithelium cells	[31]
11	Interleukin 4 receptor	IL-4R	The same	[31]
12	Micro-RNA 210	miR210	Liver cells, leukocytes	[38, 46]
13	8-oxo-2-deoxyguanosine	8-oxo-G	Kidney cells	[41]
15	Tumor transformation promoter	AP-1	Skin cells	[54]
16	Proto-oncogenes	R-Ras, C-myc, C-Jun, p65, p50, JNK1	Skin cells	[54]
17	Apoptotic antigen 1	Fas (CD95)	Skin cells	[43]

Table 1 summarizes data on the most informative biomarkers showing toxic effects produced by Ni-containing nanomaterials revealed in experiments on cell cultures.

Conclusion. Therefore, literature analysis has revealed that NPs of metallic nickel and its compounds (NiO, $Ni(OH)_2$) as well as nickel nanofiber and nanorods are highly toxic. At cellular level such apparent toxicity signs are detected as oxidation stress, disorders in cellular membranes and mitochondria functions, expression of nuclear transcription factors that are responsible for apoptosis, caspases, as well as some proto-oncogenes. It is a paradox, but both apoptosis stimulation and its inhibitions with inducing malignant transformations are typical for NPs of Ni and its compounds at different doses. Presumably, these contradictory effects occur due to difference in sensitivity to high and low doses of Ni++ ions in a chain of apoptosis that is mediated by mitochondrial Bax/Bcl-2 and a cascade of oncogenes activation via MAPK-signal pathway. There seems to be no principle differences in toxic effects produced by nanomaterials based on Ni, its oxide, as well as its soluble salts (chloride, nitrate, and sulfate) on cells; so, we can conclude that it is Ni++ ions emission from them that plays the leading role in toxicity of these nanomaterials. Ni-containing nanomaterials differ substantially in this respect from those nanoparticles that are practically insoluble in biological media such as previously described nanoparticles of amorphous silicon dioxide [61] with the greatest contribution into their toxic effects being made by catalytic ROS generation on their surface; as well as partially soluble silver nanoparticles that exert intense influence on microelement homeostasis [62]. But at the same time, effective doses detected for NPs of Ni and its compounds turn out to be lower than those detected for its soluble salts and it highlights the significant role in cytotoxic effects that belongs to ability of these nanomaterials to penetrate into cells more easily.

The next necessary stage in risk assessment is to characterize a hazard, that is, to determine toxic and no-observed adverse effect levels (NOAEL) of an adverse chemical factor for different ways it can penetrate a body, that is, through respiratory organs, undamaged skin or gastrointestinal tract. Such data can't be obtained only via *in vitro* testing since such studies don't take into account biokinetic regularities of an adverse factor, its ability to penetrate through biological area and bioaccumulation; so, it is necessary to perform experiments *in vivo* on laboratory animals as well as to generalize available data obtained via clinical observations. All these issues in relation to Ni-containing nanomaterials will be dealt with in the next review.

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Abbreviations: 8-oxo-G – 8-oxo-2-desoxyguanosine; MMP – matrix metalloproteinase; MP – microparticles; NP – nanoparticles; ROS – reactive oxygen species; Bax – Bcl-associated X-protein; Bcl-2 – intracellular apoptosis regulator; HIF – hypoxia-induced factor; HO-1 – hemoxygenase-1; IARC – Internaitonal Agency for Research on Cancer; IC50 – 50 % inhibition concentration; IL – interleukin; INF – interferon; MAPK – mitogen-activated protein kinase; miR – micro-RNA; p53 – apoptosis stimulating factor; SOD – superoxide dismutase; TGF – transforming growth factor; TIMP – tissue inhibitor of metalloproteinase

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