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Research article

ON ASSESSING IMPACTS EXERTED BY OBJECTS OF ACCUMULATED ENVIRONMENTAL DAMAGE ON HUMAN HEALTH AND LIFE EXPECTANCY

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This research work is topical since there are a lot of objects of accumulated environmental damage (AED) in the Russian Federation and the task to eliminate them is fixed in the country legislation. These objects are typically brownfields, abandoned industrial building or constructions, abandoned waste disposal landfills etc. In accordance with the "General cleaning" Federal project we have developed methodical approaches to assessing impacts exerted by AED objects on human health and life expectancy. The aim of the methodology is to spot out priority objects which are to be eliminated as soon as possible.

Fuzzy set theory is chosen as a basic method. A unified set of indicators (40 and more) has been developed for each type of AED objects; this set allows assessing how hazardous an object is for population health. The indicators are combined into several conditional groups: overall profile; climatic and spatial characteristics; geological and hydrological properties of a territory; indicators related to quality of the environment in a zone influenced by a specific object. We have used scales to grade a health hazard taking into account weight contributions made by specific indicators and a group of them to the total risk of health disorders. Impacts are assessed allowing for types and severity of potential functional disorders of critical organs and systems in the human body under exposure to contamination.

We suggest an algorithm and techniques for calculating risks of negative impacts. A scale with risk ranges (from 0 to 1) allows determining several risk rates including "low", "moderate", "average", "high" and "extremely high" risk. An AED object is assigned into a risk category which corresponds to the maximum value of the membership function.

Impacts exerted by objects assigned into "high" and "extremely high" risk categories are to be assessed more profoundly and assessment should involve specific medical and biological examinations.

The methodology was tested successfully. The results proved that the selected approaches were relevant and that it was extremely important to collect complete and actual initial data of environment quality in zones influenced by AED objects.

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In 2022 approximately 192 objects are to be assessed; the express-evaluation is to be accomplished by experts of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing. As per the evaluation results, all AED objects are to be ranked and those creating the highest health risks are to be detected. The latter are to be eliminated immediately and complete profound assessment is to be performed at them.

Key words: *"General cleaning" Federal project, objects of accumulated environmental damage, population health, exposure assessment, algorithm and methodology.*

Long-term, variable and not always environmentally friendly anthropogenic activities have created a lot of objects which are located both on natural and highly urbanized areas. Some of them are no longer used but they still pollute the environment. In Russia these objects are called "objects of accumulated environmental damage" (AED objects) and are typically represented by brownfields; abandoned waste disposal landfills, industrial buildings or constructions; agricultural chemicals which haven't been utilized; semi-finished products or package which hasn't been salvaged etc. [1–3]. The problem exists practically in all developed countries and each of them creates its own system of legal and organizational solutions [4, 5]. There are some basic concepts accepted by states which have accumulated considerable experience in liquidating environmental damage created by past activities (Denmark[1], the Netherlands[2], Great Britain[3], etc. [4]):

– making those who are responsible for occurrence of AED objects provide finance for their elimination; making the state bear all the costs in case those at fault can't be found, are not solvent, or the limitation period has expired;

– making regional authorities bear the primary responsibility for discovering and eliminating such objects; in this case regional authorities have the right to issue their own legal documents in the sphere which take peculiarities of a given territory into account;

– making rehabilitation of certain territories the top priority; usually, the top priority is assigned to territories with their influence on the environment and human health causing the greatest concern. Other objects can remain sealed (but not eliminated) for a long period of time;

– mandatory examinations of a land spot aimed at detecting any hazardous chemicals when there are changes in its legal status or functional purpose;

– creating and keeping publicly available information resources (web-sites, registers, etc.) with comprehensive data on environmental conditions existing on a given territory.

In the Russian Federation, such legal concepts as "accumulated environmental damage" and "an object of accumulated environmental damage" were first introduced by the Federal Law issued on July 3, 2016 No. 254-FZ[5]. According to it, objects of accumulated environmental damage included "*territories and water areas where environmental damage has been detected which occurred as a result of past economic and other activities; obligations to eliminate this damage haven't been fulfilled, partially or completely*". The Federal Law

[1] Environmental Liability Directive Guidelines. *Environmental Protection Agency, Agency for Spatial and Environmental Planning*, 2012. Available at: https://ec.europa.eu/environment/legal/liability/pdf/eld_guidance/denmark.pdf (December 31, 2021).

[2] Guidelines for Part 17.2 of the Dutch Environmental Management Act: measures in the event of environmental damage or its imminent threat. The Netherlands, 2008. Available at: https://ec.europa.eu/environment/legal/liability/pdf/eld_guidance/netherlands.pdf (December 31, 2021).

[3] The Environmental Damage (Prevention and Remediation) Regulations 2009. Guidance for England and Wales. *Department for Environment, Food and Rural Affairs (Defra)*, 2009. Available at: https://webarchive.nationalarchives.gov.uk/ukgwa/20130402151656/http://archive.defra.gov.uk/environment/policy/liability/pdf/indepth-guide-regs09.pdf (December 31, 2021).

[4] The Environmental Liability (Prevention and Remediation) Regulations (Northern Ireland) 2009. *Department of Environment for Northern Ireland (DOENI)*, 2009. Available at: https://www.legislation.gov.uk/nisr/2009/252/regulation/1/made (December 31, 2021).

[5] O vnesenii izmenenii v otdel'nye zakonodatel'nye akty Rossiiskoi Federatsii: Federal'nyi zakon ot 03.07.2016 № 254-FZ [On making alterations into certain legal acts of the Russian Federation: The Federal Law issued on July 3, 2016 No. 254-FZ]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_200513/ (January 24, 2022) (in Russian).

"On environmental protection"[6] was added a chapter (XIV.1) which regulated issues related to discovering, evaluating, accounting and eliminating accumulated environmental damage (AED).

The law stipulates that objects of accumulated environmental damage should be assigned into certain categories and priority ones are to be spotted out, *"the aim being to substantiate the order in which objects of accumulated environmental damage are to be eliminated and emergency measures are to be taken"* (item 6 in Clause 80.1 of the Federal Law No. 7-FZ). There are seven specific indicators which determine a category an object should be assigned into. Two of them should directly describe population exposure: *"a number of people living on a territory where the environment is under negative influence due to an object of accumulated environmental damage"* and *"a number of people living on a territory where there are environmental threats due to an object of accumulated environmental damage"*. Unfortunately, at present there are no unambiguous criteria to clearly identify "territories under negative influence by AED objects" or "territories where there are threats of such influence". We haven't been able to find them in any regulatory or methodical document, including the Order by the RF Ministry of the Natural Resources and the Environment issued on August 04, 2017 No. 435 "The criteria for determining a category of objects of accumulated environmental damage elimination of which is the top priority"[7]. Accordingly, it is extremely difficult to estimate how many people are directly exposed or threatened to be exposed by an AED object. It is also rather difficult to assess exposure essence and intensity.

But at the same time it is extremely vital to produce objective assessments regarding these issues. Most AED objects are located in close proximity to settlements (cities, urban settlements, or villages) since they were initially located either close to places where there were certain economic activities (industrial wastes disposal landfills, abandoned industrial sites, buildings and constructions, etc.) or places where people lived (tips and landfills for communal wastes disposal). Such objects often create chemical, biological, or radiation hazards for human health and can cause medical and demographic losses which are not taken into account in environmental criteria [6–8].

The "General cleaning" Federal project stipulates developing methodical guidelines on assessing risks of exposure to objects of accumulated environmental damage and their impacts on human health and life expectancy[8]. The purpose of the document is to create instruments for spotting out objects which can potentially exert the most considerable negative impacts on human health. The document doesn't cancel any environmental criteria; instead, it gives an opportunity to take into account certain aspects related to exposure to objects of accumulated environmental damage which have similar importance. These aspects are impacts on human health and life expectancy.

Our research goal was to develop and test methodical approaches stipulated by the federal legislation which made it possible to assess influence exerted by objects of accumu-

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[6] Ob okhrane okruzhayushchei sredy: Federal'nyi zakon ot 10.01.2002 № 7-FZ (poslednyaya redaktsiya) [On environmental protection: The Federal Law issued on January 10, 2002 No. 7-FZ (the last edition)]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_34823/ (January 24, 2022) (in Russian).

[7] Ob utverzhdenii kriteriev i sroka kategorirovaniya ob"ektov, nakoplennyi vred okruzhayushchei srede na kotorykh podlezhit likvidatsii v pervoocherednom poryadke: Prikaz Ministerstva prirodnykh resursov i ekologii Rossiiskoi Federatsii ot 04.08.2017 № 435 [On Approval of the criteria and the term categorizing objects of accumulated environmental damage elimination of which is the top priority: The Order by the RF Ministry of Natural Resources and the Environment issued on August 4, 2017 No. 435]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/456089663 (January 24, 2022) (in Russian).

[8] Pasport federal'nogo proekta «General'naya uborka» [The profile of the "General cleaning" Federal project]. *The RF Government*. Available at: http://static.government.ru/media/files/DoFhF6zbaji5mAKgkefAjTssLoyUOyS.pdf (February 08, 2022) (in Russian).

lated environmental damage on human health and life expectancy.

Materials and methods. When developing these approaches, we took into account substantial experience accumulated in examining polluted, cluttered and other territories and objects which are considered to be "AED objects". We bore in mind that, when describing threats and hazards caused by objects of accumulated environmental damage, many experts stressed out the necessity to take into account the whole range of chemical ambient air pollution [9, 10], chemical and microbial contamination of soils [11–14] and surface water objects [15–17]. Some research works focused on significance of soil filtration parameters in soil profiles since they enabled correct predictive and analytical evaluation of pollution spread beyond landfills where liquid and semi-liquid wastes were accumulated and stored, including sludge accumulators [18, 19]. Recently, there have been a lot of discussions regarding threats and hazards imposed by objects of accumulated environmental damage in the Arctic zone [20–22]. It is also vital to give some attention to radiation safety of AED objects [23–25] etc.

As a result, we developed our methodology with an effort to create as a comprehensive list of indicators as possible trying to take into account all relevant ones which could describe influence exerted by an AED object on the environmental quality and human health.

We considered the fuzzy set theory (fuzzy logic theory) to be a relevant methodical basis for assessing impacts exerted by AED objects on human health and life expectancy [26]. Fuzzy logic methods are generally described in the standard[9] which was developed taking into account international approaches to risk management and risk assessment technologies. The reason we selected this method was that fuzzy sets modeling makes it possible to include both quantitative and qualitative variables into analysis, operates with fuzzy initial data with an opportunity to rapidly create models (including scenarios) of complicated dynamic situations and to perform comparative assessments with preset precision [27, 28].

To assess impacts exerted by each indicator on human health, we used scales to grade a health hazard taking into account weight contributions made by specific indicators and a group of indicators as a whole (component risks of a specific indicator and a group as a whole) and the aggregated risk of health disorders and shorter life expectancy for people who permanently live in a zone influenced by an AED object.

Impacts were assessed allowing for types and severity of potential functional disorders of critical organs and systems in the body under exposure to pollution created by a specific AED object. Critical organs and systems were defined in accordance with the methodical documents issued by the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing[10]. Severity of health disorders was determined based on data provided by the WHO and other relevant sources [29].

When developing the methodology, we took into account that AED objects were divided into several large groups (types) according to the Federal Law:

– territories where AED objects have been discovered;

– water areas where AED objects have been discovered;

– capital construction objects which are AED sources;

– wastes disposal landfills.

To assess exposure as correct as possible, we divided wastes disposal landfills into those where solid wastes were stored and those with liquid wastes.

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[9] State Standard GOST R 58771-2019. Risk management. Risk assessment technologies (approved and introduced by the Order of the Federal Agency on Technical Regulation and Metrology issued on December 17, 2019 No. 1405-st). *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200170253 (February 08, 2022) (in Russian).

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

Our methodical approaches involve two-stage assessment of impacts exerted by objects of accumulated environmental damage on human health and life expectancy:

– express evaluation that involves assessing impacts exerted on population using documents, results produced by single and/or sample measurements of the environmental quality, or general medical statistics;

– complete profound assessment that involves targeted examinations of population health under exposure to an AED object, peculiarities of exerted impacts taken into account.

Express evaluation was considered to be a procedure aimed at calculating comparative profiles for objects of different types, capacity, duration of existence, and with different impacts exerted on the environment and human health. Another purpose was to rank AED objects as per their potential impacts on human health and life expectancy in order to spot out objects which should be eliminated immediately, their elimination being the top priority.

Complete profound assessment involved verifying negative exposure levels calculated by express evaluation; accumulating evidence-based data on the actual medical and demographic losses over the period of an AED existence; and assessing actual effects, including economic ones, achieved due to elimination of an AED object in a post-project period (after an AED objects has been eliminated).

We suggested an algorithm to determine priorities as per population exposures which included the following steps:

– collecting as many data on an AED object as it is only possible;

– express evaluation of impacts exerted by an AED object on human health and life expectancy and calculating a value to describe risks of negative health outcomes;

– ranking objects as per risks of negative outcomes;

– spotting out objects belonging to categories of "high" and "extremely high" health risks.

Basic results. We developed a unified set of indicators (40 and more) to make a profile of each AED object highlighting peculiar influence exerted by it on environmental objects and how hazardous it was for human health.

The indicators were combined into several conditional groups:

– general profile of an AED object (duration of existence, a square of an AED object, volume/mass of accumulated wastes or a number of abandoned buildings and/or constructions, availability of an owner, location of an object in a permafrost area, how cluttered an area is around an AED object, etc.);

– climatic profile of a territory where an AED object is located (climate, frequency of winds blowing towards residential areas, precipitations, etc.);

– spatial characteristics of an AED object with respect to residential areas and places used by population (a distance to the closest settlement; a number of people who permanently live in a zone influenced by an AED object; existing sanitary protection zones; a distance to the closest water source; location of an AED objects regarding sanitary protection zones drinking water sources etc.);

– geological and hydrological parameters of a territory (subsoil types; how deep underground waters are located; existing waterproofing screens, dikes, derivation canals, etc.);

– quality of environmental objects in a zone influenced by an AED object (chemical, microbiological, and radiation indicators of ambient air quality, natural and drinking water quality, quality of soils and agricultural products grown in a zone influence by an AED object). This group also includes people's complaints about quality of environmental objects in a zone influenced by an AED object.

Negative effects produced by AED objects on human health are assessed as per the unified algorithm taking into account the whole set of potential threats and hazards which are typical for a given object. As a result, we obtain unified risk indicators which describe this negative influence on human health and life expectancy. These indicators make it possible to compare different AED objects and assign them into a specific risk category:

– 1st category (negligibly low risk of exposure);

– 2nd category (low risk);
– 3rd category (average risk);
– 4th category (high risk);
– 5th category (extremely high risk).

It is standard practice that if an object is assigned into high or extremely high risk category as per results produced by express evaluation, then it is advisable to perform complete profound assessment together with analyzing exposed population's health and creating an evidence base proving that health risks have actually been realized.

Express evaluation of impacts exerted by an AED object on human health and life expectancy relies on general profiles of AED objects, data on quality of the environment in a zone influenced by an AED object, and medical statistics about health of people who permanently live in a zone influenced by an AED object. Each relevant indicator is evaluated with interval values (ranges) and then assigned into a specific range on the scale with preset risk rates (negligibly low, low, moderate, high, and extremely high).

We suggest considering a zone influenced by an object of accumulated environmental damage as a territory (water area) described with a conditional boundary. This boundary is located at a distance equal to at least a twofold size of a sanitary protection zone of an object or up to 1 km downstream away from the boundary of a land spot an AED object is located on. Capital buildings or constructions for which sanitary protection zones are not stipulated in the sanitary classification are assigned into the 5th hazard category. The boundary of an influenced zone is considered to be located 100 meters away from the boundaries of a land spot where such an object is located.

Table 1 provides an example (a fragment) of an initial matrix applied to assess risks created by an object of accumulated environmental damage from the "solid wastes" group.

As we can see in the Table 1, quantitative indicators are given with a range of values which is divided into ranges with fuzzy boundaries. A number of such ranges is equal to a number of hazard categories. Using fuzzy sets involves a 20 % intersection of two neighboring ranges.

Each range of values for each quantitative indicator is a trapezoid fuzzy number with the membership function within a certain risk category which is given with four numbers (a_1, a_2, a_3, a_4). Generally the membership function for a value of an indicator is given as per the following formula (1):

$$\mu(x)=\begin{cases}0, & \text{if } x<a_1,\\ \dfrac{x-a_1}{a_2-a_1}, & \text{if } a_1\le x<a_2,\\ 1, & \text{if } a_2\le x\le a_3,\\ \dfrac{x-a_4}{a_3-a_4}, & \text{if } a_3<x\le a_4,\\ 0, & \text{if } x>a_4.\end{cases} \qquad (1)$$

Table 1

The list of indicators describing hazards caused by waste disposal landfills (solid chemical wastes) which are a source of accumulated environmental damage, hazard ranges provided: a fragment

Indicator	Unit of measurement	An AED object hazard category				
		Negligibly low	Low	Average	High	Extremely high
General profile of an AED object						
Duration of existence	years	[0; 2); [40; +∞]	(40; 30]	(30; 20]	(20; 10]	(10; 2]
Wastes mass / Wastes volume	thousand tons	[0; 50)	(50; 250]	(250; 500]	(500; 1000]	(1000; +∞)
Square of an object	hectares	[0; 0,1]	(0,1; 1]	(1; 100]	(100; 500]	(500; +∞)
A share of wastes from the 1st–3rd hazard category	%	(0; 10]	(10; 25]	(25; 40]	(40; 50]	(50; +∞)
A share of biologically degradable mass	%	[0; 10]	(10; 30]	(30; 60]	(60; 80]	(80; 100]
Carcinogenic and/or embryotoxic chemicals	–	no	no	yes	yes	yes

Table 1 (continued)

Indicator	Unit of measurement	An AED object hazard category				
		Negligibly low	Low	Average	High	Extremely high
Untreated medical wastes	–	no	no	no	no	yes
Wastes hazard category	–	[5]	[4; 5]	[3; 5]	[2; 5]	[1; 5]
Climatic profile of a territory where an AED object is located						
Permafrost	–	no	no	no	yes	yes
Climatic zone	zone	moderate	moderate	moderate	subtropical	arctic, subarctic
Precipitations	mm/year	[0; 800]	(800; 1000]	(1000; 1500]	(1500; 2000]	(2000; +∞)
Frequency of winds blowing towards at residential areas	%	[0; 5]	(5; 10]	(10; 20]	(20; 40]	(40; +∞)
Probability and scales of emergencies	–	no	no	no	yes	yes
Location in a zone where hazardous natural phenomena can occur	–	no	no	no	yes	yes
Spatial characteristics of an AED object with respect to residential areas and places used by population						
A distance to the closest settlement	m	(2000; +∞)	(1000; 2000]	(500; 1000]	[500; 0)	0
A number of people living in the closets settlement	thousand people	[0; 1]	(1; 5]	(5; 50]	(50; 100]	(100; +∞)
A distance to the closest water object	m	(1000; +∞)	[1000; 800]	(800; 500]	(500; 300]	[0; 300]
Location of an AED object regarding sanitary protection zones around water sources	–	Beyond SPZ	Beyond SPZ	In the 3rd subzone of SPZ	In the 2nd subzone of SPZ	In the 1st subzone of the SPZ
A distance from an AED object to a recreation zone/resort	m	(1500; +∞)	(1500; 1000]	(1000; 700]	(700; 300]	(300; –∞) / (300; within such a zone)
A distance to agricultural lands	m	(1000; +∞)	(500; 1000]	(300; 500]	[300; 0)	[0)
Incidence rates among population in the closest settlement against regional ones	times	[1]	(1; 1.2]	(1.2; 1.5]	(1.5; 2]	(2; +∞)
A number of people living in a zone which can potentially be polluted in case of emergency	Thousand people	[0; 1]	(1; 10]	(10; 40]	(40; 75]	(75; +∞)
Geological and hydrological parameters of a territory						
Subsoil filtration coefficient	m/sec	$1.0 \cdot 10^{-9}$	$1.0 \cdot 10^{-8}$	$1.0 \cdot 10^{-7}$	$1.0 \cdot 10^{-6}$	$1.0 \cdot 10^{-5}$
Depth of underground water occurrence	m	[5; +∞)	[4]	[3]	[1; 2]	[0; 1)
Quality of environmental objects						
Ambient air quality in a zone influenced by an AED object * (as per certain indicators)	shares of MPC or TSEL	[0; 0.5MPC]	(0.5MPC; 1MPC]	(1MPC; 2MPC]	(2MPC; 5MPC]	(5MPC; +∞)
People's complaints about ambient air quality	quantity/year	[0]	[0]	[1; 5)	(5; 10)	(10; +∞)
Drinking water quality in the closest settlements	measurement units	[0; BOR1]**	(BOR1; BOR2]	(BOR2; BOR3]	(BOR3; BOR4]	(BOR4; +∞)
People's complaints about drinking water quality	quantity/year	[0]	[0]	[1; 5)	(5; 10)	(10; +∞)
Soil quality	measurement units	[0; BOR1]**	(BOR1; BOR2]	(BOR2; BOR3]	(BOR3; BOR4]	(BOR4; +∞)
Quality of food products grown in a zone influenced by an AED object	measurement units	[0; BOR1]**	(BOR1; BOR2]	(BOR2; BOR3]	(BOR3; BOR4]	(BOR4; +∞)

N o t e : * The list of indicators is not ultimate and is determined only by specific features of an object and its influence on the environment; ** – BOR1, BOR2, BOR3, BOR4 are the upper limits of indicators describing quality of environmental objects in accordance with their belonging to 5 health risk categories accordingly.

For example, a value of an indicator is $x = 0.23$. If we consider the interval [0.2; 0.4], then a fuzzy number which corresponds to this section is equal to (0.16, 0.24, 0.32, 0.48), where $a_1 = 0.2 \cdot 0.80 = 0.16$, $a_2 = 0.2 \cdot 1.2 = 0.24$, $a_3 = 0.4 \cdot 0.8 = 0.32$, $a_4 = 0.4 \cdot 1.2 = 0.48$ (the interval boundaries were "blurred" by 20 %). Since $a_1 < 0.23 < a_2$, then the membership function value for the value of an indicator being $x = 0.23$, according to the formula (1), is equal to

$$\mu(x) = (0.23 - 0.16) / (0.24 - 0.16) = \\ = 0.07/0.08 = 0.875$$

This means that the examined indicator belongs to the given section by 87.5 %.

The value $\mu(x)$ describes belonging of a range for a value of an indicator within a corresponding hazard category.

The membership function is given as (2) for quantitative indicators:

$$\{x / \mu(x)\} = \\ = \{value1 / \mu 1, value2 / \mu 2, value3 / \mu 3, ...\} \quad (2)$$

Weights are fixed for each indicator or a group of indicators; they are taken into account when an aggregated risk of negative impacts is calculated. Weights fixed for groups of indicators are different for different types of AED objects and take into account their specific influence on the environment and human health.

If critical organs and systems are determined regarding a chemical and, accordingly, there are established average levels of severity for a given nosology (within a range from 0 to 1), then a weight is determined as per Fishburne's Rule [30] taking into account the most severe health disorder (3):

$$G\_l = (2\,(n\text{-}l\text{+}1)) / ((n\text{+}1)\,n), \quad (3)$$

where

G_l is a weight of an indicator for which critical organs or systems are determined (a negative response) holding the l-th rank as per their severity;

n is a total number of nosologies determined in the aggregated negative response;

l is a rank of a negative response (a nosology) as per its severity.

Initial tables which create a profile of a specific AED object are filled in based on available documents (project documentation, documents in the AED objects register, data taken from publicly available cadastre maps, research reports, test reports, expert examination reports, and other relevant ones).

Values of the membership function ($\mu(x)$) of each indicator falling within a certain hazard category are determined in accordance with preset scaling conditions as per the formulas (1)–(2).

A risk rate is calculated for each group of indicators as per the formula (4):

$$R_j = \sum_k \overline{R}_k w_{kj}, \quad (4)$$

where

R_j is a health risk rate caused by the j-th group of indicators;

w_{kj} is average weighted membership of the j-th group of parameters to the k-th hazard category;

$\overline{R}_k$ is the middle of a scale range corresponding to the k-th hazard category.

Average weighted membership of a group of indicators to hazard categories w_{kj} is determined as per the formula (5)

$$w_{kj} = \sum_{i \in j} G_i \, \mu_k(x_i), \quad (5)$$

where $\mu_k(x_i)$ is the membership function of the i-th indicator within the k-th hazard category; G_i is a weight of the i-th indicator.

Risk scale ranges and their middles are given in Table 2.

The aggregated risk (R) as per all the groups of indicators is calculated as per the following formula (6):

$$R = \sum_j R_j v_j, \quad (6)$$

where v_j is a weight contribution by the j-th group of indicators into the aggregated risk.

A weight contribution made by a group of indicators into the aggregated health risk is determined according to the Table 3.

A risk rate of harmful impacts on human health is used as a basis for AED objects ranking. An object is assigned into a specific risk category as per its impacts on human health depending on the membership of the value R determined for this object within a range given in Table 1.

Since a risk rate can be on a boundary between values and belong to two different ranges simultaneously (for example, $R = 0.22$ belongs simultaneously to the "moderate" range and "low" range), an AED object is ultimately assigned into a specific risk category in accordance with the procedure outlined in Table 4.

An AED object is assigned into a risk category which corresponds to the highest value of the membership function.

Table 2

Ranges on the risk rates scale and their mean values

Indicator	Health risk categories				
	Low	Moderate	Average	High	Extremely high
Range ($\overline{R}_k$)	(0; 0.25]	(0.15; 0.45]	(0.35; 0.65]	(0.55; 0.85]	(0.75; 1.0]
Mean value in range ($\overline{R}_k$)	0.125	0.3	0.5	0.7	0.875

Table 3

Weights for groups of indicators describing different types of AED objects

Groups of indicators	Solid wastes	Liquid chemical industrial wastes	Liquid organic wastes	Capital buildings and constructions	Territories	Water areas
General profile	0.1	0.1	0.1	0.15	0.1	0.1
Climatic profile	0.1	0.1	0.1	0.1	0.1	0.1
Spatial characteristics	0.3	0.3	0.3	0.3	0.3	0.4
Geological and hydrological parameters	0.15	0.25	0.2	0.35	0.15	0
Quality of environmental objects	0.35	0.25	0.3	0.1	0.35	0.4

Table 4

A scale with ranges of rates and health risk categories

A range of health risk rates	The membership function for a risk rate falling within a specific range on the scale	Health risk category
[0; 0.25]	$\mu_1(R)=\begin{cases}1, & \text{if } 0 \le R \le 0.15,\\ 10(0.25-R), & \text{if } 0.15 \le R \le 0.25\end{cases}$	Low
(0.15; 0.45]	$\mu_2(R)=\begin{cases}1-10(0.25-R), & \text{if } 0.15 \le R \le 0.25,\\ 1, & \text{if } 0.25 \le R \le 0.35,\\ 10(0.45-R), & \text{if } 0.35 \le R \le 0.45\end{cases}$	Moderate
(0.35; 0.65]	$\mu_3(R)=\begin{cases}1-10(0.45-R), & \text{if } 0.35 \le R \le 0.45,\\ 1, & \text{if } 0.45 \le R \le 0.55,\\ 10(0.65-R), & \text{if } 0.55 \le R \le 0.65\end{cases}$	Average
(0.55; 0.85]	$\mu_4(R)=\begin{cases}1-10(0.65-R), & \text{if } 0.55 \le R \le 0.65,\\ 1, & \text{if } 0.65 \le R \le 0.75,\\ 10(0.85-R), & \text{if } 0.75 \le R \le 0.85\end{cases}$	High
[0.75; 1]	$\mu_5(R)=\begin{cases}1-10(0.85-R), & \text{if } 0.75 \le R \le 0.85,\\ 1, & \text{if } 0.85 \le R \le 1\end{cases}$	Extremely high

Table 5

Results produced by express evaluation of several objects of accumulated environmental damage; the evaluation was accomplished when methodical approaches were being tested

An object of accumulated environmental damage	General profile	Climatic profile	Spatial characteristics	Geological and hydrological parameters	Quality of environmental objects	Risk rate	Risk category	Rank of an object
Sludge accumulator of a former chemical plant located within a settlement	0.21	0.11	0.15	0.06	0.33	0.86	Extremely high	1
Sludge landfill in a city	0.09	0.15	0.11	0.17	0.02	0.54	Average	2
Solid communal wastes dump close to an urban settlement	0.08	0.14	0.08	0.02	0.19	0.51	Average	3
Inert industrial wastes landfill at a boundary of a settlement	0.05	0.14	0.10	0.01	0.05	0.35	Average	4
Solid communal wastes dump beyond a boundary of a rural settlement	0.06	0.14	0.02	0.01	0.02	0.25	Moderate	5
Abandoned building beyond a boundary of a rural settlement	0.00	0.09	0.01	0.01	0.01	0.12	Low	6

We assessed probable effects such as changes in life expectancy of people who permanently lived in a zone influenced by a long existing AED object. The assessment was based on relationships determined by epidemiological studies [31, 32].

A probable change in life expectancy is assessed for a specific AED object with an established risk rate of harmful impacts on health as per the following formula (7):

$$\Delta LE = R \cdot K, \qquad (7)$$

where

ΔLE is a probable decrease in average life expectancy (LE) due to impacts exerted on health by an AED object;

R is the aggregated health risk calculated taking all the groups of indicators into account;

K is the coefficient showing actual risk realization as a change in life expectancy calculated on the basis of analyzing relevant scientific literature; $K = 1.6$.

Assessment of impacts exerted by AED objects on human health and life expectancy gives grounds for ranking them in order to determine priority ones which should be eliminated immediately.

Table 5 provides the results produced by tentative express evaluation of several AED objects with initial data on them being available to us at the moment we were developing our methodical approaches.

These results, according to expert estimates, provide relevant evaluation of the examined objects. But at the same time, when testing our methodical approaches, we revealed that initial data had certain drawbacks. One of them was that there were very few or even almost no indicators which described quality of the environmental objects. Given that, we can set a priority task which has to be tackled by Rospotrebnadzor's authorities and institutions which are responsible for performing express evaluation of AED objects. This task is to accomplish comprehensive analysis of historical data on abandoned objects or to perform instrumental research of ambient air quality, quality of natural and drinking water, and quality of soils, primarily, agricultural ones, in a zone influenced by an AED object.

If an AED object is assigned into high or extremely high risk category as per results produced by express evaluation, then complete profound assessment is to be performed at it

with the focus on its impacts on human health and life expectancy.

By now substantial experience has been accumulated in Russia in performing specific studies with their focus on determining health risks caused by exposure to harmful environmental sources and factors [33–35].

An adverse impact which is a health disorder among people from risk groups living in a zone exposed to an AED object is proven by target studies focusing on human health. These studies can concentrate both on organs and systems determined as critical ones for certain exposure and on etiopathogenetic mechanisms of harmful effects developing under aggregated exposure.

Complete profound assessment gives a possibility to describe a degree and a scale of actual aggregated influence exerted by an AED object on human health and life expectancy. Health studies provide the maximum objectivity in assessing health damage, reduce social tension and help develop and implement recommendations on medical and preventive activities aimed at protecting people's health until an AED object is eliminated completely.

The suggested mathematical apparatus is implemented as a software set of instruments for automated risk calculation after all the initial data have been input.

These methodical approaches are to be tested in this year. As it is stated in the profile of the "General cleaning" Federal project (item 1.4.)[8], express evaluation is to be performed at approximately 192 AED objects by experts of the federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing. The evaluation is to be based on data taken from external sources as well as results produced by studies, examinations, and instrumental measurements performed by the Service itself.

All the examined objects of the accumulated environmental damage are to be ranked according to the results produced by the accomplished express evaluation and those which create the highest risks for human health are to be spotted out. These objects should be eliminated immediately, their elimination being the top priority. Profound medical examinations will be recommended for people living in zones influenced by some AED objects which create high and extremely high health risks.

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References

1. Alykova O., Chuikova L., Chuikov Yu. Accumulated environmental damage: problems and consequences. Message 1. State registry of objects of accumulated environmental damage. *Astrakhanskii vestnik ekologicheskogo obrazovaniya*, 2021, vol. 62, no. 2, pp. 88–113. DOI: 10.36698/2304-5957-2021-2-88-113 (in Russian).

2. Alykova O., Chuikova L., Chuikov Yu. Accumulated environmental damage: problems and consequences. Message 2. Analysis of the situation. *Astrakhanskii vestnik ekologicheskogo obrazovaniya*, 2021, vol. 62, no. 2, pp. 114–137. DOI: 10.36698/2304-5957-2021-2-114-137 (in Russian).

3. Zinoviev D.S., Pichugin E.A., Cherepanov M.V. Main problems of the state register of accumulated environmental harmfuls. *Astrakhanskii vestnik ekologicheskogo obrazovaniya*, 2021, vol. 66, no. 6, pp. 108–114. DOI: 10.36698/2304-5957-2021-6-108-114 (in Russian).

4. Goldenman G. Opyt stran Evropeiskogo soyuza i stran Tsentral'noi i Vostochnoi Evropy v reshenii problem proshlogo ekologicheskogo ushcherba. Diskussionnyi doklad dlya Vsemirnogo banka [Experience of the European Union countries and the countries of Central and Eastern Europe in solving the problems of the ecological crisis. Discussion paper for the World Bank]. InEkA-konsalting LLC, 2006. Available at: https://ineca.ru/?dr=projects&projects=social/pel/material&docname=opyt (08.02.2022) (in Russian).

5. Ledashcheva T.N., Chernyshev D.A. Analysis of international experience of cumulative environmental harm problem solution. *Naukovedenie*, 2014, vol. 25, no. 6, 12 p. DOI: 10.15862/83EVN614 (in Russian).

6. Pichugin E.A., Cherepanov M.V., Simakova E.V., Shenfeld B.E. Current issues of identification, accounting, categorization and elimination of the objects of accumulated environmental harm. *Problemy regional'noi ekologii*, 2021, no. 6, pp. 113–121. DOI: 10.24412/1728-323X-2021-6-113-121 (in Russian).

7. Pichugin E.A., Shenfeld B.E. The health of citizens and their life expectancy as a criterion for assessing the negative impact of objects of accumulated environmental damage on the state of the environment and man. *Ekologiya urbanizirovannykh territorii*, 2021, no. 3, pp. 62–70. DOI: 10.24412/1816-1863-2021-3-62-70 (in Russian).

8. Polyakov A.P., Sorokina E.G. Environmental situation as a factor of changes in state of health of population. *World Science: Problems And Innovations: sbornik statei pobeditelei V mezhdunarodnoi nauchno-prakticheskoi konferentsii.* Penza, 2016, pp. 357–360 (in Russian).

9. Ivantsova E.A. Otsenka vozdeistviya likvidatsii tekhnogennogo massiva razmeshcheniya otkhodov proizvodstva i potrebleniya na atmosfernyi vozdukh [Assessment of the impact exerted by liquidation of the technogenic array of production and consumption waste disposal on the atmospheric air]. *Innovatsionnye tekhnologii zashchity okruzhayushchei sredy v sovremennom mire: materialy Vserossiiskoi nauchnoi konferentsii s mezhdunarodnym uchastiem molodykh uchenykh i spetsialistov.* Kazan, 2021, pp. 1363–1368 (in Russian).

10. Tenodi S., Krčmar D., Agbaba J., Zrnić K., Radenović M., Ubavin D., Dalmacija B. Assessment of the environmental impact of sanitary and unsanitary parts of a municipal solid waste landfill. *J. Environ. Manage.*, 2020, vol. 258, pp. 110019. DOI: 10.1016/j.jenvman.2019.110019

11. El Fadili H., Ben Ali M., Touach N., El Mahi M., El Lotfi M. Ecotoxicological and pre-remedial risk assessment of heavy metals in municipal solid wastes dumpsite impacted soil in Morocco. *Environmental Nanotechnology, Monitoring & Management*, 2021, vol. 17, pp. 100640.

12. Ojuri O.O., Ayodele F.O., Oluwatuyi O.E. Risk assessment and rehabilitation potential of a millennium city dumpsite in Sub-Saharan Africa. *Waste Manage.*, 2018, vol. 76, pp. 621–628. DOI: 10.1016/j.wasman.2018.03.002

13. Ivanova Yu.S., Gorbachev V.N. Heavy metals pollution of soil under the influence of illegal dumping (health and environmental aspects). *Ul'yanovskii mediko-biologicheskii zhurnal*, 2012, no. 1, pp. 119–124 (in Russian).

14. Berezin G.I., Kondakova L.V., Domracheva L.I., Dabakh E.V. Features of soil microbial groups in the area Kilmezsky landfill dumping of toxic chemicals (Kirov region). *Printsipy ekologii*, 2016, vol. 18, no. 2, pp. 4–15 (in Russian).

15. Yang W., Cai C., Dai X. Interactions between virus surrogates and sewage sludge vary by viral analyte: recovery, persistence, and sorption. *Water Res.,* 2021, vol. 210, pp. 117995. DOI: 10.1016/j.watres.2021.117995

16. Sakharov V.A., Morozova O.A., Vypryazhkin E.N., I K.H., Fayzulin D.R. The impact of landfill of solid waste on water bodies (on the example of a city dump in the city of Yuzhno-Sakhalinsk). *Uchenye zapiski Sakhalinskogo gosudarstvennogo universiteta*, 2015, vol. 11–12, no. 1, pp. 87–91 (in Russian).

17. Ostanina N.V., Kuznetsova E.I., Ocheretyanaya N.N. Problemy, svyazannye s unichtozheniem nekachestvennykh lekarstvennykh preparatov [Problems associated with the destruction of low-quality medicines]. *Sotrudnichestvo dlya resheniya problem s otkhodami: tezisy dokladov konferentsii s mezhdunarodnym uchastiem*, 2009, pp. 221–229 (in Russian).

18. Mescheriykov S., Gonopolsky A., Ostakh S., Ostakh O. Forecast and analytical assessment of the spread of pollution beyond the sludge accumulators of industrial enterprises. *Ekologiya i promyshlennost' Rossii*, 2017, vol. 21, no. 10, pp. 22–27. DOI: 10.18412/1816-0395-2017-10-22-27 (in Russian).

19. Sakharov V.A., Melkii V.A., Nikonova E.V. Otsenka stepeni opasnosti vozniknoveniya neblagopriyatnoi sanitarno-epidemiologicheskoi situatsii v vodonosnykh gorizontakh territorii [Assessment of the degree of danger caused by an unfavorable sanitary and epidemiological situation in water-bearing horizons on a given territory]. *Bezopasnost' zhiznedeyatel'nosti*, 2008, vol. 89, no. 5, pp. 61–64 (in Russian).

20. Shevchuk A.V. Ecological-economic aspects of elimination of the accumulated damage in the arctic zone of the Russian Federation. *Prirodoobustroistvo*, 2013, no. 5, pp. 80–83 (in Russian).

21. Fokin S.G. The elimination of past environmental liabilities in the arctic zone of the Russian Federation. *Sbornik trudov Vserossiiskogo nauchno-issledovatel'skogo instituta okhrany okruzhayushchei sredy za 2019*. Moscow, 2019, pp. 37–42 (in Russian).

22. Orttung R.W., Anisimov O., Badina S., Burns C., Cho L., Di Napoli B., Jull M., Shaiman M. [et al.]. Measuring the sustainability of Russia's Arctic cities. *Ambio*, 2021, vol. 50, no. 11, pp. 2090–2103. DOI: 10.1007/s13280-020-01395-9

23. Dregulo A.M. Distribution and specific activity of soil radionuclides in the soils of pastenviromental damage (for example of sewage sludge landfills). *Izvestiya Tul'skogo gosudarstvennogo universiteta. Nauki o Zemle*, 2018, no. 3, pp. 27–35 (in Russian).

24. Smičiklas I., Jović M., Janković M., Smiljanić S., Onjia A. Environmental Safety Aspects of Solid Residues Resulting from Acid Mine Drainage Neutralization with Fresh and Aged Red Mud. *Water Air Soil Pollut.*, 2021, vol. 232, no. 12, pp. 490. DOI: 10.1007/s11270-021-05442-3

25. Akinci A., Artir R. Characterization of trace elements and radionuclides and their risk assessment in red mud. *Materials Characterization*, 2008, vol. 59, no. 4, pp. 417–421. DOI: 10.1016/j.matchar.2007.02.008

26. Zadeh L.A. Fuzzy sets. *Information and Control*, 1965, vol. 8, no. 3, pp. 338–353. DOI: 10.1016/S0019-9958(65)90241-X

27. Ermakov B.S. Teoriya nechetkikh mnozhestv v prinyatii reshenii [Fuzzy set theory in decision making]. *Sistemnyi analiz i logistika*, 2014, no. 11, pp. 49–53 (in Russian).

28. Zvyagin L.S., Makeichev E.D. Teoriya nechetkikh mnozhestv i funktsiya prinadlezhnosti [Fuzzy set theory and membership function]. *Mezhdunarodnaya konferentsiya po myagkim vychisleniyam i izmereniyam*, 2015, vol. 2, pp. 144–149 (in Russian).

29. Salomon J.A., Haagsma J.A., Davis A., de Noordhout C.M., Polinder S., Havelaar A.H., Cassini A., Devleesschauwer B. [et al.]. Disability weights for the Global Burden of Disease 2013 study. *Lancet Glob. Health*, 2015, vol. 3, no. 11, pp. e712–e723. DOI: 10.1016/S2214-109X(15)00069-8

30. Fishbern P.S. Utility theory for decision making. In: V.N. Vorob'eva, A.Ya. Kiruta translation. Moscow, Nauka, 1978, 352 p. (in Russian).

31. Medford A., Vaupel J.W. Human lifespan records are not remarkable but their durations are. *PLoS One*, 2019, vol. 14, no. 3, pp. e0212345. DOI: 10.1371/journal.pone.0212345

32. Mackenbach J.P., Valverde J.R., Bopp M., Brønnum-Hansen H., Deboosere P., Kalediene R., Kovács K., Leinsalu M. [et al.]. Determinants of inequalities in life expectancy: an international comparative study of eight risk factors. *Lancet Public Health*, 2019, vol. 4, no. 10, pp. e529–e537. DOI: 10.1016/S2468-2667(19)30147-1

33. Zaitseva N.V., Zemlyanova M.A. Gigienicheskaya indikatsiya posledstvii dlya zdorov'ya pri vneshnesredovoi ekspozitsii khimicheskikh faktorov [Hygienic indication of health consequences during environmental exposure to chemical factors]. Perm, 2011, 532 p. (in Russian).

34. Zaitseva N.V., May I.V., Klein S.V., Khankharev S.S., Boloshinova A.A. Scientific and methodological aspects and practical experience for the formation of the evidential base of hazard to health in the population in the zone of influence of waste from the past economic activity. *Gigiena i sanitariya*, 2017, vol. 96, no. 11, pp. 1038–1044. DOI: 10.18821/0016-9900-2017-96-11-1038-1044 (in Russian).

35. Zaitseva N.V., Ustinova O.Yu., Zemlyanova M.A. Medical and preventive technologies of the management of the risk of health disorders associated with exposure to adverse environmental factors. *Gigiena i sanitariya*, 2015, vol. 94, no. 2, pp. 109–113 (in Russian).

Zaitseva N.V., May I.V., Kleyn S.V., Kiryanov D.A., Andrishunas A.M., Sliusar N.N., Maksimova E.V., Kamaltdinov M.R. On assessing impacts exerted by objects of accumulated environmental damage on human health and life expectancy. Health Risk Analysis, 2022, no. 1, pp. 4–16. DOI: 10.21668/health.risk/2022.1.01.eng

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Research article

HYGIENIC ASSESSMENT OF CARCINOGENIC HEALTH RISKS ASSOCIATED WITH CONTAMINATION OF DEPOSITING MEDIA WITH HEAVY METALS

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In nature there are depositing media which are relatively stable macrosystems. Their contamination that occurs due to long-term exposure to contaminants influences population health and this is especially vital for urbanized territories with large city-forming enterprises.

Our research goal was to perform hygienic assessment of carcinogenic risks for population health under exposure to heavy metals contained in depositing media.

We analyzed long-term data on contents of heavy metals in such accumulating media as soils and foods collected in 2005–2018. The data were taken from the reports on social and hygienic monitoring and statistical reports provided by the Orenburg Regional Office of the Federal State Statistics Service. Carcinogenic risks were assessed in accordance with the Guide R 2.1.10.1920-04. We used data provided by the territorial section of the National Cancer Registry to analyze prevalence of oncologic diseases of the digestive organs. We performed correlation analysis to examine correlations between the analyzed factors.

The total carcinogenic risk under multi-route introduction of heavy metals from such depositing media as soils and foods has turned out to be unacceptable and amounts to 1.5E-04. The total population carcinogenic risk caused by exposure to heavy metals can reach 85 additional cases of malignant neoplasms over an averaged exposure period which is equal to 70 years.

Heavy metals were detected in soils, nickel, cadmium, and chromium VI included, that produced statistically authentic effects on occurrence of malignant neoplasms in the digestive organs.

We established an authentic correlation between developing malignant neoplasms in the digestive organs and concentrations of arsenic in foods.

We didn't detect any heavy metals with carcinogenic properties in such accumulating media as soils and foods in concentrations deviating from hygienic standards. But still, it doesn't mean there is no negative influence on population health, notably long-term effects and developing malignant neoplasms

Key words: *soil contamination, foods, heavy metals, carcinogens, morbidity, carcinogenic risk assessment, malignant neoplasms of the digestive organs.*

There are two principally different media existing as ecosystems: a transitory one (the dynamically changing atmosphere and hydrosphere being the right example) and a depositing one that gives a clear picture of processes that are extended over time and space (soils, rocks, vegetative and animal biological substrates etc.) [1–4]. Contamination of soils as

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well as vegetable and animal foods with heavy metals results from long-term accumulation of xenobiotics on environmentally unfavorable territories. Ecological condition of accumulating media deteriorates in large cities due to intensive population growth, developing ore mining and oil and gas extraction, unsanctioned deposition of solid wastes and discharge of liquid ones, uncontrollable use of agrochemicals, and ambient air pollution with industrial emissions and exhaust gases [5–10].

Soil is an open system in urban landscapes; it has tight connections with ambient air and the hydrosphere and reflects anthropogenic loads on transitory media as it accumulates and transforms technogenic contaminants [11–14].

According to data provided by the Rospotrebnadzor Regional Office in Orenburg region, a share of soils samples that deviates from hygienic standards as per sanitary-chemical parameters amounts to 1–3 %. The most unfavorable ecological situation in the country is currently in Arkhangelsk and Amur regions. Heavy metals that contaminate soils exert their influence on population both by direct contacts with soil and by toxicants being introduced through media combined with it, including ambient air, water in water sources, and foods. Therefore, it seems necessary to take into account multiple possible routes of xenobiotics introduction into the body [15–17].

Environmental contamination with heavy metals makes for their migration along food chains and accumulation in foods thus making a substantial contribution to chemical loads on population health. As it was shown in previous research performed in Arkhangelsk region and Buryatia, foods, as a rule, conformed to hygienic requirements but still there was no guarantee that health risks were completely absent even if standards as per heavy metal contents were not violated [9, 18–21].

Together with chemization of soils and foods, there is a persistent trend for growing incidence of diseases of barrier systems in the body including malignant neoplasms in the digestive organs [22–24]. Stomach, colon, and rectum tumors occupy a significant place in the structure of oncologic morbidity and their prevalence tends to grow [25, 26].

Therefore, it seems vital to assess contamination of depositing media with heavy metals which have carcinogenic properties and produce negative effects on health, especially given the fact that there is no threshold level of exposure for these chemicals and long-term effects can't be excluded.

Our research goal was to perform hygienic assessment of carcinogenic risks for population health under exposure to heavy metals contained in depositing media.

Materials and methods. We performed hygienic assessment aimed at determining heavy metals contents in soils (nickel, cadmium, chromium, cobalt, and lead) and foods (lead, arsenic, and cadmium). We took data collected over a long-term period of social and hygienic monitoring in Orenburg, data from statistical reports issued by the Orenburg Regional Office of the Federal State Statistics Service and from state reports "On sanitary-epidemiological welfare of the population in Orenburg region" issued in 2005–2018[1].

According to the Sanitary Rules and Norms SanPiN 2.1.3684-21[2] contents of chemicals that

[1] O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Orenburgskoi oblasti: Gosudarstvennye doklady (za 2005–2018 gg.) [On sanitary-epidemiological welfare of the population in Orenburg region: State reports (issued in 2005–2018)]. *Orenburg Regional office of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing*. Available at: http://56.rospotrebnadzor.ru/gosdoklady (July 11, 2021) (in Russian).

[2] SanPiN 2.1.3684-21. Sanitarno-epidemiologicheskie trebovaniya k soderzhaniyu territorii gorodskikh i sel'skikh poselenii, k vodnym ob"ektam, pit'evoi vode i pit'evomu vodosnabzheniyu, atmosfernomu vozdukhu, pochvam, zhilym pomeshcheniyam, ekspluatatsii proizvodstvennykh, obshchestvennykh pomeshchenii, organizatsii i provedeniyu sanitarno-protivoepidemicheskikh (profilakticheskikh) meropriyatii: utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha RF ot 28 yanvarya 2021 g. № 3 [SanPiN 2.1.3684-21. Sanitary-epidemiologic requirements to maintenance of territories in urban and rural settlements, to water objects, drinking water and public water supply, ambient air, soils, living spaces, exploitation of industrial and public premises, organization and c implementation of sanitary and anti-epidemic (prevention) activities: approved by the RF Chief Sanitary Inspector on January 28, 2021, Order No.3]. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573536177 (September 14, 2021) (in Russian).

are potentially hazardous for people should not exceed hygienic standards established for soils. Therefore, we analyzed chemical contamination of soils as per contents of heavy metals in their mobile and gross forms (more than 3780 samples) according to SanPiN 1.2.3685-21[3] in four administrative districts in Orenburg (Tsentralniy, Leniskiy, Dzerzhinskiy, and Promyshlenniy).

Total soil contamination (Zc) was determined according to the Methodical guidelines MU 2.1.7.730-999[4].

Quality of foods, both produced locally and brought from other regions, was analyzed according to the Customs Union Technical Regulations (TR CU) 021/2011[5] (more than 1728 samples).

Carcinogenic health risks were assessed as per the Guide R 2.1.10.1920-04[6] and the Methodical guidelines MU 2.3.7.2519-09[7]. Retrospective epidemiological analysis focused on cancer incidence of the digestive organs and was performed using data provided by the territorial section of the National Cancer Register. We took data on cancer incidence collected in 2005–2018 and distributed as per aforementioned administrative districts in Orenburg.

We used Spearman's rank correlation to determine cause-effect relations between the analyzed indicators. Correlation coefficient within $0.1 < R < 0.3$ meant a correlation was weak; within $0.3 < R < 0.5$, moderate; within $0.5 < R < 0.7$, average.

The data were statistically analyzed using Statistica 10 and MS Excel for Windows.

Results and discussion. Soil is a primary accumulating medium in any route toxicants migrate along. Given that, we performed hygienic assessment of heavy metals contents in soils in residential areas with the focus being on metals assigned into Group 1 carcinogens by the International Agency for Research on Cancer (nickel, cadmium and chromium (VI)) and Group 2A carcinogens (cobalt and lead). The assessment was performed in four administrative districts in Orenburg. We didn't detect any soil samples with carcinogens contents deviating from hygienic standards. We

[3] SanPiN 1.2.3685-21. Gigienicheskie normativy i trebovaniya k obespecheniyu bezopasnosti i (ili) bezvrednosti dlya cheloveka faktorov sredy obitaniya: utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha RF ot 28 yanvarya 2021 g. № 2 [SanPiN 1.2.3685-21. Hygienic standards and requirements to providing safety and (or) harmlessness of the environmental factors for the population: approved by the Order of the RF Chief Sanitary Inspector on January 28, 2021 No. 2]. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573500115 (September 14, 2021) (in Russian).

[4] MU 2.1.7.730-999. 2.1.7. Pochva, ochistka naselennykh mest, bytovye i promyshlennye otkhody, sanitarnaya okhrana pochvy: utv. i vved. v deistvie Glavnym gosudarstvennym sanitarnym vrachom RF 5 fevralya 1999 g. [MU 2.1.7.730-999. 2.1.7. Soils, purification in settlements, communal and industrial wastes, sanitary protection of soils: approved by the Order of the RF Chief Sanitary Inspector on February 5, 1999]. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200003852 (September 16, 2021) (in Russian).

[5] TR TS 021/2011. O bezopasnosti pishchevoi produktsii (s izmen. na 14 iyulya 2021 g.): utv. resheniem Komissii Tamozhennogo soyuza ot 9 dekabrya 2011 g. № 880 [TR CU 021/2011. On food safety (last amended on July 14, 2021): approved by the decisions of the Customs Union Commission on December 9, 2011 No. 880]. *GARANT: information and legal portal*. Available at: http://docs.cntd.ru/document/902320560 (July 13, 2021) (in Russian).

[6] R 2.1.10.1920-04. 2.1.9. Sostoyanie zdorov'ya naseleniya v svyazi s sostoyaniem okruzhayushchei prirodnoi sredy i usloviyami prozhivaniya naseleniya. Rukovodstvo po otsenke riska dlya zdorov'ya naseleniya pri vozdeistvii khimicheskikh veshchestv, zagryaznyayushchikh okruzhayushchuyu sredu: utv. i vved. v deistvie Pervym zamestitelem Ministra zdravookhraneniya RF, Glavnym gosudarstvennym sanitarnym vrachom RF G.G. Onishchenko 5 marta 2004 g. [R 2.1.10.1920-04. 2.1.9. Population health with respect to the environment and living conditions. Human health risk assessment form environmental chemicals: approved on by G.G. Onishchenko, the First Deputy to the RF Public Healthcare Minister and the RF Chief Sanitary Inspector, on March 5, 2004]. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200037399 (June 20, 2021) (in Russian).

[7] MU 2.3.7.2519-09. 2.3.7. Sostoyanie zdorov'ya naseleniya v svyazi s sostoyaniem pitaniya. Opredelenie ekspozitsii i otsenka riska vozdeistviya khimicheskikh kontaminantov pishchevykh produktov na naselenie: utv. Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom RF G.G. Onishchenko 5 iyunya 2009 g. [MU 2.3.7.2519-09. 2.3.7. Population health with respect to food quality. Determination of exposure and assessment of risks caused by population exposure to chemical contaminants in foods: approved by G.G. Onishchenko, the head of the Federal Service for Surveillance over Consumer Rights protection and Human Wellbeing and the RF Chief Sanitary Inspector, on June 5, 2009]. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200080418 (July 23, 2021) (in Russian).

also established there were no statistically authentic differences between the districts regarding contents of heavy metals in their mobile and gross forms (Table 1).

The total soil contamination (Zc) turned out to be "permissible" in all four districts and in the city as a whole (Zc < 16).

Carcinogenic health risks caused by exposure to chemical contamination in soils were calculated taking into account inhalation, oral, and skin introduction for mobile forms of heavy metals which take active part in the biological turnover (Table 2).

We comparatively assessed the total carcinogenic risks (SUM CRs) taking into account all ways of introduction and established that the indicator was the highest for people living in Dzerzhniskiy district (3.01E-08); the second place was taken by Leninskiy district (2.84E-08); the third, Promyshlenniy (2.45E-08); and the fourth, Tsentralniy (2.30E-08). The total carcinogenic risks caused by exposure to heavy metals in soils didn't differ authentically in all four districts and were assessed as negligible.

We detected some differences between different territories in share contributions made by different heavy metals to the total carcinogenic risk. This is due to industrial enterprises being located in different parts of the city (Figure 1). Chromium (VI) makes the highest contribution to the total carcinogenic risk in all four districts, but primarily in Dzerzhinskiy with 76 % and Promyshlenniy with 71 %. The highest contribution made by lead was established in Leninskiy and Tsentralniy districts, 34 % and 28 % respectively. Cadmium, cobalt and nickel make similar contributions to SUM CRs in all four districts.

Oral exposure to toxicants is among priority ones; given that it is seems vital to estimate the chemical structure of another accumulating medium, notably foods, and to specifically identify carcinogens in them.

Table 1

Contents of heavy metals in soils (mg/kg) and their shares of MPC (maximum permissible concentrations) in four administrative districts and the city as a whole

Metals	Administrative districts				
	Tsentralniy	Leninskiy	Dzrzhinskiy	Promyshlenniy	City
Mobile forms					
Ni $M \pm m$	2.29 ± 0.28	2.43 ± 0.46	1.97 ± 0.19	2.19 ± 0.22	2.22 ± 0.29
Ni MPC share	0.57	0.61	0.49	0.55	0.56
Pb $M \pm m$	1.48 ± 0.27	2.07 ± 0.84	1.01 ± 0.33	1.07 ± 0.26	1.41 ± 0.42
Pb MPC share	0.25	0.34	0.17	0.18	0.23
Cd $M \pm m$	0.06 ± 0.02	0.06 ± 0.03	0.06 ± 0.01	0.04 ± 0.01	0.05 ± 0.01
Cd MPC share	-*	-	-	-	-
Co $M \pm m$	0.49 ± 0.19	0.27 ± 0.14	0.30 ± 0.13	0.28 ± 0.09	0.34 ± 0.10
Co MPC share	0.1	0.05	0.06	0.06	0.07
Cr $M \pm m$	0.26 ± 0.12	0.36 ± 0.13	0.51 ± 0.13	0.39 ± 0.14	0.31 ± 0.09
Cr MPC share	0.04	0.06	0.08	0.06	0.05
Gross forms					
Ni $M \pm m$	63.39 ± 8.66	54.40 ± 6.38	54.57 ± 9.90	61.8 ± 6.26	59.25 ± 7.80
Ni MPC share	0.79	0.68	0.68	0.77	0.74
Pb $M \pm m$	20.53 ± 8.33	14.38 ± 4.28	14.97 ± 2.45	11.7 ± 2.89	15.79 ± 4.49
Pb MPC share	0.16	0.11	0.12	0.09	0.12
Cd $M \pm m$	0.11 ± 0.03	0.08 ± 0.04	0.05 ± 0.02	0.08 ± 0.04	0.07 ± 0.03
Cd MPC share	0.05	0.04	0.02	0.04	0.04
Co $M \pm m$	4.26 ± 1.5	4.43 ± 0.87	6.12 ± 1.23	3.32 ± 0.88	4.43 ± 1.12
Co MPC share	0.17	0.18	0.24	0.13	0.18
Cr $M \pm m$	72.85 ± 12.53	88.60 ± 10.33	77.20 ± 9.97	76.94 ± 4.18	76.97 ± 9.25
Cr MPC share	0.73	0.89	0.77	0.077	0.77

N o t e : * means MPC hasn't been established for a mobile form.

Table 2

Individual and total carcinogenic risks caused by exposure to chemical contamination of soils in four administrative districts and the city as a whole

Carcinogenic risks*	Administrative districts				
	Tsentralniy	Leninskiy	Dzrzhinskiy	Promyshlenniy	City
Ni CRsi	1.66E-10	1.82E-10	1.48E-10	1.64E-10	1.65E-10
Ni CRso	0	0	0	0	0
Ni CRsd	0	0	0	0	0
Ni CRs	1.66E-10	1.82E-10	1.48E-10	1.64E-10	1.65E-10
Pb CRsi	5.26E-12	7.731E-12	3.78E-12	4.00E-12	5.19E-12
Pb CRso	4.32E-09	6.34E-09	3.10E-09	3.28E-09	4.26E-09
Pb CRsd	2.21E-09	3.26E-09	1.59E-09	1.68E-09	2.19E-09
Pb CRs	6.53E-09	9.61E-09	4.70E-09	4.97E-09	6.45E-09
Cd CRsi	3.06E-11	3.11E-11	3.13E-11	2.42E-11	2.93E-11
Cd CRso	1.35E-09	1.38E-09	1.38E-09	1.07E-09	1.30E-09
Cd CRsd	6.95E-10	7.06E-10	7.10E-10	5.50E-10	6.65E-10
Cd CRs	2.08E-09	2.11E-09	2.13E-09	1.65E-09	1.99E-09
Co CRsi	2.98E-10	2.35E-10	2.63E-10	2.46E-10	2.60E-10
Co CRso	0	0	0	0	0
Co CRsd	0	0	0	0	0
Co CRs	2.98E-10	2.35E-10	2.63E-10	2.46E-10	2.60E-10
Cr CRsi	1.15E-09	1.35E-09	1.89E-09	1.44E-09	1.46E-09
Cr CRso	8.47E-09	9.87E-09	1.38E-08	1.06E-08	1.07E-08
Cr CRsd	4.34E-09	5.06E-09	7.10E-09	5.43E-09	5.49E-09
Cr CRs	1.40E-08	1.63E-08	2.28E-08	1.75E-08	1.76E-08
SUM CRs	2.30E-08	2.84E-08	3.01E-08	2.45E-08	2.65E-08
Rank	4	2	1	3	-

N o t e : * CR means an individual additional carcinogenic risk; indexes: *si* is inhalation exposure to contaminants in soils; *so* is oral exposure; *sd* is skin exposure; SUM CRs is the total carcinogenic risks caused by exposure to chemicals in soils.

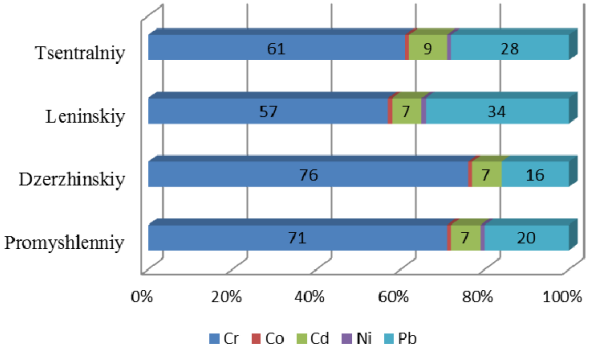

Figure 1. Contributions by priority carcinogens in soils into the total individual carcinogenic risk in all four districts (%)

Average annual contents of heavy metals in foods determined both as a median value and 90-th percentile conform to the requirements fixed in the TR CU 021/2011[5] regarding all the analyzed indicators (Table 3).

We ranked basic foods as per contributions made by specific carcinogens to the overall exposure and established that the leading rank places belonged to the following metals: cadmium in milk and milk products (34.8 %), flour-and-cereals, bakery (30.9 %), fruits and vegetables (25.9 %); lead in milk and milk products (35.3 %), fruits and vegetables (27.4 %); arsenic in fish (37.4 %).

To estimate contributions made by carcinogens in foods to risks of developing oncologic diseases, we calculated individual carcinogenic risks (Table 4).

The total carcinogenic risk caused by exposure to heavy metals in foods, calculated as per a median, conformed to the maximum permissible level; it turned out to be unacceptable for the population when calculated as per 90-th percentile. The greatest specific weight in the total carcinogenic risk belonged to arsenic (Figure 2).

The total individual carcinogenic risk caused by chemicals in soils and in foods is

Table 3

Contents of carcinogenic metals in foods (mg/kg)

Foods	Indicators	Cadmium	Lead	Arsenic
Flour-and-cereals, bakery	$M \pm m$	0.01189 ± 0.0021	0.00612 ± 0.00032	0.00577 ± 0.00042
	median	0.01	0.01	0.01
	90 %	0.014	0.01	0.01
Fruits and vegetables	$M \pm m$	0.00597 ± 0.00081	0.00649 ± 0.00084	0.00746 ± 0.0026
	median	0.01	0.01	0
	90 %	0.01	0.01	0.01
Oils and fats	$M \pm m$	0.00065 ± 0.00028	0.00313 ± 0.00134	0.00103 ± 0.00055
	median	0	0	0
	90 %	0	0.0082	0
Meat and meat products	$M \pm m$	0.00282 ± 0.00032	0.00456 ± 0.00125	0.00282 ± 0.00031
	median	0	0	0
	90 %	0.01	0.01	0.01
Milk and milk products	$M \pm m$	0.00528 ± 0.00034	0.0055 ± 0.00041	0.00524 ± 0.00034
	median	0.01	0.01	0.01
	90 %	0.01	0.01	0.01
Fish	$M \pm m$	0.0084 ± 0.00177	0.02858 ± 0.00675	0.09766 ± 0.01823
	median	0	0.01	0.024
	90 %	0.022	0.07	0.256

Table 4

Individual carcinogenic risks caused by heavy metals introduced with foods

Metal	SF_O*	ICRf** med	ICRf 90 %
Cadmium	0.38	1.6E-05	2.0E-05
Lead	0.047	2.0E-06	2.7E-06
Arsenic	1.5	4.8E-05	1.3E-04
SUM CRf***	–	6.5E-05	1.5E-04
PCR****	–	36	85

Note: * means a slope factor for oral introduction; ** means individual carcinogenic risks caused by exposure to chemicals in foods; *** means the total carcinogenic risk caused by exposure to chemicals in foods; **** means the population carcinogenic risk.

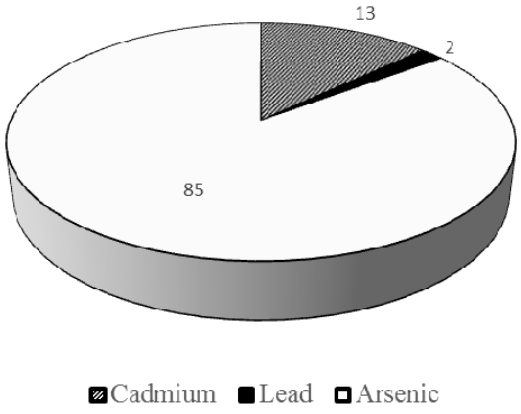

Figure 2. The structure of the total carcinogenic risk caused by exposure to carcinogens in foods taken as per 90-th percentile (%)

equal to 1.5E-04 (90-th percentile) in the city as a whole and this level is unacceptable. The total population carcinogenic risk taken as per the 90-th percentile amounted to 85 additional cancer cases among people living in Orenburg in addition to the background oncologic morbidity under 70-year exposure.

The gastrointestinal tract is the primary barrier between the body and effects produced by heavy metals in depositing media, such as soils and foods. We established that malignant neoplasms (MNs) of the digestive organs had a substantial specific weight in oncologic morbidity in Orenburg, from 24 % to 28 % depending on a district. Retrospective analysis showed a statistically significant growth in the incidence of MNs of the digestive organs over the examined period from 2008 to 2018 ($p \leq 0.05$) (Figure 3).

We ranked the incidence of MNs of the digestive organs as per four districts and established that the first rank place belonged to Leninskiy district; the second, Dzerzhinkiy; the third, Promyshlenniy; and the fourth, Tsentralniy. The incidence was authentically higher in Leninskiy and Dzerzhinskiy than on average in Orenburg ($p \leq 0.05$).

Calculated Spearman's rank correlation coefficients (R) allowed differentiating car-

cinogenic metals in soils and foods influencing MNs of the digestive organs. The incidence of MNs of the digestive organs has a direct statistically significant correlation with nickel concentration in soil (mobile form) ($R = 0.33$ for the MN of the esophagus; $R = 0.35$ for stomach cancer); cadmium (gross form) ($R = 0.5$ for the MN of the colon); chromium ($R = 0.55$ for the MN of the rectum; $R = 0.53$ for the MN of the gall bladder and extrahepatic bile ducts; $R = 0.5$ for the MN of the pancreas). We established a statistically authentic correlation between malignant neoplasms of the liver and intrahepatic bile ducts, gall bladder and extrahepatic bile ducts, and the pancreas and concentrations of arsenic in foods ($R = 0.71$, $R = 0.63$ and $R = 0.45$ respectively).

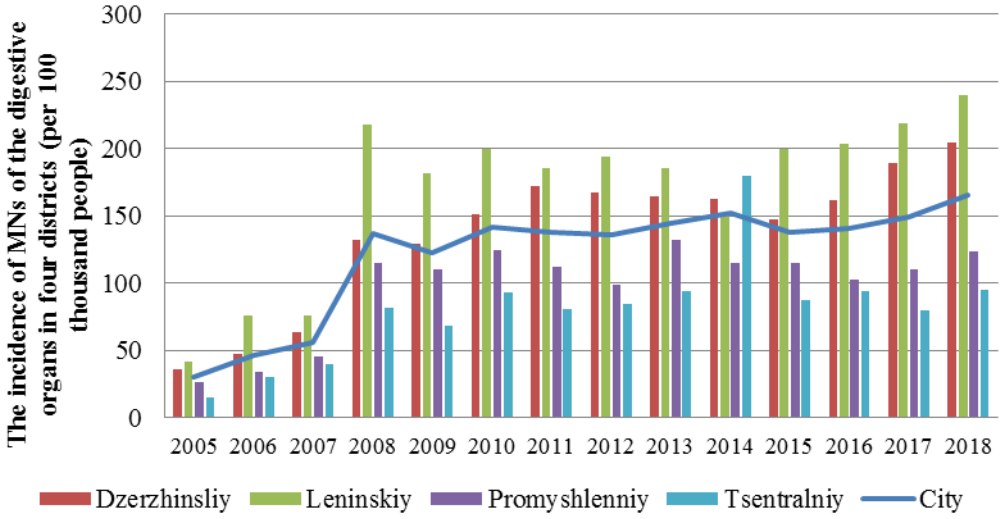

Figure 3. The incidence of malignant neoplasms of digestive organs taken in dynamics (per 100 thousand people) in different districts in Orenburg from 2008 to 2018

Table 5

Correlation coefficients for correlations between the incidence of the MNs of the digestive organs and carcinogenic chemicals in soils and foods

Localization	Carcinogens	Spearman's correlation coefficient *R*
Soil		
MNs of the esophagus	Nickel (mobile)	**0.33***
MNs of the stomach	Nickel (mobile)	**0.35***
MNs of the stomach	Cobalt (gross)	0.51
MNs of the stomach	Chromium (gross)	0.8
MNs of the colon	Cadmium (gross)	**0.5***
MNs of the rectum	Chromium (gross)	**0.55***
MNs of the liver and intrahepatic bile ducts	Chromium (gross)	0.41
MNs of the gall bladder and extrahepatic bile ducts	Chromium (mobile)	**0.53***
MNs of the pancreas	Chromium (mobile)	**0.5***
Foods		
MNs of the colon	Cadmium	0.31
MNs of the stomach	Lead	0.32
MNs of the liver and intrahepatic bile ducts	Arsenic	**0.71***
MNs of the gall bladder and extrahepatic bile ducts	Arsenic	**0.63***
MNs of the pancreas	Arsenic	**0.45***

N o t e : * means the statistical significance is taken at $p < 0.05$.

Conclusions. The total carcinogenic risk under multi-route exposure to heavy metals in such depositing media as soils and foods is unacceptable and amounts to 1.5E-04. The total population carcinogenic risk caused by exposure to heavy metals can reach 85 additional cancer cases over an average exposure period of 70 years.

We have detected carcinogenic heavy metals in soils that produce statistically authentic effects on developing MNs of the digestive organs: nickel (mobile form), MNs of the esophagus and stomach; cadmium (gross form), MNs of the colon; chromium VI (both mobile and gross form) MNs of the gall bladder, extrahepatic bile ducts, and the pancreas.

We established a statistically authentic correlation between arsenic concentrations in foods and malignant neoplasms of the liver and intrahepatic bile ducts, gall bladder and extrahepatic bile ducts, and the pancreas (R = 0.71, R = 0.63 and R = 0.45 respectively).

Therefore, even if contents of carcinogenic heavy metals do not violate hygienic standards in such accumulating media as soils and foods, it doesn't completely eliminate probable negative influence on health including long-term effects and developing malignant neoplasms.

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

References

1. Kargapolov N.V. Geochemical studies in city ecosystems. *Sotsial'no-ekologicheskie tekhnologii*, 2016, no. 3, pp. 31–37 (in Russian).

2. Zamotaev I.V., Ivanov I.V., Mikheev P.V., Belobrov V.P. Assessment of the state of soils and vegetation in areas of landfills and municipal solid waste sites (a review). *Eurasian soil science*, 2018, vol. 51, no. 7, pp. 827–842. DOI: 10.1134/S1064229318070104

3. Edmondson J.L., Stott I., Davies Z.G., Gaston K.J., Leake J.R. Soil surface temperatures reveal moderation of the urban heat island effect by trees and shrubs. *Sci. Rep.*, 2016, vol. 6, no. 1, pp. 33708. DOI: 10.1038/srep33708

4. Benhaddya M., Boukhelkhal A., Halis Y., Hadjel M. Human health risks associated with metals from urban soil and road dust in an oilfield area of Southeastern Algeria. *Arch. Environ. Contam. Toxicol.*, 2016, vol. 70, no. 3, pp. 556–571. DOI: 10.1007/s00244-015-0244-6

5. Zharikova E.A. Assessment of heavy metals content and environmental risk in urban soils. *Izvestiya Tomskogo politekhnicheskogo universiteta. Inzhiniring georesursov*, 2021, vol. 332, no. 1, pp. 164–173. DOI: 10.18799/24131830/2021/1/3009 (in Russian).

6. Grishchenko S.V., Grishchenko I.S., Kostenko V.S., Zor'kina A.V., Minakov D.G., Yakimova K.A. Sovremennye osobennosti kontaminatsii tyazhelymi metallami pishchevykh produktov, proizvedennykh iz mestnogo syr'ya v ekokrizisnom regione [Contemporary peculiarities of contamination with heavy metals of food products produced from local raw materials in the ecocrisis region]. *Vestnik gigieny i epidemiologii*, 2017, vol. 21, no. 4, pp. 283–287 (in Russian).

7. Gerson J.R., Driscoll C.T., Demers J.D., Sauer A.K., Blackwell B.D., Montesdeoca M.R., Shanley J.B., Ross D.S. Deposition of mercury in forests across a montane elevation gradient: Elevational and seasonal patterns in methylmercury inputs and production. *JGR Biogeosciences*, 2017, vol. 122, no. 8, pp. 1922–1939. DOI: 10.1002/2016JG003721

8. Eremin V.N., Reshetnikov M.V., Sheshnev A.S. Impact of waste landfills in the Saratov region on the sanitary condition of the soil. *Gigiena i sanitariya*, 2017, vol. 96, no. 2, pp. 117–121. DOI: 10.18821/0016-9900-2017-96-2-117-121 (in Russian).

9. Vekovshinina S.A., Kleyn S.V., Hankhareev S.S., Makarova L.V., Madeeva E.V., Boloshinova A.A. The assessment of environmental quality and risks for the population of the city of Zakamensk – territory of long-term storage of waste of Dzhidinsky tungsten-molybdenum combine. *Gigiena i sanitariya*, 2017, vol. 96, no. 1, pp. 15–20. DOI: 10.18821/0016-9900-2017-96-1-15-20 (in Russian).

10. Khan S., Munir S., Sajjad M., Li G. Urban park soil contamination by potentially harmful elements and human health risk in Peshawar city, Khyber Pakhtunkhwa, Pakistan. *Journal of Geochemical Exploration*, 2016, vol. 165, pp. 102–110. DOI: 10.1016/j.gexplo.2016.03.007

11. Kumar S., Ghosh S., Mukherjee S., Sarkar S. Chromium and nickel migration study through fine grained soil. *J. Hazard. Mater.*, 2009, vol. 170, no. 2-3, pp. 1192–1196. DOI: 10.1016/j.jhazmat.2009.05.097

12. Aydinov G.T., Marchenko B.I., Deryabkina L.A., Sinelnikova Yu.A. Chemical factors of soil polution in Taganrog as population health risk factors. *Health Risk Analysis*, 2017, no. 1, pp. 13–20. DOI: 10.21668/health.risk/2017.1.02.eng

13. Bashkin V.N., Galiulin R.V., Galiulina R.A., Arabsky A.K. Risk of soil contamination by heavy metals through gas-dust emissions. *Problemy analiza riska*, 2019, vol. 16, no. 1, pp. 42–49. DOI: 10.32686/1812-5220-2019-16-42-49 (in Russian).

14. Kaverina N.V. Transformation of urban soils under technogenic impacts. *Problemy regional'noi ekologii*, 2020, no. 4, pp. 113–117. DOI: 10.24411/1728-323X-2020-14113 (in Russian).

15. Deryabin A.N., Unguryanu T.N., Buzinov R.V. Population health risk caused by exposure to chemicals in soils. *Health Risk Analysis*, 2019, no. 3, pp. 18–25. DOI: 10.21668/health.risk/2019.3.02.eng

16. Radomskaya V.I., Borodina N.A. Assessment of anthropogenic contamination in an urban territory by the example of Blagoveshchensk city. *Geoekologiya. Inzhenernaya geologiya, gidrogeologiya, geokriologiya*, 2019, no. 6, pp. 79–93. DOI: 10.31857/S0869-78092019679-93 (in Russian).

17. Al-Saleh I., Abduljabbar M. Heavy metals (lead, cadmium, methylmercury, arsenic) in commonly imported rice grains (Oryza sativa) sold in Saudi Arabia and their potential health risk. *Int. J. Hyg. Environ. Health.*, 2017, vol. 220, no. 7, pp. 1168–1178. DOI: 10.1016/j.ijheh.2017.07.007

18. Lyzhina A.V., Unguryanu T.N., Rodimanov A.V. Health risk assessment associated with contamination by heavy metals of food products. *Zdorov'e naseleniya i sreda obitaniya*, 2018, no. 7 (304), pp. 4–7. DOI: 10.35627/2219-5238/2018-304-7-4-7 (in Russian).

19. Ciannameo V., Ricceri F., Soldati S., Scarnato C., Gerosa A., Giacomozzi G., d'Errico A. Cancer mortality and exposure to nickel and chromium compounds in a cohort of Italian by electroplaters. *Am. J. Ind. Med.*, 2019, vol. 62, no. 2, pp. 99–110. DOI: 10.1002/ajim.22941

20. Zaitseva N.V., May I.V., Klein S.V., Khankharev S.S., Boloshinova A.A. Scientific and methodological aspects and practical experience for the formation of the evidential base of hazard to health in the population in the zone of influence of waste from the past economic activity. *Gigiena i sanitariya*, 2017, vol. 96, no. 11, pp. 1038–1044. DOI: 10.18821/0016-9900-2017-96-11-1038-1044 (in Russian).

21. Cai L.-M., Xu Z.-C., Qi J.-Y., Feng Z.-Z., Xiang T.-S. Assessment of exposure to heavy metals and health risks among residents near Tonglushan mine in Hubei, China. *Chemosphere*, 2015, vol. 127, pp. 127–135. DOI: 10.1016/j.chemosphere.2015.01.027

22. Sivukhin A.N., Markov D.S., Borisova E.A. Influence of soil contamination with heavy metals on the population health of the Ivanovo and Kostroma regions. *Problemy regional'noi ekologii*, 2019, no. 3, pp. 81–87. DOI: 10.24411/1728-323X-2019-13081 (in Russian).

23. Tikhonova Yu.L., Milushkina O.Yu., Kalinovskaya M.V., Simkalova L.M. The comparative analysis of chemical contamination of food and children's health indices in the Russian Federation. *Zdorov'e naseleniya i sreda obitaniya*, 2020, vol. 322, no. 1, pp. 13–18. DOI: 10.35627/2219-5238/2020-322-1-13-18 (in Russian).

24. Loud J.T., Murphy J. Cancer Screening and Early Detection in the 21st Century. *Semin. Oncol. Nurs.*, 2017, vol. 33, no. 2, pp. 121–128. DOI: 10.1016/j.soncn.2017.02.002

25. Borschuk E.L., Begun D.N., Klimushkin A.V., Begun T.V., Kulanova A.M. Status and trends of main indicators cancer incidence in the Orenburg region in the 2010s. *Sovremennye problemy nauki i obrazovaniya*, 2020, no. 6, pp. 127. DOI: 10.17513/spno.30281

26. Hochberg M.E., Noble R.J. A framework for how environment contributes to cancer risk. *Ecol. Lett.*, 2017, no. 20, pp. 117–134. DOI: 10.1111/ele.12726

Boev V.M., Zelenina L.V., Kudusova L.H., Kryazheva E.A., Zelenin D.O. Hygienic assessment of carcinogenic health risks associated with contamination of depositing media with heavy metals. Health Risk Analysis, 2022, no. 1, pp. 17–26. DOI: 10.21668/health.risk/2022.1.02.eng

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Research article

ASSESSMENT OF CARCINOGENIC RISK CAUSED BY ELEVATED 3,4-BENZ(A)PYRENE CONCENTRATION IN SOILS IN AN INDUSTRIAL CITY

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Apparent destructive changes in soils typically occur in residential areas within urbanized ecological systems formed in large industrial cities. Elevated concentrations of super-toxicants and xenobiotics in soils, polycyclic aromatic hydrocarbons included, create high potential health risks for city population.

Our research goal was to assess the carcinogenic risk caused by elevated 3,4-benz(a)pyrene concentrations in soils in Taganrog, an industrial city with its population being about 250 thousand people located in Rostov region. The assessment included individual and population risks. There are two basic reasons which make the research vital. First of all, 3,4-benz(a)pyrene contents in soils in residential areas exceed hygienic standards. Secondly, the incidence of malignant neoplasms has been stably high in the city.

We analyzed the results of determining 3,4-benz(a)pyrene concentrations in 384 soil samples taken in 2013–2020 at 19 monitoring posts (located within residential areas close to crossroads with intense traffic, recreational zones, and areas around pre-school children facilities). 3,4-benz(a)pyrene was established to be the priority pollutant in soils in the city with its share contribution to the complex pollution index (C_{soil}) being 55.25 %. 3,4-benz(a)pyrene concentrations were higher than maximum permissible ones in 65.63 % of all the examined soil samples; its average and maximum concentrations were equal to 2.298 and 45.525 MPC accordingly. We assessed the individual multi-route carcinogenic risk (CR) caused by elevated 3,4-benz(a)pyrene concentrations in soils. The risk turned out to be high ($2.4606 \cdot 10^{-3}$) and inhalation introduction was established as the priority one (94.84 %).

Key words: *social-hygienic monitoring, health risk, chemical soil pollution, 3,4-benz(a)pyrene, malignant neoplasms, carcinogenic risk assessment.*

Apparent destructive processes occur in soils in residential areas due to chemical contamination. This situation is typical for most industrial cities. City landscapes are open systems which are closely related to the atmosphere and hydrosphere. High contents of technogenic pollutants, xenobiotics included, in their surface horizons are a highly informative geochemical indicator showing how significantly these landscapes degrade under exposure to anthropogenic technogenic burden. This indicator should be taken into account when examining health disorders among urban population, including studies with their focus on malignant neoplasms. Concentrations of polycyclic aromatic hydrocarbons (polyarenes or PAHs) are among the most significant indicators included into hygienic and environmental profiles of soils on urbanized territories since many of such chemicals are highly carcinogenic and mutagenic. This creates elevated health risks for population [1–6]. In the Russian Federation 3,4-benz(a)pyrene, a chemical with carcinogenic and mutagenic properties which belongs to the 1st hazard category, is often used as the universal indicator and major marker of environmental contamination with PAHs which occurs both due to anthropogenic technogenic sources and natural ones. Organization of additional control over its concentra-

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tion is considered a vital trend in the development of social and hygienic monitoring systems in large cities [3, 7]. A substantial contribution to PAHs emission is made in cities, together with industrial sources and power producing enterprises, by emissions from motor transport due to incomplete fuel combustion in internal-combustion engines and wear and tear of tyres and road surfaces [8–16]. Novocherkasskaya hydro-recirculation power plant is the most powerful energy production in Rostov region and a major source of polyarenes emissions into the environment. This is confirmed by results of soils monitoring in a zone influenced by this object since elevated 3,4-benz(a)pyrene levels were detected in roots, stems, and leaves of plants growing there [17]. A substantial contribution to environmental pollution is also made by PAHs which are intensively produced by stove heating, especially when coal is used as a fuel as well as by PAHs coming from various natural sources [18–24]. Soils are a natural depot for polyarenes. It is a proven fact that only a part of hazardous chemicals is directly deposited on soil surface from ambient air as well as with precipitations. More than a half of such chemicals primarily accumulate in plants and occur in soils when the vegetation period is over [25, 26]. PAHs absorption from soils through roots of agricultural plants makes for their penetration into food chains with agricultural products and the process has an apparent biomagnification effect. Besides, soils act as the secondary contamination source for ambient air and water by accumulating these pollutants quite actively [27]. Therefore, results produced by monitoring of 3,4-ben(a)pyrene concentrations in urban soils are highly informative integral indicators for creating an objective hygienic and environmental profile of a territory within social and hygienic monitoring activities and environmental analytics [28].

We selected Taganrog as our research object. The city is a large industrial center located in Rostov region; its population is about 250 thousand people. The situation with cancer incidence is stably unfavorable in Taganrog [29]. Thus, average long-term frequency calculated for all localizations of malignant neoplasms over the last 15 years is equal to 480.11 $^{o}/_{oooo}$ which is by 1.25 times higher than the same indicator calculated for the whole Rostov region (373.98 $^{o}/_{oooo}$). The city holds the first rank place in the region as per this parameter. Average annual growth in long-term total cancer incidence in Taganrog amounted to +0.28 % in 2006–2020. These stable ascending trends in frequency have been detected for such localizations of malignant neoplasms as oral cavity and pharynx (average annual growth in long-term trend is +1.15 %), rectum (+0.57 %), skin (without melanoma) (+1.89 %), breast (+1.95 %), uterine neck (+3.44 %), prostate (+3.95 %), thyroid gland (+4.42 %), and malignant lymphomas (+1.04 %). The first rank place among oncologic pathologies belongs to malignant neoplasms of skin (without melanoma) with their specific weight being 15.08 %; the second, malignant neoplasms of breast (12.50 %); the third, malignant neoplasms of trachea, bronchi and lung (9.14 %). The next are malignant neoplasms of colon, prostate, and stomach, 6.84, 6.14 and 6.04 % accordingly. Frequency of malignant neoplasms taken in long-term dynamics grew by 2.06 times from 260.35 $^{o}/_{oooo}$ in 1986 up to the maximum level registered in 2017 when it was equal to 535.77 $^{o}/_{oooo}$ (Figure).

Our research goal was to assess an individual and population carcinogenic risk caused by elevated 3,4-benz(a)pyrene concentrations in soils in residential areas in Taganrog, Rostov region, based on the results produced by social and hygienic monitoring activities in 2013–2020.

Material and methods. The research was based on the results of examining 384 soils samples which were tested to determine 3,4-benz(a)pyrene contents in them as well as on data taken from the report forms No. 35 “Data on patients with diagnosed malignant neoplasms” over 1985–2015 and No. 7 “Data on malignant neoplasms” over 2016–2020.

Soil samples were taken in 2013–2020 at 19 monitoring points located in residential areas close to crossroads with intense traffic (8 points), areas around municipal preschool

children facilities (8 points), and recreation zones in Taganrog (3 points) including the embankment, a park and a beach. Mass 3,4-benz(a)pyrene concentrations in soils were determined with high performance liquid chromatography (HPLC) using "Stayer" stationary liquid chromatographer with a fluorometer. When assessing a share contribution made by 3,4-benz(a)pyrene into the total soil contamination, we calculated values of separate indicators showing contents of the examined pollutants (in MPC), their concentration coefficients taking into account regional background levels (F), the complex indicator of soil contamination (C_{soil}) and the summated technogenic contamination coefficient (Zc). Results of the studies accomplished by experts from the Academy for Biology and Biotechnology of the D.I. Ivanoskiy's Southern Federal University in the "Persianovskaya zapovednaya step" State Soil Reserve were taken as regional background levels of 3,4-benz(a)pyrene contents in common chernozem in Rostov region. Carcinogenic risks were assessed in accordance with the Guide R 2.1.10.1920-04[1].

We applied our own specialized software "Turbo oncologist", version 2.01, to create databases and to perform their statistical analysis. The software includes a package which allows implementing algorithms for retrospective epidemiological analysis of frequencies, structure, long-term dynamics, and spatial characteristics based on methods used for partial and complex assessment of an actual (epidemiological) risk. We also used "Turbo Dynamics" software package, version 1.02, (to analyze long-term trends in dynamics, to perform middle-term extrapolation prediction and modeling, non-linear regression and correlation analysis); as well as IBM SPSS Statistics ("Statistical Package for Social Science") professional statistical software, version 19.0.

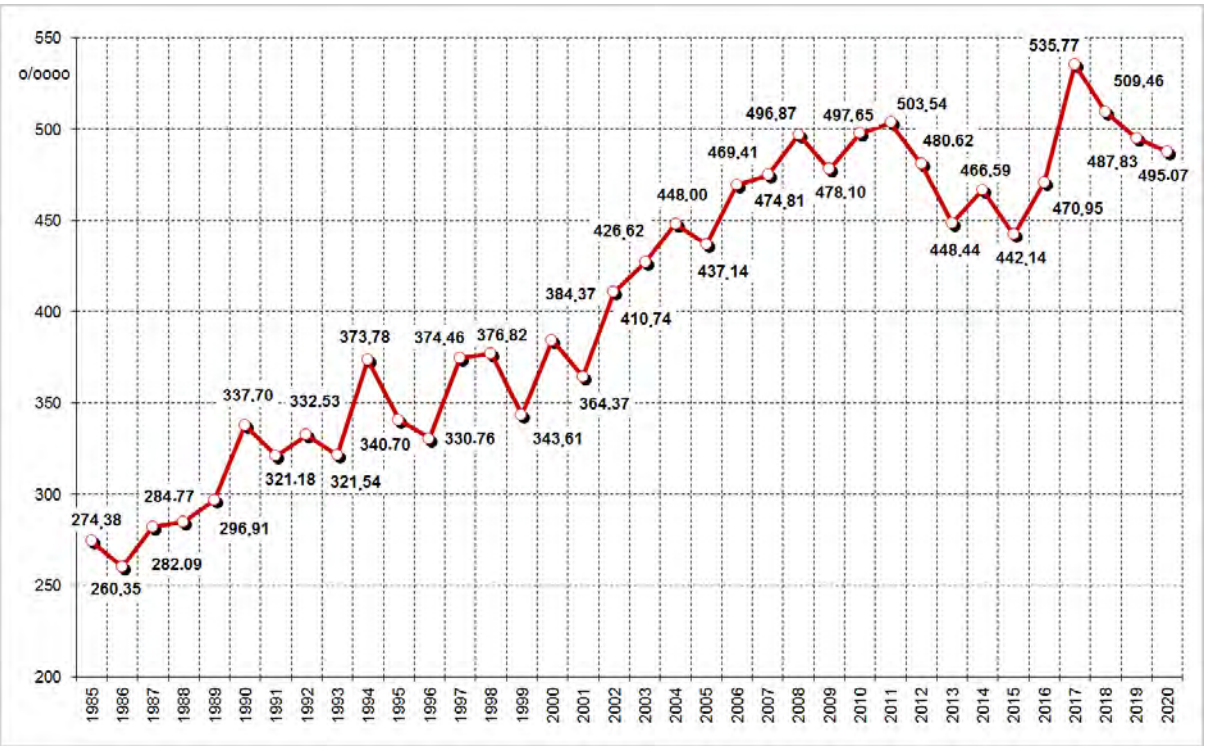

Figure. Total cancer incidence among population in Taganrog, Rostov region, taken in dynamics over 1985–2020

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

Table 1

Soil contamination with 3,4-benz(a)pyrene in Taganrog, Rostov region, taken in dynamics over 2013–2020

Indicators	Years								2013–2020
	2013	2014	2015	2016	2017	2018	2019	2020	
A share of samples with concentrations higher than MPC, %	72.9	70.8	52.1	62.5	79.2	58.3	66.7	62.5	65.63 ± 4.78
The highest concentration, mg/kg	0.3710	0.1542	0.7610	0.9105	0.1799	0.2170	0.0440	0.1710	0.9105
Contamination indicators (Imax, MPC)	18.550	7.710	38.050	45.525	8.995	10.850	2.200	8.550	45.525
Average annual concentration (Cave, mg/kg)	0.0484	0.0514	0.0471	0.0511	0.0476	0.0510	0.0227	0.0484	0.0460 ± 0.0103
Average contamination indicator (Iave, MPC)	2.422	2.570	2.353	2.553	2.382	2.550	1.136	2.422	2.298
C_{soil}	4.312	4.590	4.113	4.535	4.248	4.806	3.026	4.312	4.160
A share contribution into C_{soil}, %	56.17	56.00	57.20	56.29	56.06	53.05	37.55	56.17	55.25
The summated technogenic contamination coefficient (Zc)	6.651	7.120	6.496	7.117	6.890	6.301	6.651	6.651	6.978

Results. The results of examinations performed in 2013–2020 indicate that soils in Taganrog are heavily contaminated with 3,4-benz(a)pyrene, Thus, its concentrations were higher than MPC (0.02 mg/kg) in 65.63 ± 4.78 % of 384 examined soil samples and the average actual concentration of the pollutant was 0.0460 ± 0.0103 mg/kg (2.298 MPC). The maximum detected 3,4-benz(a)pyrene concentration was 0.9105 mg/kg (45.525 MPC). We established the priority role played by this pollutant in soil contamination in the city with its share contribution into C_{soil} being 55.25 % (Table 1).

The highest contamination with 3,4-benz(a)pyrene was detected in residential areas located close to crossroads with intense traffic (the first group of monitoring points) where a specific share of samples with the pollutant concentrations being higher than MPC amounted to 71.60 ± 5.64 %, over the last eight years and its average content was 0.0475 ± 0.0103 mg/kg (2.376 MPC). The second rank place as per frequency of concentrations exceeding MPC belonged to soils in recreation zones (58.72 ± 9.45 %); however, an average 3,4-benz(a)pyrene content turned out to be even higher there than at monitoring points from the first group (0.0498 ± 0.0241 mg/kg). The Primorskii city park is a recreation zone with the extremely high soil contamination with 3,4-benz(a)pyrene (up to 45.525 MPC); the park is located in a zone which was once influenced by emissions from production workshops of "Taganrogskii harvester plant" PLC and "Kirpichnik" PLC, two large industrial enterprises which are both closed at present. Therefore, soil contamination as per average 3,4-benz(a)pyrene contents can be considered "hazardous" in the first and second monitoring groups according to the assessment criteria applied in evaluation of chemical contamination and stipulated by the Sanitary Rules and Standards SanPiN 2.1.7.1287-03[2]. The third group of monitoring points was located on areas around municipal preschool children facilities. A specific share of soil samples with 3,4-benz(a)pyrene concentration exceeding MPC detected there was 36.00 ± 19.81 %; the average pollutant content was 0.0176 ± 0.0094 mg/kg (0.882 MPC) and its maximum content didn't exceed 3.105 MPC (Table 2).

[2] SanPiN 2.1.7.1287-03. Sanitarno-epidemiologicheskie trebovaniya k kachestvu pochvy: Sanitarno-epidemiologicheskie pravila i normativy [The sanitary-epidemiologic requirements to soil quality: Sanitary-Epidemiological Rules and Standards]. Moscow, The Federal State Sanitary and Epidemiological Surveillance Center of the RF Public Healthcare Ministry, 2004, 16 p.

Table 2

Soil contamination with 3,4-benz(a)pyrene in Taganrog, Rostov region, detected at different monitoring points taken in dynamics over 2013–2020

Indicators	Total at all monitoring points	Including:		
		Residential areas with intense traffic	Recreation zones (embankment, park)	Areas around preschool children facilities
A number of taken soil samples	384	250	109	25
A share of samples with concentrations higher than MPC (%)	65.6 ± 4.8	71.6 ± 5.6	58.7 ± 9.5	36.0 ± 19.8
Average concentration (Cave, mg/kg)	0.0460 ± 0.0103	0.0475 ± 0.0103	0.0498 ± 0.0241	0.0176 ± 0.0094
Contamination indicator as per average concentration (Iave, MPC)	2.298	2.376	2.492	0.882
Lower confidence limit of average concentration ($p < 0.05$)	0.0357	0.0372	0.0256	0.0082
Upper confidence limit of average concentration ($p < 0.05$)	0.0563	0.0579	0.0740	0.0270
Minimal concentration (Cmin, mg/kg)	0.0026	0.0038	0.0026	0.0040
Contamination indicator as per minimal concentration (Imin, MPC)	0.130	0.190	0.130	0.200
Maximum concentration (Cmax, mg/kg)	0.9105	0.7610	0.9105	0.0621
Contamination indicator as per maximum concentration (Imax, MPC)	45.525	38.050	45.525	3.105

We should note that a significant part of residential areas in Taganrog is private housing with land spots near houses where people grow agricultural products (vegetables, fruits, berries, etc.) and there is a high probability that soils there are heavily contaminated with 3,4-benz(a)pyrene, Given that, it is truly vital to assess carcinogenic risks associated with chemical contamination of soils in the city when social and hygienic monitoring is performed.

We assessed carcinogenic risks associated with elevated 3,4-benz(a)pyrene contents in city soils as per results of laboratory tests performed in 2013–2020. According to recommendation provided in [30–33] a carcinogenic risk was assessed taking into account substantiated maximum exposures calculated on the basis of upper 95 % confidence limits of average 3,4-benz(a)pyrene concentrations.

Individual multi-route carcinogenic risk rates (CR) were calculated within an exposure scenario of a typical residential area as the sums of carcinogenic risk rates caused by exposure to 3,4-benz(a)pyrene contents in soils at monitoring points taking into account oral (CRo), inhalation (CRi) and dermal (CRd) introduction into the body.

When calculating an individual carcinogenic risk caused by oral 3,4-benz(a)pyrene introduction from soils (CRo), we took a slope factor (SFo) value equal to 7.3 $(mg/(kg \cdot day))^{-1}$. CRo values calculated for separate calendar years within the examined period varied from $2.8312 \cdot 10^{-5}$ to $6.4046 \cdot 10^{-5}$, and the average long-term CRo rate calculated on the basis of the upper confidence limit ($p < 0.05$) of the average 3,4-benz(a)pyrene concentration turned out to be equal to $7.2075 \cdot 10^{-5}$ (Table 3).

Therefore, CRo falls within the second range of lifetime individual risk (maximum permissible risk or the upper limit of acceptable risk). This makes the constant control of it essential. The share contribution made by CRo to the structure of the individual multi-route carcinogenic risk (CR) is equal to 2.93 %. The lifetime population carcinogenic risk (an additional to the background absolute number of malignant neoplasms which can occur during an average lifetime of a person equal to 70 years

Table 3

Carcinogenic risk for people living in Taganrog, Rostov region, caused by 3,4-benz(a)pyrene (3,4-BP) concentrations in soils in 2013–2020

Carcinogenic risk rate	Individual multi-route carcinogenic risk	Carcinogenic risk caused by exposure to 3,4-BP in soils (an exposure scenario of a residential area)		
		Oral introduction (CRo)	Inhalation introduction (CRi)	Dermal introduction (CRd)
Risks as per average concentrations in 2013–2020	$2.0203 \cdot 10^{-3}$	$5.9179 \cdot 10^{-5}$	$1.9161 \cdot 10^{-3}$	$4.4976 \cdot 10^{-5}$
Risks as per upper confidence limits of average concentrations in 2013–2020	$2.4606 \cdot 10^{-3}$	$7.2075 \cdot 10^{-5}$	$2.3337 \cdot 10^{-3}$	$5.4777 \cdot 10^{-5}$
Carcinogenic risk structure (%)	100.00	2.93	94.84	2.23

Table 4

Population carcinogenic risk taken as per the upper confidence limits of average concentrations ($p < 0.05$) over 2013–2020

Indicator	Total risk PCR	Oral exposure (PCRo)	Inhalation exposure (PCRi)	Dermal exposure (PCRd)
Expected number of malignant neoplasms during the whole lifetime (70 years) calculated per 252,309 people (average city population)	621	18	589	14
Annual population carcinogenic risk per 100 thousand people	3.515	0.103	3.334	0.078
Contribution made by 3,4-BP in soils to cancer incidence (%)	0.729	0.021	0.692	0.016

calculated as per the average population number in Taganrog which is 252,309 people) is equal to 18 cases under oral introduction of 3,4-benz(a)pyrene from soils (PCRo). Accordingly, the annual population carcinogenic risk is equal to 0.103 $^{o}/_{oooo}$ per 100 thousand people and the share contribution made by 3,4-benz(a)-pyrene in soils to the overall cancer incidence under oral introduction equals to 0.021 % (Table 4).

Since there are no data on gastro-intestinal absorptivity (GIABS) for 3,4-benz(a)-pyrene, its value was taken as equal to 1.0 which means that 100 % of the pollutant quantity introduced into the body is absorbed [30, 31]. Therefore, when calculating the individual carcinogenic risk under dermal introduction, we took the slope factor value (SFd) as equal to the slope factor value under oral exposure (SFo), that is, 7.3 $(mg/(kg \cdot day))^{-1}$. Rates of the annual individual carcinogenic risk under dermal exposure (CRd) over the last eight years varied from $2.1517 \cdot 10^{-5}$ to $4.8675 \cdot 10^{-5}$ and its average long-term rage was $5.4777 \cdot 10^{-5}$ (the second range of the individual lifetime risk). The specific share of CRd in the individual multi-route carcinogenic risk (CR) was equal to 2.23 %. The lifetime population carcinogenic risk (PCRd) for population in Taganrog equals to 14 cases over 70 years; the annual population carcinogenic risk per 100 thousand people is 0.078 $^{o}/_{oooo}$; the share contribution made by 3,4-benz(a)-pyrene in soils to the overall cancer incidence is 0.016 % under dermal introduction.

When assessing the individual carcinogenic risk under inhalation exposure to 3,4-benz(a)pyrene in soils (CRi), we took a slope factor (SFi) equal to 3.9 $(mg/(kg \cdot day))^{-1}$. When calculating its vaporization factor (VF), we took a value equal to 0.034 $Pa \cdot m^3/mol$ as the value of the Henry's law constant. We established that the annual CRi rates varied from $9.1672 \cdot 10^{-4}$ to $2.0737 \cdot 10^{-3}$; CR rates, from $9.6655 \cdot 10^{-4}$ to $2.1865 \cdot 10^{-3}$. Their average long-term values were $2.3337 \cdot 10^{-3}$ and

$2.4606 \cdot 10^{-3}$ accordingly thus falling within the fourth risk range (more than $1.0 \cdot 10^{-3}$). This means there is *De manifestis Risk*, which is unacceptable, both for population in general or specific occupational groups. Therefore, inhalation introduction of 3,4-benz(a)pyrene from soils is the priority one with the share contribution made by CRi to the individual multi-route carcinogenic risk (CR) being equal to 94.84 %. The lifetime population carcinogenic risk for population in Taganrog under inhalation introduction of 3,4-benz(a)pyrene from soils (PCRi) is equal to 589 cases over 70 years; the lifetime multi-route population carcinogenic risk (PCR), 621 cases; the annual population carcinogenic risks per 100 thousand people are equal to 3.334 $^{o}/_{oooo}$ and 3.515 $^{o}/_{oooo}$ accordingly with the share contribution made by 3,4-benz(a)pyrene in soils to the overall cancer incidence being equal to 0.692 % and 0.729 % accordingly (Table 4).

Therefore, we corroborated that soils in Taganrog were heavily contaminated with 3,4-benz(a)pyrene and the pollutant created high carcinogenic risks for the city population. This chemical has several peculiarities: it tends to accumulate in soils and to persist there preserving its biological activity for a long period of time; it is able to create secondary contamination of ambient air and to penetrate into food chains through roots of agricultural plants; its carcinogenic and mutagenic effects on the human body are well-proven. Given that, it is advisable to include dynamic monitoring of 3,4-benz(a)pyrene concentrations into the list of mandatory soil examinations within social and hygienic monitoring activities. There are some promising trends in developing information and analytical support for hygienic assessment of chemical contamination in soils within the social and hygienic monitoring system. They include integration of profile databases into regional geoinformation systems (GIS) and new software enabling assessment of risks related to developing carcinogenic effects caused by chemical contamination in soils in Rostov region. There are plans to perform sampling studies on 3,4-benz(a)pyrene contents in fruits and vegetables grown on private land spots on the territory of Taganrog provided that such studies are included into the program of social and hygienic monitoring in the region.

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References

1. Onishchenko G.G. Khimicheskaya bezopasnost' – vazhneishaya sostavlyayushchaya sanitarno-epidemiologicheskogo blagopoluchiya naseleniya [Chemical safety is the most important constituent of the sanitary and epidemiological well-being of population]. *Toksikologicheskii vestnik*, 2014, no. 1, pp. 2–6 (in Russian).

2. Unguryanu T.N., Gudkov A.B., Nikanov A.N. Health risk assessment of soil contaminants for health of urban population. *Profilakticheskaya i klinicheskaya meditsina*, 2012, vol. 42, no. 1, pp. 101–105 (in Russian).

3. Kryatov I.A., Tonkopiy N.I., Vodyanova M.A., Ushakova O.V., Doneryan L.G., Evseeva I.S., Matveeva I.S., Ushakov D.I. Scientific evidence for hygienic standards harmonized with international recommendations for priority polluitions of soils. *Gigiena i sanitariya*, 2015, vol. 94, no. 7, pp. 42–48 (in Russian).

4. Unguryanu T.N., Novikov S.M. Approaches to assessing the health risk under exposure to chemicals with account of age peculiarities. *Gigiena i sanitariya*, 2012, vol. 91, no. 5, pp. 98–101 (in Russian).

5. Boev V.M., Zelenina L.V., Kryazhev D.A., Tulina L.M., Neplokhov A.A. Analysis on exposure carcinogenic risk of environmental factors on health largest industrial cities and malignant tumors. *ZNiSO*, 2016, vol. 279, no. 6, pp. 4–7 (in Russian).

6. Nielsen T., Jorgensen H.E., Larsen J.C., Poulsen M. City air pollution of polycyclic aromatic hydrocarbons and other mutagens: occurrence, sources and health effects. *Sci. Total Environ.*, 1996, vol. 189–190, pp. 41–49. DOI: 10.1016/0048-9697(96)05189-3

7. Rakhmanin Yu.A., Levanchuk A.V., Kopytenkova O.I. Improvement of the system of social and hygienic monitoring of territories of large cities. *Gigiena i sanitariya*, 2017, vol. 96, no. 4, pp. 298–301. DOI: 10.18821/0016-9900-2017-96-4-298-301 (in Russian).

8. Butenko G.S., Polonskaya D.E. 3,4-benz(a)pyrene availability in the technogenically polluted territory soils. *Vestnik KrasGAU*, 2012, no. 7, pp. 86–90 (in Russian).

9. Gabov D.N., Beznosikov V.A., Kondratenok B.M., Yakovleva E.V. Polycyclic aromatic hydrocarbons in the soils of technogenic landscapes. *Geochemistry International*, 2010, vol. 48, no. 6, pp. 569–579. DOI: 10.1134/S0016702910060042

10. Benhaddya M., Boukhelkhal A., Halis Y., Hadjel M. Human health risks associated with metals from urban soil and road dust in an oilfield area of Southeastern Algeria. *Arch. Environ. Contam. Toxicol.*, 2016, vol. 70, no. 3, pp. 556–571. DOI: 10.1007/s00244-015-0244-6

11. Bispo A., Jourdain M.J., Jauzein M. Toxicity and genotoxicity of industrial soils polluted by polycyclic aromatic hydrocarbons (PAHs). *Organic Geochemistry*, 1999, vol. 30, no. 8B, pp. 947–952.

12. Tsibart A.S., Gennadiev A.N. Polycyclic aromatic hydrocarbons in soils: sources, behavior, and indication significance (a review). *Eurasian Soil Science*, 2013, vol. 46, no. 7, pp. 728–741. DOI: 10.1134/S1064229313070090

13. Nikiforova E.M., Alekseeva T.A. Polycyclic aromatic hydrocarbons in the soils of roadside ecosystems of Moscow. *Eurasian soil science*, 2002, vol. 35, no. 1, pp. 42–52.

14. Sosa D., Hilber I., Faure R., Bartolome N., Fonseca O., Keller A., Bucheli T.D., Escobar A. Polycyclic aromatic hydrocarbons and polychlorinated biphenyls in urban and semi-urban soils of Havana, Cuba. *Journal of soils and sediments*, 2019, vol. 19, no. 3, pp. 1328–1341. DOI: 10.1007/s11368-018-2137-6

15. Glaser B., Dreyer A., Bock M., Fielder S., Mehring M., Heitmann T. Source apportionment of organic pollutants of a highway-traffic-influenced urban area in Bayreuth (Germany) using biomarker and stable carbon isotope signatures. *Environ. Sci. Technol.*, 2005, vol. 39, no. 11, pp. 3911–3917. DOI: 10.1021/es050002p

16. Watts A., Ballestero T., Gardner K. Soil and atmospheric inputs to PAH concentrations in salt marsh plants. *Water Air and Soil Pollution*, 2008, vol. 189, no. 1, pp. 253–263. DOI: 10.1007/s11270-007-9572-0

17. Gorobtsova O.N., Nazarenko O.G., Minkina T.M., Borisenko N.I. Soderzhanie 3,4-benz(a)pirena v rastitel'nosti, raspolozhennoi v zone vliyaniya Novocherkasskoi GRES [Content of 3,4-benz(a)pyrene in vegetation located in the zone influenced by the Novocherkassk hydro-recirculation power plant]. *Izvestiya vysshikh uchebnykh zavedenii. Severo-Kavkazskii region. Seriya: Estestvennye nauki*, 2006, no. 3, pp. 63–66 (in Russian).

18. Baek S., Field R., Goldstone M., Kirk P., Lester J., Perry R. A review of atmospheric polycyclic aromatic hydrocarbons: sources, fate and behavior. *Water, Air, and Soil Pollution*, 1991, vol. 60, pp. 279–300.

19. Gustafson P., Ostman C., Sallsten G. Indoor levels of polycyclic aromatic hydrocarbons in homes with or without wood burning for heating. *Environ. Sci. Technol.*, 2008, vol. 42, no. 14, pp. 5074–5080. DOI: 10.1021/es800304y

20. Barra R., Castillo C., Machado Torres J. Polycyclic aromatic hydrocarbons in the South American environment. *Rev. Environ. Contam. Toxicol.*, 2007, vol. 191, pp. 1–22. DOI: 10.1007/978-0-387-69163-3_1

21. Blomqvist P., Persson B., Simonson McNamee M. Fire emissions of organics into the atmosphere. *Fire Technology*, 2007, vol. 43, no. 3, pp. 213–231. DOI: 10.1007/s10694-007-0011-y

22. Callen M.S., de la Cruz M.T., Lopez J.M., Murillo R., Navarro M., Mastral A. Long-range atmospheric transport and local pollution sources on PAH concentrations in a South European urban area. Fulfilling of the European directive. *Water Air and Soil Pollution*, 2008, vol. 190, no. 1–4, pp. 271–285. DOI: 10.1007/s11270-007-9599-2

23. Dvorska A., Lammel G., Klanova J. Use of diagnostic ratios for studying source apportionment and reactivity of ambient polycyclic aromatic hydrocarbons over Central Europe. *Atmospheric Environment*, 2011, vol. 45, no. 2, pp. 420–427. DOI: 10.1016/j.atmosenv.2010.09.063

24. Wilcke W. Global patterns of polycyclic aromatic hydrocarbons (PAHs) in soil. *Geoderma,* 2007, vol. 141, no. 3–4, pp. 157–166. DOI: 10.1016/j.geoderma.2007.07.007

25. Yakovleva E.V., Beznosikov V.A., Kondratenok B.M., Gabov D.N., Vasilevich M.I. Bioakkumulyatsiya politsiklicheskikh aromaticheskikh uglevodorodov v sisteme pochvarastenie [Bioaccumulation of polycyclic aromatic hydrocarbons in the soil-plant system]. *Agrokhimiya*, 2008, no. 9, pp. 66–74 (in Russian).

26. Yakovleva E.V., Beznosikov V.A., Kondratenok B.M., Gabov D.N. Bioaccumulation of polycyclic aromatic hydrocarbons in the soil-plant systems of the Northern-Taiga biocenoses. *Eurasian Soil Science*, 2012, vol. 45, no. 3, pp. 309–320. DOI: 10.1134/S1064229312030143

27. Deryabin A.N., Unguryanu T.N. Assessment of biological pollution of soil in the Arkhangelsk region. *ZNiSO*, 2017, no. 7 (292), pp. 18–21. DOI: 10.35627/2219-5238/2017-291-7-18-21 (in Russian).

28. Vodianova M.A., Kriatov I.A., Donerian L.G., Evseeva I.S., Ushakov D.I., Sbitnev A.V. Ecological hygienic assessment of soils quality in urban areas. *Gigiena i sanitariya*, 2016, vol. 95, no. 10, pp. 913–916. DOI: 10.18821/0016-9900-2016-95-10-913-916 (in Russian).

29. Aydinov G.T., Marchenko B.I., Kovalev E.V. Modern epidemiological features of cancer incidence of population of Rostov region. *ZNiSO*, 2017, vol. 296, no. 11, pp. 7–15. DOI: 10.35627/2219-5238/2017-296-11-7-15 (in Russian).

30. Onishchenko G.G., Novikov S.M., Rakhmanin Yu.A., Avaliani S.L., Bushtueva K.A. Osnovy otsenki riska dlya zdorov'ya naseleniya pri vozdeistvii khimicheskikh veshchestv, zagryaznyayushchikh okruzhayushchuyu sredu [Basics of health risk assessment under exposure to chemicals which pollute the environment]. Moscow, NII ECh i GOS Publ., 2002, 408 p. (in Russian).

31. Popova A.Yu., Gurvich V.B., Kuzmin S.V., Mishina A.L., Yarushin S.V. Modern issues of the health risk assessment and management. *Gigiena i sanitariya*, 2017, vol. 96, no. 12, pp. 1125–1129. DOI: 10.18821/0016-9900-2017-96-12-1125-1129 (in Russian).

32. Zaytseva N.V., Popova A.Yu., May I.V., Shur P.Z. Methods and technologies of health risk analysis in the system of state management under assurance of the sanitation and epidemiological welfare of population. *Gigiena i sanitariya*, 2015, vol. 94, no. 2, pp. 93–98 (in Russian).

33. Kurchanov V.I., Lim T.Ye., Voyetsky I.A., Golovin S.A. The relevance of assessment of multicompartment carcinogenic risk to health from exposure to chemicals that pollute the environment. *ZNiSO*, 2015, vol. 268, no. 7, pp. 8–12 (in Russian).

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Research article

ANTHROPOMETRIC MEASUREMENTS IN NEWBORN CHILDREN OF PERSONNEL EMPLOYED AT RADIATION-HAZARDOUS PRODUCTION AS INDICATORS USED IN MONITORING OVER CONSEQUENCES OF PARENTAL EXPOSURE TO RADIATION

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Physical development of offspring can be an important criterion applied to assess effects produced by parental exposure. The cohort that includes workers employed at Mayak Production Association (PA), the first nuclear fuel cycle production facility in Russia, is a valuable information source for analyzing consequences of occupational exposure.

Our objective was to analyze somatometric parameters of newborn children of Mayak PA workers who were occupationally exposed to pre-conception external gamma-radiation.

We retrospectively analyzed anthropometric measurements of 13,880 newborn children, all born in 1949–1973; 9321 children were conceived by parents who were long-term occupationally exposed to radiation at Mayak PA. The analysis covered the core anthropometric elements including height, weight, head circumference, and chest circumference. Development proportionality was estimated by using Quetelet, Vervek – Vorontsov's, and Erismann indexes. We estimated a correlation between anthropometric measurements and accumulated parental pre-conception external gamma radiation dose and calculated relative risk coefficients and odds ratio with 95 % confidence interval.

We established that parents were exposed to a wide range of external gamma radiation doses, up to 4075.6 mGy to the ovaries and 5653.1 mGy to the testicles. There was a weak correlation between newborns' height and weight and parental exposure. We also detected a trend for a decrease in newborns' body mass with increasing accumulated pre-conception dose of external gamma radiation to the ovaries and, conversely, for an increase in it with a growing dose to the testicles. We revealed a statistically significant increase in height and weight among children conceived and born by Mayak PA workers, namely, a greater share of children with high body mass at birth. Analysis of children's somatotypes confirmed excessive values of proportionality indexes that showed height and weight measurements among children of exposed parents. Additional analysis of firstborns and children with proper duration of gestation produced the same results. Risk assessment indicated there was significant prevalence of children with high body mass among offspring of exposed people.

We also assessed physical development of Mayak PA workers' newborns taking into account the latest data on long-term occupational exposure; this assessment is vital for epidemiological monitoring over health of children born by personnel employed at radiation-hazardous production facilities.

Key words: *physical development, newborns, radiation-hazardous production facilities, pre-conception exposure, dose to the gonads, Mayak PA personnel, offspring, Quetelet index, Vervek – Vorontsov's index, Erismann index.*

Consequences of parental exposure for their offspring's health are an open issue that should be given attention by scientific experts [1, 2]. It particular, it is vital to directly assess risks of heritable effects [3, 4] since there are rather few research papers on the matter. Anthropometric measurements of offspring reflect a significant aspect in ontogenetic development and can be used as a valuable criterion in assessing effects produced by preconception exposure.

At present there are rather controversial estimates given to peculiar physical development of children born to parents who were exposed to radiation prior to conception. N.N. Evtushnko with colleagues [5] examined 653 infants who were born in families living in settlements alongside the Techa river and exposed to ioniz-

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ing radiation due to emergencies at nuclear productions. The authors described retarded physical development in 3-month infants in families where parents were exposed to higher doses (27.3 sSv to the gonads and 109 sSv to the hypophysis) against the offspring of unexposed parents. S. Chen and others [6] examined 92,492 infants; 9,275 of them had low birthweight. The authors detected that fathers' preconception exposure was the primary risk factor causing low birthweight among children (odds ratio (OR) was 1.537, confidence interval (CI) was 1.083–2.181). Besides, they noted that exposed fathers tended to have premature babies more frequently.

Similar trends were described by M.G. Andreassi with colleagues [7] when they assessed influence exerted by occupational exposure on reproductive outcomes among personnel working at a heart catheterization laboratory and exposed to an annual dose equal to 1–10 mSv/year. They showed that chronic occupational exposure of male workers correlated with higher prevalence of low birthweight among their offspring (OR = 2.7, CI 1.1–6.3).

N.P. Petrushkina performed a prospective complex assessment of physical development parameters among 606 children born by parents who were employed at a nuclear enterprise. She noted that "deteriorated physical development" was authentically more frequent among children with both parents being occupationally exposed and among children born by mothers with accumulated dose up to 100 sGy[1].

Meanwhile, Magnusson L.L. with colleagues [8] described disharmonic physical development and high birth weight among offspring of males who were occupationally exposed to radioactive isotopes in biomedical research laboratories (OR = 1.8, CI 1.0–3.2). T. Herrmann with colleagues [9] analyzed criteria of normal development and biological maturation terms in families where a parent had radiation therapy due to a malignant neoplasm with a dose to the gonads varying from 0.01 to 2 Gy. The authors detected a trend for preterm delivery (52.5 % children were born prematurely) but still, birthweight was normal in all cases and though the skeleton maturing was a bit retarded, otherwise children developed within physiological standards.

Therefore, at present there are no unified conclusions with respect to assessing risks of somatometric deviations in children whose parents were exposed to radiation prior to conception. This proves the necessity to examine offspring's health involving assessment of contribution made by parental exposure.

"Mayak" Production Association ("Mayak" PA) is the first industrial nuclear facility. In 1948 the first uranium-graphite industrial reactor in Russia (and on the continent as well) was put into operation there and reached its planned operation capacity. Mayak PA personnel, the major part of them being at their reproductive age, might have been exposed to substantial doses at their workplaces. Examining health risks for offspring of people who are occupationally exposed to technogenic ionizing radiation seems interesting not only as a scientific issue but also as a vital aspect in regulating hygienic standards at radiation-hazardous production facilities.

Our objective was to analyze somatometric parameters of newborn children of Mayak PA workers who were occupationally exposed to preconception external gamma-radiation.

Materials and methods. Necessary data for a retrospective epidemiological study were taken from the Ozersk Children's Health Register. Ozersk is a closed town located in the vicinity of the nuclear enterprise. The register was created and has been kept at the Radiation Epidemiology Laboratory, Southern Urals Biophysics Institute of FMBA of Russia; it contains medical and social data from archive out-patient case histories of children living in Ozersk [10]. Data on parental individual occupational exposure were taken from the Mayak-2013 Workers Dosimetric System [11]. The system provides data on accumulated external gamma-radiation doses to the gonads and equivalents of photon radiation doses Hp (10).

[1] Petrushkina N.P. Zdorov'e potomkov (1-2-e pokoleniya) rabotnikov pervogo predpriyatiya atomnoi promyshlennosti – proizvodstvennogo ob"edineniya «Mayak» (kliniko-epidemiologicheskoe issledovanie) [Health of offspring (the 1st – 2nd generation) born by parents who were employed at Mayak PA, the first nuclear industrial enterprise in the country (clinical-epidemiological research)]: the thesis for the Doctor of Medical Sciences degree. Moscow, 2003, 371 p. (in Russian).

Table 1

Data taken from the Ozersk Children's Health Register (children born in 1949–1973)

Years of birth	A number of people in the Ozersk Children's Health Register										
	Male	Female	Total	Offspring of Mayak PA workers		Including measured accumulated occupational preconception exposure					
						Only father		Only mother		Both parents	
				abs.	%	abs.	%*	abs.	%*	abs.	%*
1949–1953	594	711	1305	539	41.3	193	35.8	97	18.0	58	10.8
1954–1958	1903	1880	3783	1619	42.8	753	46.5	257	15.9	391	24.2
1959–1963	3386	3151	6537	2877	44.0	1996	69.4	201	7.0	330	11.5
1964–1968	2596	2437	5033	2285	45.4	1691	74.0	103	4.5	157	6.9
1969–1973	2854	2771	5625	2001	35.6	1426	71.3	83	4.1	97	4.8
1949–1973	11,333	10,950	22,283	9321	41.8	6059	65.0	741	7.9	1033	11.1

N o t e : * means the shares from the number of Mayak PA workers' offspring.

The present work covers a 25-year observation period focusing on children living in Ozersk (born in 1949–1973) including the first generation of Mayak PA workers' offspring. Initial data are outlined in Table 1.

We created our examined groups as follows:

– the test group: we extracted data from the Ozersk Children's Health Register on the first generation of Mayak PA workers' offspring; workers were hired in 1948–1982 and were occupationally exposed to radiation prior to conception; children were born in Ozersk in 1949–1973. Our ultimate sampling to be examined amounted to 9321 children, 51.2 % (4776) boys and 48.8 % (4545) girls;

– the reference group: we extracted data from the Ozersk Children's Health Register on children born by non-exposed parents (parents had not been occupationally exposed prior to conception, had never taken part in eliminating consequences of radiation emergencies, and hadn't moved to the city from territories with radioactive pollution); children were born in Ozersk in 1949–1973. The reference group was made up of 4559 children, 43.8 % (1996) boys and 56.2 % (2563) girls.

Both groups were comparable as per years of birth, sex, and the place of birth being the same, Ozersk. We excluded children who weren't born in the city and came to live there in their childhood from our research. It was done to ensure that our analyzed groups had the same climatic and geographic living conditions and the same scope and quality of available medical services.

Somatometric parameters were estimated bearing in mind physiological norms for children development, both those that were applied in pediatrics during the first decades in the observation period[2] and established later [12–14]. We examined the core anthropometric elements of newborns including weight, height, head circumference, and chest circumference. Development proportionality was estimated by calculating the following indexes:

– Quetelet index I or weight-height index (QI):

$$\text{QI} = \frac{\text{weight (g)}}{\text{height (cm)}}$$

– Vervek – Vorontsov's index (VVI):

$$\text{VVI} = \frac{\text{height (cm)}}{2 \cdot \text{weight (kg)} + \text{chest circumference (cm)}}$$

– Erismann index (EI):

$$\text{EI} = \text{chest circumference (cm)} - \frac{\text{height (cm)}}{2}$$

[2] Rukovodstvo po pediatrii: v 10 t. [Guide on pediatrics: in 10 volumes]. In: A.F. Tur ed. Moscow, Medgiz, 1960, vol. 1, Anatomo-fiziologicheskie osobennosti detskogo vozrasta [Anatomic and physiological peculiarities of children], 576 p. (in Russian); Mazurin A.V., Vorontsov I.M. Propedevtika detskikh boleznei [Preliminary study of children diseases]. Moscow, Meditsina, 1985, 432 p. (in Russian).

The data were statistically analyzed with Statistica Version 10 software package (StatSoft, USA). We applied Kolmogorov – Smirnov test to check whether distribution was normal. Descriptive statistics for normally distributed indicators was given as mean values (M) ± standard quadratic deviation (s); in case distribution wasn't normal they were given as median (Me) and interquartile range (25-th and 75-th percentiles). When comparing values in two groups that were not normally distributed, we applied non-parametric Kolmogorov – Smirnov and Mann – Whitney tests. We determined statistical significance of differences between the analyzed groups using χ^2 test.

We estimated correlations between anthropometric measurements and parental accumulated preconception exposure dose of external gamma-radiation using Spearman's rank correlation coefficient. A share of dispersion that could be explained was calculated as per the following formula: $r^2 \times 100$ (%). Differences were considered statistically significant at $p < 0.05$. We calculated relative risk (RR) and odds ratio (OR) of deviations in physical development among offspring of exposed and non-exposed parents with 95 % confidence interval (CI).

Results and discussion. Mayak PA workers might have been exposed to excessive radiation at their workplaces during the first years of the facility operations since they had to manufacture ionizing radiation sources for industrial and military use in a short time, they lacked necessary experience in working with such materials, technologies were rather underdeveloped, and radiation safety standards existing at the moment were also inadequate.

We analyzed accumulated preconception exposure in parents employed at Mayak PA and detected apparent spread in values caused by variable occupational exposure scenarios (Table 2). Overall, paternal preconception exposure was higher than maternal exposure according to dosimetric data on a range of accumulated technogenic external gamma-radiation. At the same time there were only slight differences in medians of parental doses both to the gonads and individual equivalents of photon radiation doses Hp (10).

We comparatively analyzed data taken from children's out-patient case histories and revealed certain differences in newborns' clinical records between the groups. According to data on gestation, a specific share of children with normal gestation was similar in both groups and amounted to 84.8 % (7903 children) in the test group and 84,5 % (3851 children) in the reference group, $p > 0.05$. But at the same time premature children were significantly more frequently detected in the reference group against the test one (4.7 % (214 children) against 3.4 % (319) accordingly, $p < 0.01$) as well as postmature children (0.7 % (34 cases) against 0.4 % (41) accordingly, $p = 0.02$). There were no archive data regarding gestation age on 1058 children (11.4 %) in the test group and 460 (10.1 %) in the reference one ($p = 0.025$).

Majority of children in both groups were born in single pregnancies and only a very small share were born in multiple ones, 1.3 % (119) in the test group and 1.2 % (54) in the reference group, $p > 0.05$.

Compromised obstetric-gynecological case history was detected significantly more frequently in mothers of children from the test group, 33.7 % (3143 against 30.1 % (1373) in the reference group, $p < 0.01$. Induced abortion prevailed among such pathologies and it could probably be due to underdeveloped contraceptive techniques, especially during the first years of the observed period. Two and more medical abortions were detected in 19.3 % cases (1799 mothers) in the test group and in 17.4 % (791 mothers) in the reference one, $p > 0.05$.

Besides, we can't exclude a probable risk of miscarriage caused by occupational exposure. It is well-known, that exposure of the female reproductive system and a mother's body as a whole can not only induce mutations in ovules and their predecessors but also result in distorted intrauterine development due to changes in the physiological condition of the reproductive organs, placenta, and organs responsible for neuroendocrine regulation as well as due to a decrease in adaptive capabilities of the body [15]. However, it is impossible to spot out miscarriages caused by occupational exposure in obstetric-gynecological case histories since there are no available data on the matter.

Table 2

Accumulated parental preconception doses of external gamma-radiation

Preconception doses	Range of doses	*M* ± *s*	*Me* [Q25; Q75]
Mother preconception exposure			
Doses to the ovaries, mGy	0.01–4075.6	385.9 ± 525.3	166.1 [37.0; 540.5]
Hp (10) doses, mSy	0.01–6697.3	564.6 ± 788.2	235.1 [51.4; 782.3]
Father preconception exposure			
Doses to the testicles, mGy	0.01–5653.1	422.9 ± 634.6	168.4 [45.6; 510.0]
Hp (10) doses, mSy	0.01–6918.3	489.9 ± 723.4	195.8 [48.2; 600.3]

N o t e : *M* is mean value, *s* is standard deviation; *Me* is sampling median, [Q25; Q75] is interquartile range.

Table 3

Parameters of newborn's physical development

Parameters	*M* ± *s*			*Me* [Q25; Q75]		
	Total	Boys	Girls	Total	Boys	Girls
Test group						
BW, kg	3.47 ± 0.52*	3.54 ± 0.52*	3.39 ± 0.5*	3.5 [3.2; 3.8]	3.55 [3.23; 3.86]	3.4 [3.1; 3.7]
H, cm	51.7 ± 2.5*	52.1 ± 2.5	51.3 ± 2.43*	52 [50; 53]	52 [51; 54]	51 [50; 53]
HC, cm	35.6 ± 1.5*	35.9 ± 1.5*	35.4 ± 1.43	36 [35; 36]	36 [35; 37]	35 [35; 36]
CC, cm	34.7 ± 1.6	34.9 ± 1.6	34.4 ± 1.52	35 [34; 36]	35 [34; 36]	35 [34; 35]
Reference group						
BW, kg	3.39 ± 0.53	3.47 ± 0.54	3.33 ± 0.52	3.4 [3.1; 3.7]	3.5 [3.15; 3.8]	3.35 [3.03; 3.65]
H, cm	51.4 ± 2.5	51.9 ± 2.61	51.1 ± 2.4	52 [50; 53]	52 [50; 53]	51 [50; 52]
HC, cm	35.5 ± 1.5	35.75 ± 1.53	35.25 ± 1.5	36 [35; 36]	36 [35; 37]	35 [35; 36]
CC, cm	34.5 ± 1.6	34.78 ± 1.68	34.3 ± 1.6	35 [34; 35]	35 [34; 36]	34 [34; 35]

N o t e : BW is body weight, H is height, HC is head circumference; CC is chest circumference; *M* is mean value, *s* is standard deviation; *Me* is sampling median, [Q25; Q75] is interquartile range; * means difference between the groups are significant.

A number of stillbirths was comparable in both groups, 1.7 % (160 cases) in the test group and 1.6 % (74 cases) among offspring of unexposed parents, the reference group, $p > 0.05$.

We detected a statistically significant difference between the groups in distribution of pregnancies as per their ordinal number. Secundiparas were more frequent in the test group (42.3 % cases or 3940 women), whereas there were only 37 % such cases in the reference group (1687), $p < 0.001$. Average age of a mother at the moment of birth amounted to 25.9 years in the test group and to 25.1 in the reference group; average age of a father, 27.1 and 25.1 years accordingly.

Parameters of newborns' physical development are comparatively described in Table 3.

Our analysis of somatometric parameters revealed statistically significant differences between the groups as per the following anthropometric measurements: weight, height, and head circumference. Figure 1 shows graphic description of birthweight.

Despite apparent similarities and relatively close values, newborn's weights were still significantly higher in the test group than in the reference one, both totally ($p < 0.001$), and when distributed as per sex ($p < 0.001$).

Newborns' heights had a wider spread of values among offspring of Mayak PA workers, a higher median value (Figure 2) and were statistically significantly different from values detected in the reference group, both totally ($p < 0.001$) and among girls ($p < 0.001$).

We established a small but still statistically significant difference in head circumference among offspring of exposed parents, both in the whole group ($p < 0.001$) and among boys ($p = 0.02$). A range of head circumference values was wider in the reference group where we detected the maximum values in children with hydrocephaly. Minimal

values of head circumference were detected among Mayak PA workers' children; however, a number of newborns with head circumference being lower than the 10-th percentile (less than 33 cm) was significantly higher in the reference group, 5.6 % (254) against 4.4 % (410) in the test group, p = 0.0024.We comparatively analyzed gestation age of these children and didn't establish any significant differences ($p > 0.05$).

There were slight differences in chest circumference between the groups, and, as a rule, the parameter corresponded to physiological standards of newborns development. Having compared the parameters between the groups, we didn't detect any statistically significant differences.

Table 4 provides data on estimates of development proportionality with determined anthropometric indexes.

Orientation estimates of somatotype with Erismann index didn't detect any significant differences between the two groups and in general conformed to age standards. At the

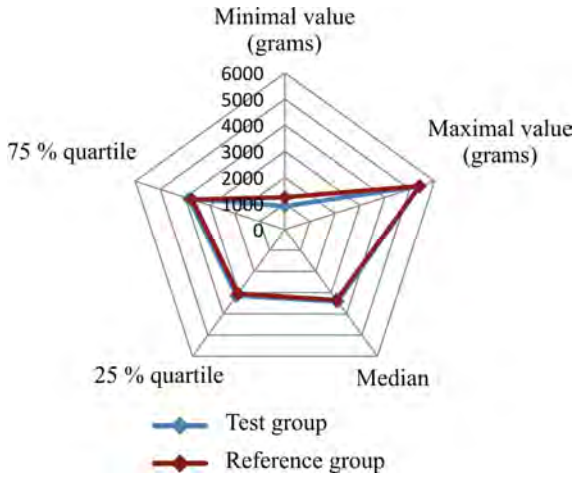

Figure 1. Description of newborns' birthweight in the groups

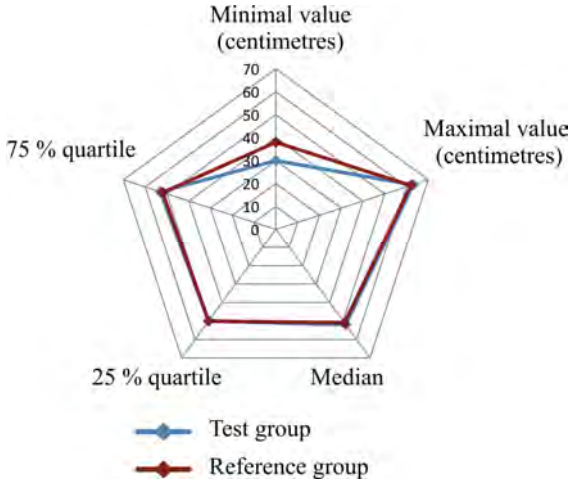

Figure 2. Newborns' heights in two groups

Table 4

Comparative characteristics of proportionality indexes

Index	$M \pm s$			*Me* [Q25; Q75]		
	Total	Boys	Girls	Total	Boys	Girls
The test group						
QI	66.9 ± 7.9*	67.7 ± 7.8*	66.0 ± 7.8*	67.3 [62.0; 71.8]	68.2 [63.0; 72.5]	66.5 [61.2; 71]
VVI	1.24 ± 0.05*	1.24 ± 0.04*	1.25 ± 0.05	1.24 [1.22; 1.27]	1.24 [1.21; 1.27]	1.24 [1.22; 1.27]
EI	8.79 ± 0.01	8.85 ± 0.02	8.75 ± 0.02	9.0 [8.0; 9.5]	9.0 [8.0; 9.5]	9.0 [8.0; 9.5]
The reference group						
QI	65.6 ± 8.1	66.6 ± 8.2	64.9 ± 8.0	66.0 [60.8; 70.6]	67.3 [61.8; 71.6]	65.4 [60.0; 70]
VVI	1.25 ± 0.05	1.25 ± 0.04	1.25 ± 0.05	1.24 [1.22; 1.27]	1.24 [1.22; 1.27]	1.24 [1.22; 1.28]
EI	8.8 ± 0.02	8.84 ± 0.04	8.78 ± 0.03	9.0 [8.0; 9.5]	9.0 [8.0; 9.5]	9.0 [8.0; 9.5]

N o t e : *M* is mean value, *s* is standard deviation; *Me* is sampling median, [Q25; Q75] is interquartile range; * means difference between the groups are significant.

same time, higher values of Vervek – Vorontsov's index were authentically more frequent among unexposed parents' offspring, both in the group as a whole (p = 0.013), and among boys as well (p = 0.033). This is additional evidence that birthweight values were higher in the test group than in the reference one.

Vervek – Vorontsov's index shows how proportionate development is if taken as per ratio of lateral and longitudinal sizes. Having comparatively analyzed its structure as per its numeric values, we didn't detect any significant differences. There were no newborns with the index being lower than 0.85 (indicating brachymorph, that is lateral sizes being greater than longitudinal ones) in either group. Mesomorph type (0.85–1.25 VVI) was detected in more than a half children in each group, 58.4 % (3694) in the test group and 57.6 % (1844) in the reference one, $p > 0.05$. There wasn't any statistically significant difference in a number of newborns with VVI value exceeding 1.25 (which indicates dolichomorphic body type or moderate prevalence of longitudinal sizes) either.

We detected the most significant differences between the two groups when comparing Quetelet I index that reflected weight and height and allowed determining whether a child had good nutrition during its antenatal life. There was a great variability in the index values in the test group (Figure 3). And though average values of the index in both groups generally conformed to the standards of newborns' physical development, our comparative analysis established significant higher Quetelet I index values in children born in families of Mayak PA workers, both in the group as a whole ($p < 0.001$) and distributed as per sex ($p < 0.001$).

Long-term observations over people who lived on territories alongside the Techa river with considerable radioactive pollution [16] established that in general physical development of offspring in that exposed population was within its physiological standards. Still, there was a trend for growing frequency of newborns with high birth weight and "low birthweight" ones.

Table 5 provides data on distribution of newborns in the analyzed groups as per their weights: low birthweight (500–2499 grams), normal weight (2500–3499 grams) and high birthweight (3500 grams and more) with calculated median of parental preconception occupational exposure doses for each interval. There were data on birthweight of 8480 children in the test group (51.2 % (4339) boys and 48.8 % (4141) girls) and 4186 children in the

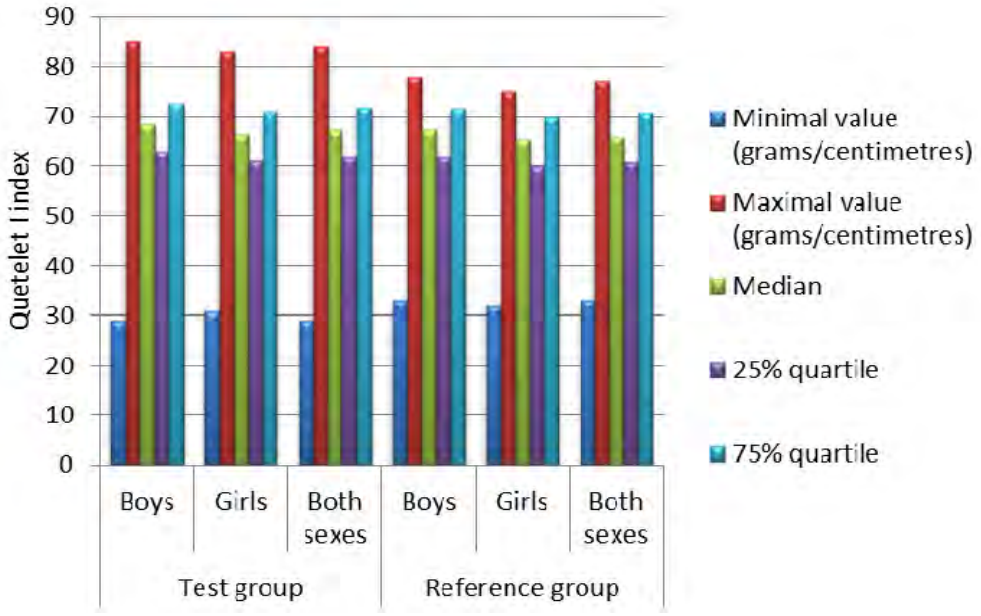

Figure 3. Quetelet I index in the groups

Table 5

Newborns distributed as per birthweight

Sex	Low birthweight (500–2499 grams)			Normal birthweight (2500–3499 grams)			High birthweight (3500 and more)		
	Abs. (%)	Mother dose	Father dose	Abs. (%)	Mother dose	Father dose	Abs. (%)	Mother dose	Father dose
Test group (n = 8480)									
Total	278* (3.3)	189.1	134.5	3926* (46.3)	167.4	145.4	4276* (50.4)	153.6	184.9
Boys	114* (1.3)	85.4	129.3	1784* (21)	161.2	143.4	2441* (28.8)	149.1	188.9
Girls	164 (2.0)	190.2	134.5	2142* (25.3)	180.4	150.5	1835* (21.6)	159.4	179.4
Reference group (n = 4186)									
Total	188 (4.5)	–	–	2117 (50.6)	–	–	1881 (44.9)	–	–
Boys	72 (1.7)	–	–	816 (19.5)	–	–	949 (22.7)	–	–
Girls	116 (2.8)	–	–	1301 (31.1)	–	–	932 (22.3)	–	–

N o t e : Dose is a median of accumulated external gamma-radiation to the gonads prior to conception, mGy; * means differences from the reference group are statistically significant.

reference group (43.9 % (1837) boys and 56.1 % (2349) girls). Data on the remaining children were missing due to absence of information about physical development during the neonatal period in some archive case histories.

Development of newborns estimated as per birthweight had statistically significant differences in the analyzed groups. Thus, a share of newborns with their birthweight exceeding 3500 grams was higher in the test group than in the reference one (50.4 % and 44.9 % accordingly, $p < 0.001$). The same statistically significant prevalence of high birthweight babies was detected among boys in the test group against the reference one (28.8 % and 22.7 % accordingly, $p < 0.001$). At the same time a number of low birthweight newborns with prenatal hypotrophy was higher in the reference group among boys ($p = 0{,}008$) and in the whole group ($p < 0.001$).

Normally developed children significantly prevailed among unexposed parents' offspring, both in the group as a whole and among girls ($p < 0.001$ and $p = 0.005$ accordingly) whereas a number of newborn boys with normal development was significantly higher in the test group ($p = 0.017$).

When we tried to determine any correlations between accumulated parental preconception doses of external gamma-radiation and newborns' weights, we had rather ambiguous results. Thus, as accumulated doses to the ovaries grew, there was a trend for decreasing birthweight both in the group as a whole and among girls whereas low birthweight among boys was associated with low preconception exposure of mothers. Meanwhile, all the correlations between paternal preconception exposure and newborns' weight had the same directions: as an accumulated preconception dose of external gamma radiation to the testicles grew, there was an apparent trend for a growing birthweight of offspring.

Growing birth parity is likely to result in higher birthweight and this can be a reason of greater weight-height parameters in newborns. Since there was a significantly higher number of secundiparas in the test group ($p < 0.001$), we analyzed anthropometry among newborns again, having excluded children who were born in the second delivery (Table 6).

Average age of parents when their firstborns were born amounted to 23.2 years among mothers in the test group and 22.5 years in the reference group; 24.5 years and 22.3 years among fathers accordingly. Just as before, the comparative analysis showed that heights and weights were significantly greater among firstborns in the test group, both in the group as a whole and among girls. At the same time there was no difference in anthropometric measurements of boys, and we didn't find any

Table 6

Parameters of physical development estimated only among firstborns

Parameters	*M* ± *s*			*Me* [Q25; Q75]		
	Total	Boys	Girls	Total	Boys	Girls
	Test group (*n* = 4058)					
BW, kg	3.37 ± 0.47*	3.44 ± 0.48	3.31 ± 0.46*	3.4 [3.1; 3.68]	3.45 [3.15; 3.71]	3.3 [3.0; 3.6]
H, cm	51.5 ± 2.3*	51.8 ± 2.2	51.2 ± 2.31*	52 [50; 53]	52 [50; 53]	51 [50; 53]
HC, cm	35.5 ± 1.4	35.7 ± 1.3	35.2 ± 1.35	36 [35; 36]	36 [35; 37]	35 [34; 36]
CC, cm	34.5 ± 1.5	34.7 ± 1.5	34.3 ± 1.44	35 [34; 35]	35 [34; 36]	34 [33; 35]
	Reference group (*n* = 2282)					
BW, kg	3.32 ± 0.49	3.41 ± 0.51	3.26 ± 0.47	3.35 [3.0; 3.64]	3.43 [3.1; 3.7]	3.3 [3.0; 3.55]
H, cm	51.3 ± 2.4	51.7 ± 2.44	50.9 ± 2.2	51 [50; 53]	52 [50; 53]	51 [50; 52]
HC, cm	35.4 ± 1.5	35.66 ± 1.47	35.17 ± 1.4	35 [35; 36]	36 [35; 37]	35 [34; 36]
CC, cm	34.4 ± 1.6	34.67 ± 1.67	34.2 ± 1.6	35 [34; 35]	35 [34; 36]	34 [33; 35]

N o t e : BW is body weight, H is height, HC is head circumference; CC is chest circumference; *M* is mean value, *s* is standard deviation; *Me* is sampling median, [Q25; Q75] is interquartile range; * means difference between the groups are significant.

confirmation of group differences as per newborns' head circumference ($p > 0.05$).

We also additionally compared anthropometric measurements of children with proper gestation, having excluded children born in a premature or retarded birth; the results were similar: significantly greater body weight and height of children in the test group, both as a whole ($p < 0.001$ and $p < 0.025$ accordingly) and among girls ($p < 0.05$).

Therefore, having analyzed somatometry, we established significantly greater weight and height among offspring of Mayak PA workers with long-term preconception occupational exposure. We also performed a correlation analysis to quantitative estimate correlations between parental doses and newborns' anthropometric measurements (Table 7).

Correlations between newborns' heights and weights and maternal doses of occupational exposure were characterized with authentic significance levels both for girls and boys; however, correlation coefficients were rather low (0.036–0.051). A weak, though statistically significant correlation was detected between birthweight and paternal accumulated doses of occupational exposure in the test group as a whole and among boys. We didn't detect any correlations between newborns' height and doses of external gamma-radiation accumulated by fathers.

A share of dispersion that could be explained as per the maximum value of the coefficients didn't exceed 0.3 %. Therefore, our analysis established a weak correlation between height and weight at birth and accumulated doses of parental preconception occupational exposure to external gamma radiation.

We estimated risk coefficients with respect to deviations in anthropometric measurements of newborns born by exposed and intact parents. The estimations confirmed all the aforementioned peculiarities (Table 8).

Babies of high birth weight were statistically significantly more frequently detected in families of Mayak PA workers: RR 1.12 (CI 1.08–1.17), OR 1.25 (1.16–1.34). This regularity was authentic both among boys: RR 1.09 (1.03–1.15), OR 1.2 (1.08–1.34), and among girls: RR 1.12 (1.05–1.19), OR 1.21 (1.09–1.34). Low and normal weights were significantly less frequent among newborns of parents with preconception occupational exposure. The lowest risk of low birthweight was detected for boys of exposed parents: OR 0.66 (0.49–0.89).

Undoubtedly, it would be a mistake to assume that newborns' physical development is associated solely with parental preconception exposure. There is a great variety of factors that determine how a fetus grows and develops, including genetic and biological ones, trace element deficiency, antenatal pathologies, infectious and somatic pathologies of a fetus [17, 18]. It is rather difficult to spot out

Table 7

Correlations between parental preconception exposure and newborns' height and weight

Sex	Mother's preconception exposure				Father's preconception exposure			
	Dose to gonads		Hp (10) dose		Dose to gonads		Hp (10) dose	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Birthweight								
Boys	0.051	< 0.001	0.051	< 0.001	0.041	< 0.01	0.04	< 0.01
Girls	0.036	0.019	0.036	0.019	0.022	> 0.05	0.022	> 0.05
Both sexes	0.043	< 0.001	0.043	< 0.001	0.033	< 0.01	0.032	< 0.01
Height at birth								
Boys	0.037	0.016	0.037	0.016	0.024	> 0.05	0.022	> 0.05
Girls	0.038	0.016	0.038	0.017	0.01	> 0.05	0.01	> 0.05
Both sexes	0.038	< 0.001	0.038	< 0.001	0.017	> 0.05	0.016	> 0.05

Note: *r* is correlation coefficient; *p* is the significance level.

Table 8

Relative risk (RR) and odds ratio (OR) of deviations in birthweight

Birthweight	Group	Outcome		RR (95 % CI)	OR (95 % CI)
		Yes	No		
Boys					
Low weight	Exposed*	114	4225	0.67 (0.5–0.9)	0.66 (0.49–0.89)
	Non-exposed	72	1765		
Normal weight	Exposed	1784	2555	0.93 (0.87–0.98)	0.87 (0.78–0.97)
	Non-exposed	816	1021		
High weight	Exposed	2441	1898	1.09 (1.03–1.15)	1.2 (1.08–1.34)
	Non-exposed	949	888		
Girls					
Low weight	Exposed	164	3977	0.8 (0.64–1.01)	0.79 (0.62–1.01)
	Non-exposed	116	2233		
Normal weight	Exposed	2142	1999	0.93 (0.89–0.98)	0.86 (0.78–0.96)
	Non-exposed	1301	1048		
High weight	Exposed	1835	2306	1.12 (1.05–1.19)	1.21 (1.09–1.34)
	Non-exposed	932	1417		
Both sexes					
Low weight	Exposed	278	8202	0.73 (0.61–0.87)	0.72 (0.6–0.87)
	Non-exposed	188	3998		
Normal weight	Exposed	3926	4554	0.91 (0.88–0.95)	0.84 (0.78–0.91)
	Non-exposed	2117	2069		
High weight	Exposed	4276	4204	1.12 (1.08–1.17)	1.25 (1.16–1.34)
	Non-exposed	1881	2305		

Note: * means children whose parents were occupationally exposed prior to conception.

a leading factor that makes for developing ontogenetic disorders.

Previously we assessed physical development of newborns born by female Mayak PA workers with preconception occupation exposure to external gamma-radiation by performing a factor analysis. Apart from maternal exposure to radiation (15.3 % of dispersion) the analysis highlighted antenatal factors (13.8 %), obstetric-gynecologic case history (13.5 %), and mothers having bad habits (9.7 % of dispersion) [19]. Besides, a great contribution to children's physical development could be made by medical and social peculiarities of families living in the analyzed closed town [20]. This requires certain attention and further investigation and analysis including those focused on estimating contributions made by non-occupational parental exposure.

Conclusion. Anthropometric measurements are among the most significant parameters of a fetus and a newborn and they can be valuable for assessing effects produced by preconception exposure. We performed this retrospective analysis of newborns' anthropometric measurements covering data on 13,880 children born in Ozersk in 1949–1973, 9321 of them being born by parents with long-term preconception occupational exposure at Mayak PA.

Our overall research results indicate that, together with significant differences between the groups as per gestation age, birth parity, and mothers' reproductive health, height and weight at birth were significantly higher among newborns of Mayak PA. Distribution as per different birthweight categories revealed a greater contribution made by babies of a high birth weight (more than 3500 grams) among offspring of people with preconception occupational exposure against the reference group, $p < 0.001$. We comparatively assessed somatotypes using proportionality indexes and established both significance of anthropometric measurements showing height and weight parameters and their higher values among children of Mayak PA workers.

Having examined possible correlations between anthropometric measurements and dosimetric characteristics of parental exposure, we established an apparent trend for growing birthweight with increasing accumulated preconception doses of external gamma-radiation to the testicles and a trend for decreasing birthweight with growing accumulated preconception doses to the ovaries. At the same time quantitative assessment of an association between parental preconception occupational exposure and newborns' height and weight showed a statistically significant but rather weak correlation.

Our assessment of risk coefficients showed that low birthweight and normotrophy were statistically significantly less frequent among offspring of Mayak PA workers. At the same time, newborns of high birth weight (more than 3500 grams) significantly prevailed in this group and this fact confirms all our previous calculations.

By using a cohort including offspring of Mayak PA workers, we obtained an up-to-date estimation of anthropometric measurements at birth taking into account updated data on doses of long-term parental occupational exposure. The established peculiarities of newborns' physical development can enhance our overview of trends in epidemiologic monitoring over health of children born by workers employed at radiation-hazardous productions and determine new prevention strategies.

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

References

1. UNSCEAR. Sources, Effects and Risks of Ionizing Radiation. UNSCEAR 2013 Report. Volume II. Scientific annex B: Effects of radiation exposure of children. New York, 2013, 284 p.

2. Tatsukawa Y., Cologne J.B., Hsu W.L., Yamada M., Ohishi W., Hida A., Furukawa K., Takahashi N. [et al.]. Radiation risk of individual multifactorial diseases in offspring of the atomic-bomb survivors: a clinical health study. *J. Radiol. Prot.*, 2013, vol. 33, no. 2, pp. 281–293. DOI: 10.1088/0952-4746/33/2/281

3. ICRP Publication 103. The 2007 Recommendations of the International Commission on Radiological Protection. In: J. Valentin ed. *Annals of the ICRP*, Elsevier, 2007.

4. Ozasa K., Cullings H.M., Ohishi W., Hida A., Grant E.J. Epidemiological studies of atomic bomb radiation at the Radiation Effects Research Foundation. *Int. J. Radiat. Biol.*, 2019, vol. 95, no. 7, pp. 879–891. DOI: 10.1080/09553002.2019.1569778

5. Evtushenko N.N., Volosnikov D.K., Akleev A.V. Fizicheskoe razvitie detei pervogo goda zhizni, roditeli kotorykh podvergalis' khronicheskomu radiatsionnomu vozdeistviyu [Physical development of children during the first year of life whose parents were chronically exposed to radiation]. *Pediatriya*, 2010, vol. 89, no. 6, pp. 52–57 (in Russian).

6. Chen S., Yang Y., Qv Y., Zou Y., Zhu H., Gong F., Zou Y., Yang H. [et al.]. Paternal exposure to medical-related radiation associated with low birthweight infants: A large population-based, retrospective cohort study in rural China. *Medicine (Baltimore)*, 2018, vol. 97, no. 2, pp. e9565. DOI: 10.1097/MD.0000000000009565

7. Andreassi M.G., Borghini A., Vecoli C., Piccaluga E., Guagliumi G., Del Greco M., Gaita F., Picano E. Reproductive outcomes and Y chromosome instability in radiation-exposed male workers in cardiac catheterization laboratory. *Environ. Mol. Mutagen.*, 2020, vol. 61, no. 3, pp. 361–368. DOI: 10.1002/em.22341

8. Magnusson L.L., Bodin L., Wennborg H. Adverse pregnancy outcomes in offspring of fathers working in biomedical research laboratories. *Am. J. Ind. Med.*, 2006, vol. 49, no. 6, pp. 468–473. DOI: 10.1002/ajim.20317

9. Herrmann T., Thiede G., Trott K.R., Voigtmann L. Offsprings of preconceptionally irradiated parents. Final report of a longitudinal study 1976–1994 and recommendations for patients' advisory. *Strahlenther. Onkol.*, 2004, vol. 180, no. 1, pp. 21–30. DOI: 10.1007/s00066-004-1223-4 (in German).

10. Sosnina S.F., Kabirova N.R., Okatenko P.V., Rogacheva S.A., Tsareva Yu.V., Gruzdeva E.A., Sokolnikov M.E. Ozyorsk Children's Health register: development results, management guidelines, potential and prospects. *Meditsina ekstremal'nykh situatsii,* 2017, vol. 61, no. 3, pp. 95–103 (in Russian).

11. Napier B.A. The Mayak Worker Dosimetry System (MWDS-2013): an introduction to the documentation. *Radiat. Prot. Dosimetry*, 2017, vol. 176, no. 1–2, pp. 6–9.

12. Grantz K.L., Hediger M.L., Liu D., Buck Louis G.M. Fetal growth standards: the NICHD fetal growth study approach in context with INTERGROWTH-21st and the World Health Organization Multicentre Growth Reference Study. *Am. J. Obstet. Gynecol.*, 2018, vol. 218, no. 2S, pp. S641–S655.e28. DOI: 10.1016/j.ajog.2017.11.593

13. Kildiyarova R.R. Assessing physical development of children with percentile diagrams. *Voprosy sovremennoi pediatrii*, 2017, vol. 16, no. 5, pp. 431–437. DOI: 10.15690/vsp.v16i5.1808 (in Russian).

14. Chernaya N.L., Maskova G.S., Ganuzin V.M., Ermolina E.A. Comparative evaluation of postnatal growth of premature babies using different regulations and standards. *Prakticheskaya meditsina*, 2018, vol. 16, no. 8, pp. 79–83 (in Russian).

15. Pastukhova E.I., Shalaginov S.A., Akleev A.V. Chislo beremennostei i rodov u zhenshchin, podvergshikhsya deistviyu khronicheskogo ioniziruyushchego izlucheniya na reke Teche [The number of pregnancies and births in women exposed to chronic ionizing radiation on the Techa river]. *Vestnik Chelyabinskogo gosudarstvennogo universiteta*, 2013, vol. 298, no. 7, pp. 82–84 (in Russian).

16. Akleev A.V., Krestinina L.Yu., Varfolomeeva T.A., Ostroumova E.V., Pushkarev S.A., Shalaginov S.A., Khudyakova O.I., Veremeeva G.A. [et al.]. Mediko-biologicheskie effekty khronicheskogo vozdeistviya ioniziruyushchei radiatsii na cheloveka [Medico-biological effects of chronic exposure to ionizing radiation on humans]. *Meditsinskaya nauka i obrazovanie Urala*, 2008, vol. 9, no. 2 (52), pp. 8–10 (in Russian).

17. C A.K., Basel P.L., Singh S. Low birth weight and its associated risk factors: Health facility-based case-control study. *PLoS One,* 2020, vol. 15, no. 6, pp. e0234907. DOI: 10.1371/journal.pone.0234907

18. Sirotina Z.V., Sokolov V.N. High risk factors for fetal development (clinical lecture). *Zdravookhranenie Dal'nego Vostoka*, 2020, vol. 84, no. 2, pp. 59–65 (in Russian).

19. Sosnina S.F., Okatenko P.V. Physical development of newborns of female radiation workers. *Profilakticheskaya i klinicheskaya meditsina*, 2017, vol. 64, no. 3, pp. 14–20 (in Russian).

20. Volosnikov D.K., Sosnina S.F. Mediko-sotsial'naya kharakteristika semei, prozhivayushchikh v zakrytom administrativnom territorial'nom obrazovanii (g. Ozersk), imeyushchikh detei podrostkovogo vozrasta [The medical and social characteristics of families with children of adolescent age residing in the closed administrative territorial formation Ozersk]. *Sotsiologiya meditsiny*, 2010, no. 2, pp. 59–61 (in Russian).

Sosnina S.F., Okatenko P.V., Sokolnikov M.E. Anthropometric measurements in newborn children of personnel employed at radiation-hazardous production as indicators used in monitoring over consequences of parental exposure to radiation. Health Risk Analysis, 2022, no. 1, pp. 36–47. DOI: 10.21668/health.risk/2022.1.04.eng

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Research article

SUBSTANTIATING METHODICAL APPROACHES TO QUANTIFYING REPRODUCTIVE HEALTH RISKS CAUSED BY HARMFUL OCCUPATIONAL AND WORK-RELATED FACTORS

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The article dwells on methodical approaches to quantifying occupational risk (OR) which give an opportunity to spot out priority trends in prevention of reproductive losses caused both by occupational diseases (ODs) and work-related diseases (WRDs).

OR quantitative assessment takes into account an additional probability of developing disorders and their severity. When assessing OR for reproductive health, it is advisable to take into account sex-related peculiarities, sensitive periods in the reproductive cycle, variable physiological states, as well as health disorders in offspring caused by parental occupational exposures. The assessment is based on epidemiological research. The algorithm also involves determining OR of reproductive disorders; determining an integral OR of reproductive disorders (as a combined account of both ODs and WRDs caused by exposure to different factors); determining OR categories and assessing their acceptability regarding reproductive health. It is suggested to determine severity of reproductive health outcomes (health effects) using conventional coefficients recommended by the WHO and "loss of fertility" level which is significant in assessing consequences for offspring. In case a risk is detected, both for exposed workers and their offspring, it is recommended to consider selecting the priority (maximum) risk level to be the ultimate assessment result.

The suggested methodical approaches were tested on a group of women employed at a petrochemical production and exposed to several harmful occupational factors (chemical factor and labor intensity) with working conditions at their workplaces belonging to the hazard category 3.1. The assessment revealed the integral risk for reproductive health to be equal to $1.6 \cdot 10^{-2}$ thus indicating that the risk was unacceptable. Besides, occupational factors influencing a mother create an unacceptable risk for development of healthy offspring (the detected risk is $3 \cdot 10^{-3}$). Such a reproductive disorder as infertility causes "insignificant" risks for women whereas they grow up to being "high" for their potential offspring. The ultimate assessment result is selecting the maximum risk levels, that is, the "high" risk for offspring's health.

Key words: *methodical approaches, quantitative assessment, risk assessment, reproductive health, occupational factors, work-related factors, petrochemical production.*

The Concept of the demographic policy in the Russian Federation up to 2025 (approved by the Order of the RF President issued on October 09, 2007 No. 1351)[1] and tasks set within the "Demography" National Project which is to be implemented by 2024 determine several significant strategic trends. One of them is a growth in the total fertility rate (up to 1.7 children per 1 woman)[2].

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[1] Ob utverzhdenii Kontseptsii demograficheskoi politiki Rossiiskoi Federatsii na period do 2025 goda: Ukaz Prezidenta RF ot 09.10.2007 № 1351 [On Approval of the Concept of the demographic policy in the Russian Federation up to 2025: The Order by the RF President issued on October 9, 2007 No. 1351]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_71673/7a46cb13de731db3333fcd77a4f7887e468287e3/ (December 26, 2021) (in Russian).

[2] Pasport natsional'nogo proekta «Demografiya» (utv. Prezidentom Soveta pri Prezidente RF po strategicheskomu razvitiyu i natsional'nym proektam, protokol ot 24.12.2018 g. № 16) [The profile of the "Demography" National Project (approved by the RF Presidential Council on strategic development and national projects, the meeting minutes dated December 24, 2018 No. 16)]. *The RF Ministry of Labor*. Available at: https://mintrud.gov.ru/ministry/programms/demography/ (December 26, 2021) (in Russian).

In 2010 a positive trend appeared in dynamics of demographic rates in the country; but by now this trend has reversed. Today the demographic situation is characterized with the decreasing fertility rate and growing mortality. According to the official statistic data in 2020 the total fertility rate amounted to 1.5 against 1.77 in 2015 when it reached its maximum value over the previous 20 years. The overall birthrate went down to 9.8 ‰ (or by 26 % lower than in 2015) but the overall mortality grew up to 14.6 ‰ (or by 12 % higher than in 2015); as a result, there was a natural decrease equal to 4.8 ‰.

Harmful occupational and work-related factors can both cause occupational diseases (ODs) and induce pathogenetic mechanisms of developing and progressing work-related diseases (WRDs) [1]. There are good examples of exposure to certain harmful chemicals detected at workplaces and known for a long period of time; one of them is exposure to lead at workplaces of female potters which can cause miscarriage, still birth and infertility among them. It has been established recently that harmful working conditions cause up to 61 % of female infertility cases and up to 87 % of uterine fibroids. An etiological fracture of negative impacts on the reproductive system is greater at workplaces with working conditions being more hazardous (belonging to higher hazard categories). Moreover, when a pregnant woman is exposed to harmful working conditions at her workplace, a contribution made by this exposure is significantly greater for a newborn than for her [2].

Hygienic assessment of working conditions doesn't rely on health disorders, including reproductive ones, as estimation criteria, there is a rather limited number of research works which mention established relationships between developing reproductive disorders and occupational exposures and descriptions of such relationships lack any quantitative parameters. Given that, in most cases it is not reasonable to perform a priori assessment of reproductive risks. A posteriori semi-quantitative assessment is accomplished only in case of ODs. So, it seems vital to develop methodical approaches to occupational risk (OR) quantification since this gives an opportunity to spot out priority activities aimed at preventing reproductive losses caused by both ODs and WRDs.

Our research goal was to substantiate methodical approaches to quantifying reproductive health risks caused by exposure to occupational and work-related factors.

Materials and methods. Science-based approaches and an algorithm for quantitative risk assessment were developed based on analysis of literature sources and regulatory and methodical documents containing some fundamentals regarding OR assessment. We also analyzed some studies with data on peculiarities of developing reproductive disorders and negative health outcomes in future offspring caused by exposure to harmful environmental factors [3, 4].

The approaches and algorithm were to be tested using a previously published study where the authors established cause-effect relations between reproductive health and harmful working conditions. To select an appropriate study, we analyzed publications in the conventional citation databases (eLibrary, CyberLeninka, GoogleScholar, Web of Science, Scopus, RSCI, HAC, etc.). Approximately 800 publications issued from 2011 to 2021 (a 10-year period) were found as per such key words as "occupational risk" and "reproductive health". The most interesting ones were those which described cross-sectional analytical epidemiological studies with detected probabilities of a negative response from the female reproductive system and offspring development in test and control groups. Working conditions in a test group should include harmful occupational factors and belong to a hazard category not lower than 3.1 (hazardous, class 1).

We chose a study by M.K. Gainullina who examined frequency of gynecological morbidity, fertile functions, and pregnancy outcomes in female workers employed at a petrochemical production (chemical engineers, chemical analysts, samplers, etc.). The overall sampling was made of 512 people [5]. Approaches to OR quantitative assessment are based on key stages in any risk assessment: hazards identification, exposure assessment, assessment of "exposure – response" relationship, and risk characterization [6].

Research results. There are peculiarities in development of reproductive disorders which require certain adjustments to be made at some stages in risk assessment. When a hazard is identified, it is advisable to anticipate negative answers which are specific for a male or female body due to sex-related physiological differences between them. There can also be certain responses specific for couples, that is, responses where both sexes play an important role in case both partners are exposed. Besides, it is necessary to take into account probable negative responses (health outcomes) in future offspring since they correlate with working conditions of a mother with their etiological fraction reaching 78 % [7–9]. An important difference is that some sensitive periods in the reproductive development (cycle) and certain physiological conditions (pregnancy or breast-feeding a newborn) also determine different reproductive outcomes and don't exclude their occurrence in a long-term period after an exposure to a factor has ended [4]. For example, when it comes down to the chemical factor, it is known that specific toxicants are hazardous in different periods in the reproductive cycle as it will be clearly stated in a marking provided for a specific substance[3].

Based on literature data, all the responses (outcomes) can be conditionally divided into specific and non-specific damages. Specific damages are such responses (outcomes) which most probably occur due to a relative number and a list of harmful factors as well as intensity of their influence. Non-specific responses (outcomes) develop due to weakened immune resistance, deteriorated detoxification functions, vegetative disorders etc.[4] [8–12]. Table 1 provides systemically organized data on responses (outcomes) represented by reproductive disorders caused by exposure to occupational and work-related factors. The systematized responses allow for such criteria as specificity of an outcome, sex-related peculiarities, different stages in the reproductive cycle, and different physiological conditions.

But at the same time regulatory and methodical documents determine only two negative reproductive outcomes as occupational diseases; they are female genital prolapse (N81) caused by hard physical labor (lifting and moving heavy weights combined with a forced working posture) and malignant neoplasms of female genital organs and breast (C50–C58) caused by exposure to ionizing radiation of chemicals[5].

The stage when "exposure – response" relationship is assessed involves determining cause-effect relations between levels of exposure to a factor and a probability (frequency) of negative health responses (outcomes) in workers. This allows spotting out quantitative regularities in changeability. Epidemiological criteria ($RR \geq 1.5$)[6] are usually applied to establish cause-effect relations between exposure and negative changes.

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[3] GOST R 58474-2019. Predupreditel'naya markirovka khimicheskoi produktsii. Obshchie trebovaniya: utv. i vved. v deistv. Prikazom Federal'nogo agentstva po tekhnicheskomu regulirovaniyu i metrologii ot 8 avgusta 2019 g. N 455-st (vstupaet v silu s 01.06.2022) (vzamen GOST 31340-2013) [GOST R 58474-2019. Precautionary marking of chemical products. General requirements: approved and introduced by the Order of the Federal Agency on Technical Regulation and Metrology dated August 8, 2019 No. 455-st (comes into force on June 01, 2022) (to replace GOST 31340-2013)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200167657 (December 16, 2021) (in Russian).

[4] Metodicheskie rekomendatsii № 11-8/240-09. Gigienicheskaya otsenka vrednykh proizvodstvennykh faktorov i proizvodstvennykh protsessov, opasnykh dlya reproduktivnogo zdorov'ya cheloveka: utv. Departamentom Gossanepidnadzora RF 12.07.2002 [Methodical guidelines No. 11-8/240-09. Hygienic assessment of harmful occupational factors and production processes which are hazardous for reproductive health: approved by the Department of the RF State Sanitary Epidemiological Surveillance on July 12, 2002]. *GARANT: information and legal support*. Available at: https://base.garant.ru/4180225/ (December 16, 2021) (in Russian).

[5] Ob utverzhdenii perechnya professional'nykh zabolevanii: Prikaz Minzdravsotsrazvitiya Rossii ot 27.04.2012 N 417n [On Approval of the list of occupational diseases: The Order by the RF Ministry for Public Healthcare and Social Development dated April 27, 2012 No. 417n]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/902346847 (December 27, 2021) (in Russian).

[6] R 2.2.1766-03. Rukovodstvo po otsenke professional'nogo riska dlya zdorov'ya rabotnikov. Organizatsionno-metodicheskie osnovy, printsipy i kriterii otsenki: utv. Glavnym gosudarstvennym sanitarnym vrachom, Pervym zamestitelem Ministra zdravookhraneniya RF G.G. Onishchenko 24.06.2003 [R 2.2.1766-03. The Guide on assessment of occupational risks for workers' health. Organizational and methodical grounds, principles, and assessment criteria: approved by G.G. Onishchenko, the RF Chief Sanitary Inspector, the First Deputy to the RF Public Healthcare Minister on June 24, 2003]. Moscow, Rospotrebnadzor's Federal Center for Hygiene and Epidemiology, 2004, 24 p. (in Russian).

Table 1

The list of reproductive disorders caused by exposure to occupational and work-related factors [8–17]

Sex and a period in the reproductive cycle	Specific responses (outcomes) represented by reproductive disorders	Non-specific responses (outcomes) represented by reproductive disorders
A woman not pregnant	– weaker fertilization or loss of it – disorders of menstrual function (N91, N92, N94), female infertility (N97), untimely menopause (N95); – non-inflammatory disorders of female genital tract (N80–N98): endometriosis (N80); non-inflammatory disorders of ovary (N83); hyperplasia in uterus (N85); dysplasia and leukoplakia of cervix uteri (N87–N88); – neoplasms in female genital organs (D25–D28): uterine fibroid (D26); – benign mammary dysplasia (N60); – *female genital prolapse* (N81); – *malignant neoplasms of female genital organs and breast* (C50–C58); – disorders of population hormonal markers profile in urine during two cycles to estimate ovarian dysfunction (LH, FSH, HCG in 100 women) (E28);	– non-specific inflammatory disorders of female pelvic organs (N60–N73, N76, N77);
A pregnant woman	– unfavorable conception outcome – spontaneous abortion (O03), ectopic pregnancy (O00), hydatidiform mole (O01), other abnormal products of conception (O02), habitual aborter (N96), stillbirth (Z37); threat of miscarriage (O20.0);	– complications of an existing somatic pathology – anemia of pregnant (O99); – pregnancy complications – excessive vomiting in pregnancy (O21), gestosis in the second half of pregnancy (O10–O16); – premature delivery (O42, O60), abnormalities of forces of labor (O62);
Negative responses (outcomes) in offspring	– effects on a developing fetus – congenital malformations (Q00–Q89), lesions of a fetus including those due to an occupational injury, poisoning, or occupational disease (P00); – physical (R20) and mental retardation (F80–F89), behavioral disorders (F91–F92), malignant and benign neoplasms in the first and next generations (D10–D36, C00–C97);	– fetus development disorders – intrauterine hypoxia (P20), slow fetal growth and fetal malnutrition (P05), certain conditions originated in the perinatal period (P00–P96);
A breast-feeding woman after a recent childbirth	– lactation disorders (O92);	
A fertile man	– weaker fertilization abilities (gonadotropic, gonadotoxic effects действие) – male infertility (N46) due to decreased sperm concentration in ejaculate, 2 mln/ml and lower, lower sperm motility and other deteriorated parameters of functional activity (sperm quality); – endocrine disorders – changes in the population profile of male hormones concentrations in blood serum (follicle-stimulating hormone, luteinizing hormone, testosterone, prolactin in 3-time detection in 50–100 men); – malignant neoplasms of testis (C62).	– sexual dysfunction (F52).

A design of an epidemiological study which is aimed at assessing reproductive health risks can change depending on a type of an examined outcome and a period when it occurs. A cross-sectional study or a prevalence study is preferable to assess risks of developing diseases in women who are not pregnant or in men since it usually describes health of a workers' group at a given moment of time [18]. But if we want to assess risks of reproductive disorders which occur in a certain period of time after an exposure to an occupa-

tional factor has ended both in women and men and their offspring, we should use a case-control study or case-referent study [19].

Risk characterization usually involves calculating risk rates, assigning them into risk categories, and detecting priority occupational and work-related factors which cause OR.

The algorithm applied to quantify OR for reproductive health include the following fundamental sequence:

– calculating probability, including additional one, that reproductive disorders would develop in a test and a control group;

– calculating an OR of reproductive disorders;

– calculating an integral OR of reproductive disorders;

– determining categories of OR rates and assessing acceptability of OR for reproductive health.

A probability that *i*-th reproductive disorder would develop ($p_{rd}^{\ i}$) in a test group (or "case") and a control group ("control") is determined by calculating frequency of such a disorder as per the following formula 1:

$$p_{rd}^{\ i} = n_{rd}^{\ i} / N^i, \qquad (1)$$

where $n_{rd}^{\ i}$ is a number of people with *i*-th reproductive disorder in each group, N^i is a number of workers in each group.

An additional probability $p_{rd\ add}^{\ i}$ that *i*-th reproductive disorder would develop in workers is determined by calculating a difference between probabilities of such a disease in a test group $p_{rd}^{\ i}$ and in a control one $p_{rd\ ref}^{\ i}$ as per the formula 2:

$$p_{rd\ add}^{\ i} = p_{rd}^{\ i} - p_{rd\ ref}^{\ i} \qquad (2)$$

A group risk of *i*-th reproductive disorder ($R_{rd}^{\ i}$) is calculated in analyzed groups as per the formula 3:

$$R_{rd}^{\ i} = p_{rd\ add}^{\ i} \cdot G^i, \qquad (3)$$

where $p_{rd\ add}^{\ i}$ is an additional probability that *i*-th reproductive disorder would develop, G^i is severity of outcomes caused by a reproductive disorder.

An integral risk allows for probable negative outcomes under exposure to a set of harmful occupational and work-related factors. An integral risk caused by both occupational and work-related reproductive disorders developing under exposure to harmful factors is calculated as per the formula 4:

$$R_{rd}^{int} = 1 - \prod_{i=1}^{n} \cdot \left(1 - R_{rd}^{i}\right). \qquad (4)$$

Risks are assigned into different risk categories as per the criteria suggested in the work by N.V. Zaitseva [3]. Negligible and low occupational risks are considered to be acceptable.

Severity of outcomes caused by an exposure to a harmful factor is a risk-characterizing determinant. It is advisable to determine severity of outcomes caused by variable responses (effects) of reproductive health using coefficient values recommended by the WHO [20, 21]. However, bearing in mind that the same outcomes can potentially be significant not only for workers but also for their offspring (a possibility to have any offspring), we suggest using "fertility loss" as a basic indicator. Its value is determined based on data about duration of a fertility period and a period during which all the attempts to conceive a child have failed. Thus, in case a man or a woman has completely lost a possibility to conceive a child, "fertility loss" is recommended to be taken as equal to 1; if this loss is only partial, it is necessary to calculate its value. Necessary data can be provided by social surveys or taken from clinical case histories. We should note that the final assessment takes into account all detected risks, both for exposed workers and outcomes for their offspring together with selecting the priority (maximum) risk level.

Therefore, when assessing reproductive risks, it is necessary to take into account sex-specific peculiarities, sensitive periods in the reproductive cycle, different physiological states, as well as health disorders in offspring caused by parental occupational exposures. Risk quantification involves taking into account an additional probability of developing disorders and their severity. Results produced by epidemiological studies are suggested as grounds for such quantitative risk assessment. Epidemiological studies can have various de-

signs depending on a type of an examined outcome and a period of its occurrence. A certain peculiarity of assessment which concentrates on severity of outcomes is its focus being not only on health losses borne by potential parents but also on damage caused by declining birthrates and developing disorders and diseases, including congenital ones, in children.

The suggested algorithm was tested on the results produced by a study which focused on gynecological morbidity, fertile functions, and pregnancy outcomes in women employed at a petrochemical production (chemical engineers, chemical analysts, samplers, etc.) [5]. Working conditions at their workplaces corresponded to hazard category 3.1 (hazardous, class 1). These conditions occurred due to a combined exposure to chemical factors (saturated, unsaturated, aromatic hydrocarbons and their derivatives, vapors of fatty acids and spirits, phenol, non-organic toxic compounds of carbon, sulfur, nitrogen, etc.) and labor intensity (work was organized in three shifts).

Table 2 provide initial data on the frequency of negative responses (outcomes) from women's reproductive health taking into account the reproductive cycle as well as epidemiological criteria (relative risk, *RR*; etiological fraction, *EF*) which confirm intensity of a correlation between a pathology and harmful occupational factors.

We determined an additional probability of each response (Table 3) using data on frequencies of reproductive losses borne by female workers employed at a petrochemical production in the test and reference group.

Reproductive risks were calculated and assessed bearing in mind severity of established health outcomes; the results are given in Table 3.

We established that a risk of infertility amounted to $4 \cdot 10^{-4}$ for female workers employed at a petrochemical production during a period in the reproductive cycle when they were not pregnant. This risk was classified as "low" whereas a risk of menstrual function

Table 2

Frequencies of negative responses from reproductive health of women employed at a petrochemical production and epidemiological criteria

A period in the reproductive cycle	Disease (ICD-10 code)	Frequency of a response	*RR*	*EF*, %	Intensity of a correlation
A woman not pregnant	Menstrual function disorders (N91, N92, N94)	27.1 ± 1.9	4.3	79.6	Very high
	Benign neoplasms (D25–D28)	18.7 ± 1.7	2.5	60.0	High
	Female infertility (N97)	9.4 ± 1.3	2.2	54.5	High
A pregnant woman	Threat of miscarriage (O20.0)	41.9 ± 2.7	1.6	37.5	Average
	Gestosis in the 2nd half of pregnancy (O10–O16)	48.9 ± 2.7	1.9	47.4	Average
Offspring	Intrauterine hypoxia (P20)	39.1 ± 2.6	5.2	80.8	Very high

Table 3

Results produced by calculating reproductive risks for female workers employed at a petrochemical production

A period in the reproductive cycle	Disease (ICD-10 code)	$p_{rd\ add}^{i}$	G^i	R^i	Risk category
A woman not pregnant	Menstrual function disorders (N91, N92, N94)	0.208	0.011	$2 \cdot 10^{-3}$	Moderate
	Benign neoplasms (D25–D28)	0.112	0.011	$1 \cdot 10^{-3}$	Moderate
	Female infertility (N97)	0.051	0.008	$4 \cdot 10^{-4}$	Low
A pregnant woman	Threat of miscarriage (O20.0)	0.157	0.008	$1 \cdot 10^{-3}$	Moderate
	Gestosis in the 2nd half of pregnancy (O10–O16)	0.232	0.049	$1.1 \cdot 10^{-2}$	Average
Offspring	Intrauterine hypoxia (P20)	0.316	0.01	$3 \cdot 10^{-3}$	Moderate

N o t e : $p_{rd\ add}^{i}$ is an additional probability of *i*-th reproductive disorder; G^i is severity of an outcome caused by a reproductive disorder; R^i is a risk level of a developing *i*-th reproductive disorder.

disorders and developing benign neoplasms rose up to being "moderate" and amounted to $2 \cdot 10^{-3}$ and $1 \cdot 10^{-3}$ accordingly. We established that pregnant woman were exposed to a "moderate" risk of developing disorders which threatened normal course of a pregnancy ($1 \cdot 10^{-3}$) and an "average" risk of gestosis during the second half of a pregnancy ($1.1 \cdot 10^{-2}$). Since we didn't detect any ODs causing reproductive losses, we assumed that the integral risk for women's reproductive age was created only by WRDs and amounted to $1.6 \cdot 10^{-2}$ ("average" risk).

As we noted earlier, occupational factors which parents (mothers) are exposed to have a correlation with development of healthy offspring. In our example a direct response from offspring is intrauterine hypoxia with its risk being "moderate" ($3 \cdot 10^{3}$).

Besides, certain occupational gynecologic diseases of a mother can have some influence on offspring's health. Thus, bearing in mind "fertility loss" indicator which should be considered equal to 1 in case of infertility, severity of health outcomes for offspring is also taken as equal to 1. Consequently, a risk rate rises and a risk becomes "high" ($5 \cdot 10^{-2}$) whereas it was only "low" for a woman herself. The ultimate assessment should be based on selecting the priority risk rate, that is, the health risk is "high".

Therefore, the results produced by testing the suggested methodical approaches to assessing reproductive risks indicate that working conditions at workplaces of female workers employed at a petrochemical production create unacceptable health risks both for women themselves (menstrual function disorders, developing benign neoplasms, unfavorable course of a pregnancy) and their offspring.

Discussion. The methodology for assessing OR has several key points; they are top priority assigned to safety, exposure assessment based on using the most relevant measurement techniques, and sticking to the correct order of stages in assessment[6]. We substantiated the necessity to take into account sex-related differences, sensitive periods in the reproductive cycle, and different physiological conditions when assessing reproductive risks. It is also important to remember that certain health disorders in offspring can be caused by parental occupational exposures.

Unfortunately, specific assessment of working conditions (a priori assessment) doesn't involve assessing workers' health or severity of probable health outcomes; as for semi-quantitative assessment, it focuses solely on those ODs which are proven to be related to a specific occupation. Given that, we have suggested new approaches to quantifying health risks which allow for an additional probability of health disorders and their severity.

Quantitative risk assessment should be based on results produced by epidemiological studies which establish and prove cause-effect relations between a health outcome and an occupational factor. These studies may have different design depending on a type of an examined reproductive disorder and a period of time when it occurs. Assessment of outcome severity has a peculiarity which is its focus being not only on health losses born by potential parents but also damage caused by declining birthrates and developing disorders and diseases in offspring, including congenital ones. According to the Order by the RF Ministry for Public Healthcare and Social Development No. 160[7], such reproductive health disorders as "abortion" and "loss of reproductive functions and ability to procreate" are considered to be severe damage (severe health outcomes). However, the Order doesn't provide any quantification to assess them. Therefore, we recommend using the coefficients developed by

[7] Ob opredelenii stepeni tyazhesti povrezhdeniya zdorov'ya pri neschastnykh sluchayakh na proizvodstve: Prikaz Minzdrava i sotsial'nogo razvitiya RF ot 24.02.2005 № 160 [On determining severity of damage to health caused by an occupational injury: The Order by the RF Ministry for Public Health and Social Development issued on February 24, 2005 No. 160]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/901927104 (December 27, 2021) (in Russian).

the WHO to assess severity of outcomes for reproductive health [20, 21]. We suggest using "fertility loss" as an indicator which helps determine severity of outcomes for offspring (a possibility to procreate). The indicator is calculated based on a duration of a fertility period and a period during which all the attempts to conceive a child have failed. It should be noted, that a reduction in a fertility period can be a deliberate choice made by a woman (contraception) and this, in its turn, creates an uncertainty in assessing severity of outcomes for offspring.

The results produced by testing the suggested approaches give an opportunity to detect an unacceptable occupational risk caused by chemical factors and labor intensity for reproductive health of women employed at a petrochemical production. The highest health risk for female workers was associated with developing gestosis during the 2nd half of pregnancy (moderate occupational causation); moderate health risks were associated with developing disorders of the menstrual function (very high occupational causation), benign neoplasms (high occupational causation) as well as threat of miscarriage (average occupational causation). We detected a moderate risk for offspring's health associated with intrauterine hypoxia (very high occupational causation) and a high risk associated with infertility (high occupational causation). Occurrence of such negative outcomes is quite probable and is explained with data available in literature. For example, benign neoplasms are assumed to develop under exposure to harmful working conditions which don't correspond to adaptation capabilities of a female body. Changes in the hormonal status and subsequent disorders of the menstrual function as well as infertility can be caused by chronic occupational stress (or labor intensity) and inhalation exposure to chemicals [10]. Chemicals which are used in production operations include saturated aromatic hydrocarbons, toxic carbon compounds, and vapors of various spirits. They exert negative influence on development thus creating unacceptable risks for offspring[8]. Obviously, the situation requires immediate actions aimed at elimination these risk factors. To do that, we can recommend using an algorithm for managing occupational risks for the reproductive system developed by experts from N.F. Izmerov's Scientific Research Institute for Occupational Medicine.

Conclusions:

1. Quantitative assessment of occupational health risks involves taking into account an additional probability of developing disorders and their severity. When assessing occupational risks for reproductive health, it is advisable to pay attention to sex-related peculiarities, sensitive periods in the reproductive cycle, different physiological conditions, as well as occupational causation of health outcomes in offspring caused by parental exposures.

2. The suggested methodical approaches involve epidemiological research with its results giving grounds for assessing an additional probability of developing reproductive disorders (a difference between a probability of negative health outcomes in test and control groups); determining OR rates as regards reproductive disorders; determining an integral OR of reproductive disorders; assigning occupational risks into risk categories and assessing acceptability of reproductive OR rates.

3. It is suggested to determine severity of responses (outcomes) for reproductive health and an indicator which describes a risk and is necessary to quantify it by using coefficients recommended by the WHO, in particular, "fertility loss" indicator since it is significant for assessing severity of outcomes for offspring.

[8] R 2.1.10.1920-04. Rukovodstvo po otsenke riska dlya zdorov'ya naseleniya pri vozdeistvii khimicheskikh veshchestv, zagryaznyayushchikh okruzhayushchuyu sredu: utv. Pervym zamestitelem Ministra zdravookhraneniya RF, Glavnym gosudarstvennym sanitarnym vrachom RF G.G. Onishchenko 05.03.2004 [Guide R 2.1.10.1920-04. Human Health Risk Assessment from Environmental Chemicals: approved by G.G. Onishchenko, the RF Chief Sanitary Inspector, the First Deputy to the RF Public Healthcare Minister on March 5, 2004]. Moscow, Rospotrebnadzor's Federal Center for Hygiene and Epidemiology, 2004, 143 p. (in Russian).

4. An integral risk of reproductive losses caused by harmful occupational and work-related factors covers both occupational and work-related diseases. Moreover, in cases when detected risks concern not only exposed workers but their offspring as well, it is recommended to select the priority (maximum) risk rate as the ultimate assessment result.

5. We tested the methodical approaches on a group of women employed at a petrochemical production and exposed to such harmful occupational factors as chemicals and labor intensity which allowed ranking working conditions at their workplaces as belonging to hazard category 3.1. The testing results revealed that the integral risk for their reproductive health amounted to $1.6 \cdot 10^{-2}$ thus indicating that the group risk was unacceptable. We detected such probable negative health outcomes as disorders of the menstrual function, developing benign neoplasms, and unfavorable course of pregnancy. Besides, when a mother is exposed to the examined occupational factors, this creates an unacceptable health risk for offspring, in particular, a risk of intrauterine hypoxia ($3 \cdot 10^{-3}$). Such a reproductive disorder as infertility creates "low" risks for a woman whereas the risk rate grows up to "high" risk when it comes to potential offspring. The ultimate assessment result is selecting the maximum risk rate, that is, the 'high" risk for offspring's health.

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References

1. Frazier L.M. Workplace reproductive problems. *Prim. Care*, 2000, vol. 27, no. 4, pp. 1039–1056. DOI: 10.1016/s0095-4543(05)70188-3

2. Sivochalova O.V., Fesenko M.A., Golovaneva G.V., Denisov E.I. Protection and Improvement of Reproductive Health of Workers with High Risk Professions. *Vestnik RGMU*, 2013, no. 5–6, pp. 73–77 (in Russian).

3. Zaitseva N.V., Shur P.Z., Alekseev V.B., Savochkina A.A., Savochkin A.I., Khrushcheva E.V. Methodical approaches to assessing categories of occupational risk predetermined by various health disorders among workers related to occupational and labor process factors. *Health Risk Analysis*, 2020, no. 4, pp. 23–30. DOI: 10.21668/health.risk/2020.4.03.eng

4. EPA/630/R-96/009. Guidelines for Reproductive Toxicity Risk Assessment. *US EPA*, 1996, 143 p. Available at: https://www.epa.gov/sites/default/files/2014-11/documents/guidelines_repro_toxicity.pdf (16.12.2021).

5. Gainullina M.K., Shaikhlislamova E.R., Karimova L.K., Teregulov B.F., Karimova F.F. Protection of workers' reproductive health – a factor promoting the improvement of the demographic situation. *Meditsina truda i ekologiya cheloveka*, 2021, vol. 25, no. 1, pp. 61–72. DOI: 10.24411/2411-3794-2021-10106 (in Russian).

6. Analiz riska zdorov'yu v strategii gosudarstvennogo sotsial'no-ekonomicheskogo razvitiya [Analysis of health risk in the strategy of state socio-economic development]. In: G.G. Onishchenko, N.V. Zaitseva eds. Perm, Perm National Research Polytechnic University Publ., 2014, 738 p. (in Russian).

7. Izmerov N.F., Sivochalova O.V., Fesenko M.A., Denisov E.I., Golovaneva G.V. The issues of workers reproductive health protection from harmful occupational and environmental exposures. *Vestnik RAMN*, 2012, no. 12, pp. 47–53 (in Russian).

8. Babanov S.A., Strizhakov L.A., Agarkova I.A., Tezikov Yu.V., Lipatov I.S. Workplace factors and reproductive health: causation and occupational risks assessment. *Ginekologiya*, 2019, vol. 21, no. 4, pp. 33–43 (in Russian).

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

10. Sivochalova O.V., Fesenko M.A., Gainullina M.K., Denisov E.I., Golovaneva G.V. Occupational risk for reproductive disturbances, problems and principles of their prediction in workers exposed to chemical factors. *Meditsina truda i ekologiya cheloveka*, 2015, no. 4, pp. 192–198 (in Russian).

11. Golovaneva G.V., Sivochalova O.V., Fesenko M.A., Denisov E.I., Morozova T.V. The risk of developing disease in female workers involved in modern sector employment and the health of their children. *Gigiena i sanitariya*, 2015, vol. 94, no. 5, pp. 80–86 (in Russian).

12. Kukhtina E.G., Solionova L.G., Fedichkina T.P., Zykova I.E. Night shift work and health disorder risk in female workers. *Gigiena i sanitariya*, 2015, vol. 94, no. 5, pp. 86–91 (in Russian).

13. Amirov N.Kh., Berkheeva Z.M., Garipova R.V. Assessment of occupational risk of violations for health of medical workers by results of periodic medical examination. *Vestnik sovremennoi klinicheskoi meditsiny*, 2014, vol. 7, no. 2, pp. 10–14 (in Russian).

14. Babanov S.A., Kosareva O.V., Vorobyeva E.V. Impact of local and general vibration on male reproductive health. *Gigiena i sanitariya*, 2012, vol. 91, no. 1, pp. 27–29 (in Russian).

15. Potapenko A.A. Reproduktivnoe zdorov'e meditsinskikh rabotnikov-zhenshchin [Reproductive health of female medical workers]. *Zdravookhranenie*, 2013, no. 2, pp. 80–85 (in Russian).

16. Swan S.H., Elkin E.P., Fenster L. The question of declining sperm density revisited of 101 studies published 1934–1996. *Environ. Health Perspect.*, 2000, vol. 108, no. 10, pp. 961–966. DOI: 10.1289/ehp.00108961

17. Ristovska G., Laszlo H.E., Hansell A.L. Reproductive outcomes associated with noise exposure – a systematic review of the literature. *Int. J. Environ. Res. Public Health.*, 2014, vol. 11, no. 8, pp. 7931–7952. DOI: 10.3390/ijerph110807931

18. Grjibovski A.M., Ivanov S.V. Cross-sectional studies in health sciences. *Nauka i Zdravookhranenie*, 2015, no. 2, pp. 5–18 (in Russian).

19. Kholmatova K.K., Grjibovski A.M. Case-control studies in medicine and public health. *Ekologiya cheloveka*, 2016, no. 8, pp. 53–60 (in Russian).

20. WHO methods and data sources for global burden of disease estimates 2000–2019. *WHO*, 2020. Available at: https://cdn.who.int/media/docs/default-source/gho-documents/global-health-estimates/ghe2019_daly-methods.pdf?sfvrsn=31b25009_7 (16.12.2021).

21. Global Burden of Disease Study 2019 (GBD 2019) Disability Weights. Seattle, USA, Institute for Health Metrics and Evaluation (IHME), 2020. Available at: https://ghdx.healthdata.org/record/ihme-data/gbd-2019-disability-weights (16.12.2021).

Shur P.Z., Zaitseva N.V., Lir D.N. Substantiating methodical approaches to quantifying reproductive health risks caused by harmful occupational and work-related factors. Health Risk Analysis, 2022, no. 1, pp. 48–57. DOI: 10.21668/health.risk/2022.1.05.eng

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Review

CONTEMPORARY ASPECTS IN CONTROL OVER RESISTANT TO ANTIBIOTICS MICROBIAL CONTAMINANTS OF FOOD, TAKING INTO ACCOUNT PECULIARITIES OF RELATED HEALTH RISK ASSESSMENT. PART 1

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Antimicrobials are widely used in agriculture to prevent and treat diseases and to stimulate growth of food-producing animals. However, this induces developing antimicrobial resistance among animal bacteria, and this resistance is then transmitted along food chains and spreads in the environment. It is commonly accepted at the moment that effective measures should be taken to contain it in food production, to prevent it from spreading on the global scale and to minimize related negative health outcomes. This can be achieved, among other things, due to intensifying inter-branch interactions.

This review aimed to consider contemporary aspects in preventing development of antimicrobial resistance in microorganisms that contaminate raw materials and processed food products; to dwell on how the issue is controlled in food production both in Russia and abroad; to focus on trends and prospects of developing new effective measures in the sphere.

The review involved analyzing domestic and foreign regulatory and legal documents concerning prevention of antimicrobial resistance and analysis of related risks; generalizing and analyzing latest scientific research works published in reference databases including Web of Science, Scopus, PubMed, Google scholar.

As a result, we described the experience accumulated in organizing monitoring over prevalence of antimicrobial resistance in foreign countries, to generalize international recommendations as well as regional and national ones on monitoring over microorganisms that are resistant to antimicrobials, and to highlight practical activities aimed at preventing occurrence and spread of antimicrobial resistance in food production. We substantiated certain peculiarities of related health risk assessment, namely, occurrence of genetic determinants of antimicrobial resistance and antibiotic residues in food together with resistant microorganisms. We also formulated basic principles of organizing and conducting monitoring over antimicrobial resistance in food chains (with the focus on antimicrobial medications that are crucially important in medicine). These principles can be applied in the Russian Federation within programs aimed at preventing antimicrobial resistance.

Key words: *antimicrobial resistance, antimicrobial veterinary medications, monitoring over antimicrobial resistance, sub-inhibitory doses of antimicrobials, food safety, harmful factors related to antimicrobial resistance, markers of antimicrobial resistance in food, antibiotic residues, genes of antimicrobial resistance in food isolates, food isolates with antimicrobial resistance.*

Annually approximately 500,000 people die due to antimicrobial resistance all over the world [1].

Multiple efforts have been made recently, both at the international and local level, to prevent zoonotic agents from becoming resistant as a response to antimicrobial use in veterinary; a lot is done to prevent incidence among population caused by this resistance. The Global Action plan on antimicrobial resistance

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which was approved on the 68th WHO General Assembly introduced "One Health" interbrunch approach. This approach involves implementing complex activities aimed at fighting the phenomenon both in healthcare and agriculture. There are several directions within it including monitoring over resistance of circulating agents, prevention of infections, rational antimicrobial use and implementation of alternatives to antimicrobials, etc. The WHO and FAO approved on several policy documents for supporting actions taken in different countries in agriculture, including the Guidelines on use of medically important antimicrobials in food-producing animals and the FAO Action plan on antimicrobial resistance 2016–2020 [2, 3].

In 2017 the Strategy for preventing spread of antimicrobial resistance for the period up to 2030 was adopted in the Russian Federation. The document fixes the necessity to examine prevalence of antimicrobial resistance, develop relevant legislation in due time and implement activities aimed at containing it in food production[1]. At the same time Rospotrebnadzor and FAO started a joint project aimed at assisting their partner states in the Eastern Europe and Central Asia in developing national strategies and action plans on fighting against antimicrobial resistance[2]. The primary tasks of the project are to enhance a country potential regarding monitoring over pathogen resistance and to organize systems for laboratory control over this resistance regarding food products with the major project reference center to be located in Russia.

All the aforementioned strategies are undoubtedly justified, first of all, with respect to food products being the primary object under surveillance since basic quantities of environmental contaminants (up to 70 %) enter the body with food and resistance is known to be the most important attribute of microbial contaminants. Control over it in various pathogens is vital since it is necessary to minimize abovementioned outcomes of foodborne toxicoinfections (FBTIs) and to search for effective therapy.

However, we should point out that fighting against antimicrobial resistance in foodborne bacteria is primarily aimed at preventing its occurrence and spread along food chains as well as its transmission to gut microbiota [2, 3]. Monitoring which is limited to pathogens (in most countries they are predominantly Salmonella in raw foods) can't give a clear picture of the examined phenomenon even if it is well-organized and efficient. Population exposure to non-pathogenic potential resistance transmitters in cooked foods is much higher than that covered by such monitoring and therefore should be estimated as per relevant indicators.

This example provides clear evidence that certain weak spots can be detected already at an initial stage in developing and implementing activities aimed at fighting antimicrobial resistance. Accordingly, it is necessary to constantly apply logical thinking to understand the problem better, to adjust measures and to harmonize them with the best available practices if we want to enhance surveillance over antimicrobial resistance in every country all over the world.

Aim. This review aimed to consider contemporary aspects in containing and controlling antimicrobial resistance in microbial contaminants in food as well as trends and prospects of developing effective measures in the sphere.

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[1] Strategiya preduprezhdeniya rasprostraneniya antimikrobnoi rezistentnosti v Rossiiskoi Federatsii na period do 2030 goda: utv. rasporyazheniem Pravitel'stva Rossiiskoi Federatsii ot 25.09.2017 № 2045-r [The Strategy for preventing spread of antimicrobial resistance in the Russian federation for the period up to 2030: approved by the RF Government Order on September 25, 2017 No. 2045-r]. *GARANT: the information and legal portal*. Available at: https://www.garant.ru/products/ipo/prime/doc/71677266/ (November 29, 2021) (in Russian).

[2] O realizatsii rasporyazheniya Pravitel'stva Rossiiskoi Federatsii ot 03.02.2017 № 185-r: Prikaz Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka ot 26.02.2018 № 97 [On implementation of the RF Government Order dated February 03, 2017 No. 185-r: The Order by the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing issued on February 26, 2018 No. 97]. *KODEKS*. Available at: http://docs.cntd.ru/document/551223268 (November 29, 2021) (in Russian).

Materials and methods. The review involved analyzing domestic and foreign regulatory and legal documents specifying how to contain antimicrobial resistance and analyze related risks. We generalized and analyzed latest scientific research works published in 2005–2021 in reference databases including Web of Science, Scopus, PubMed, and Google scholar. We searched for literature sources using the following key words: antimicrobial resistance, food isolates resistant to antimicrobials, antimicrobials in forage, veterinary antimicrobials, monitoring over antimicrobial resistance, horizontal transfer of antimicrobial resistance genes, sub-inhibitory doses of antimicrobials.

To organize an activity: what is necessary for its effectiveness? The first step in implementing activities against antimicrobial resistance in any country is to develop and adopt a national action plan. The RF Government approved a middle-term action plan for 2019–2024 within the Strategy for preventing spread of antimicrobial resistance for the period up to 2030[3]. Given specific tasks on fighting against resistance in food chains, two sets of measures were included into the plan; they were aimed at preventing both its occurrence and spread. The first set is aimed at developing a regulatory base in the short-term (prohibiting use of veterinary antimicrobials with non-therapeutic purposes or use of medications not included in sanctioned lists as well as stricter regulation of such substances in forage production). Non-therapeutic use means that healthy animals are fed with forages which contain antimicrobials in low doses; though, it is still permitted to apply antimicrobial prevention in intensive animal farming when there is a danger of a mass infection among cattle and poultry.

The second set is aimed at preventing and containing circulation of infectious agents which have antimicrobial resistance. The key component here is organizing and conducting monitoring over antibiotic residues in food raw materials and food products and resistance of bacteria isolated from animals, raw materials and food products; this monitoring can also be conducted within international cooperation. According to the plan, a unified interdepartmental database is to be created with participation by the RF Public Healthcare Ministry, Rospotrebnadzor, and other concerned federal executive authorities. This database will contain data on prevalence of antimicrobial resistance. Other important steps are to optimize and standardize methods applied to monitor microbial resistance. These tasks are being tackled at the moment and there are two active platforms: AMRmap[4] in medicine and AMRCloud[5] in veterinary medicine.

In 2021 the plan envisaged creating a list of veterinary antimicrobials with limitations on their use including in food-producing animals. We should note that similar lists created by the WHO and EU contain, for example, chloramphenicol, nitrofuranes, and metronidazole[6] [4], whereas these important provisions have been approved on in the RF for the first time only recently and after a long-term discussion.

At the same time there are very few concrete data in the plan on interdepartmental interactions in RF regions and terms are not specified (2019–2024). This will require certain adjustments to provide implementation of actual activities.

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[3] Ob utverzhdenii plana meropriyatii na 2019–2024 gg. po realizatsii Strategii preduprezhdeniya rasprostraneniya antimikrobnoi rezistentnosti v RF na period do 2030 g.: rasporyazhenie Pravitel'stva RF ot 30.03.2019 № 604-r [On Approval of the action plan for the period 2019–2024 on implementing the Strategy for preventing spread of antimicrobial resistance in the Russian Federation for the period up to 2030 dated March 30, 2019 No. 604-r]. *The RF Government*. Available at: http://government.ru/docs/36320/ (November 29, 2021) (in Russian).

[4] AMRmap: online platform for analyzing data on antimicrobial resistance in Russia. Available at: https://amrmap.net/ (November 24, 2021).

[5] AMRcloud: web platform for analysis and sharing of AMR surveillance data. Available at: https://amrcloud.net/en/ (November 29, 2021).

[6] Reglament Evropeiskoi Komissii 37/2010 ot 22.12.2009 o farmakologicheski aktivnykh veshchestvakh i ikh klassifikatsii v otnoshenii maksimal'no dopustimykh ostatkov v pishchevykh produktakh zhivotnogo proiskhozhdeniya [Commission Regulation (EU) No. 37/2010 of 22 December 2009 on pharmacologically active substances and their classification regarding maximum residue limits in foodstuffs of animal origin]. Saratov, IPR media, 2019, 144 p. (in Russian).

As the action plan was being discussed and approved by the RF Federal Assembly, the senators adopted several legislative initiatives for the highest federal executive authorities. Thus, the RF Public Healthcare Ministry was given a task to create a federal system for monitoring over resistance of the leading infectious agents causing human infections. The system is to be created on the basis of a network comprising local centers (laboratories at medical and prevention organizations) in RF regions with its methodical verification center located in Smolensk Medical University. The Ministry will also be responsible for providing finance and material and technical support for these centers. This initiative fixes and enhances the potential of the former federal scientific and methodical center for monitoring over antimicrobial resistance which was previously created by the Ministry in 2015 and provides the logistics for the national database on antibiotic resistance and control over it in clinical medicine[7,8].

However, no similar decisions have been made with respect to monitoring over non-clinical strains, first of all, foodborne ones. The federal executive authorities who are responsible for the sphere are to develop a proper scientific-methodical and regulatory base. Thus, Rospotrebnadzor should develop relevant clinical recommendations and harmonize them with the existing clinical recommendations on determining antimicrobial sensitivity of bacteria isolated from food products and food raw materials. These recommendations should be based on using epidemiological boundary values of strain sensitivity estimation. The RF Agricultural Ministry is to develop unified veterinary rules for use of veterinary antimicrobials in animal farming[7].

We remember that all the aforementioned documents are significant; still, their development is only a step in a whole set of activities aimed at creating a necessary system in the country for control over antimicrobial resistance which is transmitted with food. In all developed countries such transmission is given the same attention as clinical one due to objectively higher volumes of antimicrobials used in contemporary food production. Thus, the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) provides data on how antibiotics are distributed in the world and thereby indicates that ratio of hospital purchases and chemists' sales to purchases by manufacturers using antibiotics in food-producing animals and plants is 20 % : 80 %. When recalculated per 1 kg of a standardized body mass of an ultimate consumer, 1.5 times higher volumes of such medications are sold to be used in animal farming than in treating people [5].

Therefore, given the selective exposure to antibacterial medications from all possible sources, occurring resistance determinants unavoidably penetrate the environment and are involved into the joint circulation (Figure) [6].

This situation calls for counteractions in two directions, by imposing limits on use of antimicrobials and making it rational in all possible spheres and by breaking paths of resistance spreading in the environment, including food chains as the objects being the most susceptible to contamination. The most effective way is to combine efforts by all concerned parties, to create a common database on preparations applied in medicine and veterinary medicine and on resistant isolates, and to coordinate all the activities from a common center.

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[7] Antibiotikorezistentnost' v Rossii: rasprostranennost' i zakonodatel'nye initsiativy v reshenii problem: reshenie zasedaniya Ekspertnogo soveta po zdravookhraneniyu Komiteta SF po sotsial'noi politike ot 03.07.2018 № 3.8-13/1616 [Antibiotic resistance in Russia: prevalence and legislative initiatives on finding solutions to the related issues: the decision made at the meeting by the Expert Council on Public Healthcare of the Federal Assembly Committee on social policy dated July 3, 2018 No. 3.8-13/1616]. *The National Association of experts on infection control*. Available at: http://nasci.ru/?id=4261 (November 29, 2021) (in Russian).

[8] O federal'nom nauchno-metodicheskom tsentre monitoringa rezistentnosti k antimikrobnym preparatam: Prikaz Minzdrava Rossii ot 03.06.2015 № 302 [On the federal scientific-methodical center for monitoring over antimicrobial resistance: the Order by the RF Public Healthcare Ministry issued on June 03, 2015 No. 302]. *KODEKS*. Available at: https://docs.cntd.ru/document/420281390 (November 29, 2021) (in Russian).

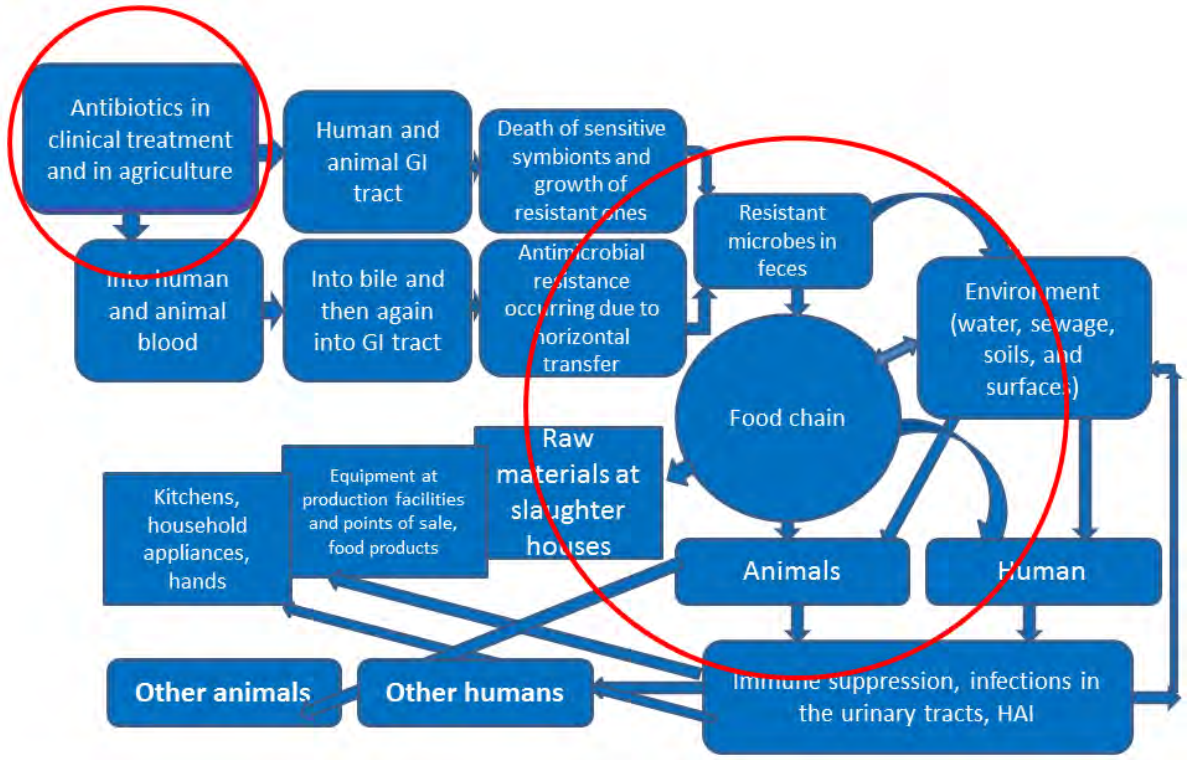

Figure. Circulation of resistance determinants in the environment

In our country, there are monitoring activities regarding antimicrobial resistance in bacteria circulating in various environmental objects, including the food chain, but this monitoring cannot yet be considered systematized.

Laboratory services existing at medical organizations deal with strains which spread from sick people and objects in in-patient hospitals but their target microbes are those which cause suppurative infections or so called Healthcare-Associated Infections (HAIs) and they don't usually pay any attention to agents causing FBTIs. And we should remember that nosocomial enteric bacteria acquire the highest resistance to semi-synthetic penincillins and 3rd – 4th generation cephalosporins (from 75 to 98 % strains), as well as to 3rd generation fluoroquinolones (70 %) [7].

Regional veterinary laboratories analyze microorganisms isolated from sick and dead animals at animal farms. According to data provided by Rossel'khoznadzor (the Federal Service for Veterinary and Phytosanitary Surveillance) in 2012 50–90 % of *E. coli*, *Salmonella*, *Enterococcus spp.* were highly resistant to tetracyclines, chloramphenicol, furazolidone; there was also growing resistance of *Salmonella spp.* to ampicillin, doxycillin, streptomycin, ciprofloxacin and norfloxacin in comparison with 2009.

Isolates of nontyphoidal salmonella from people and environmental objects, including food, are examined in Rospotrebnadzor's national reference center. In 2017 isolates turned out to be resistant in 58.5 % cases overall, including 93 % cases among *S. infantis*; *S. typhimurium*, 69 %; *S. enteritidis*, 47.5 %. 4 % of strains were resistant to 10 and more medications. Predominantly, isolates were resistant to cefurotoxime (44 %), cefalotin (29 %), ticarcillin (16 %), amoxicillin (15.5 %), piperacillin and tucarcillin / clavulanic acid (15 % each), cefotaxime (12 %) and co-trimaxozole (11 %)[9].

[9] O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2017 godu: Gosudarstvennyi doklad [On sanitary-epidemiologic welfare of the population in the Russian Federation in 2017: The State Report]. *Rospotrebnadzor*, 2018, 268 p. Available at: https://www.rospotrebnadzor.ru/documents/details.php?ELEMENT_ID=10145 (November 29, 2021) (in Russian).

Since 2018 monitoring over antibiotic residue and resistance of bacteria isolated from food raw materials and food products has been conducted by a reference center organized within the above-mentioned international project at Rospotrebnadzor's Central Scientific Research Institute for Epidemiology[2]. By the beginning of 2019, experts created profiles of 1068 pathogenic strains (*Salmonella spp.*, *S. aureus*, *L. monocytogenes*) isolated from food samples which were selected in 7 different food product groups with elevated total microbial contamination [8]. 42.7 %, 38.7 % and 18.6 % strains accordingly turned out to be resistant.

Non-pathogenic food isolates are not monitored in the RF. There are data in scientific publications that coliform bacteria and enterococci occurring in qualitative domestic milk and meat products have some resistance to antimicrobials which varies from 10 to 90 %. Enterococci resistant to ciprofloxacin are detected in 80–90 % cases. *Klebsiella* and *E. coli* with multi-resistance (up to 8 antibiotics) are detected in 17.4 % cases [9, 10]. Campylobacteria in poultry meat are practically totally resistant to 3rd generation fluoroquinolones (96 %), highly resistant to tetracyclines (88 %) and semi-synthetic penicillins (57 %) [11].

Obviously, in the RF resistant strains prevail not only in clinical environment but also in food chains and antimicrobial resistance is detected for clinically important antimicrobials of the latest generations. But even if we have this latest data, we still can't get a clear picture of resistance as a whole and any effects produced by the introduced measures. The reason is that, apart from separate monitoring activities in different spheres, there is no common functional network comprising local centers for control over non-clinical isolates. There aren't any decisions either on how to provide such centers with financial and logistic support.

So, we generalized international recommendations and experience accumulated by regional and national systems for monitoring over antimicrobial resistance [3, 12, 13]. As a result, we were able to formulate optimal principles for monitoring over it in food chains at the national level:

- aim: to protect human and animal health by managing risks and minimizing resistance in zoonotic agents, commensal and technological microorganisms as well as by selecting effective therapies;
- interdepartmental interactions and coordination by a national reference center(s);
- taking samples of strains alongside the whole food chain: healthy and sick animals, forages, food raw materials and food products, sick people (consumers);
- standardized sampling protocols;
- sampling design and criteria which conform to validity requirements;
- target strains: pathogenic bacteria which cause food-borne infections, non-pathogenic microorganisms (gut microbiota, biotechnological microorganisms);
- strain identification down to genus / species;
- determining phenotypic sensitivity of strains to antimicrobials using standardized techniques;
- systemic control over research quality;
- use of common and harmonized assessment criteria (boundary values) for minimal inhibitory concentrations (MIC) and zones where a growth in quantities of "epidemiological" bacteria could be slowed down;
- identifying determinants, nature and mechanisms of antimicrobial resistance using reproducible analysis techniques, including molecular and genetic ones;
- storage of original strains in cryobanks for further studies focusing on resistance mechanisms;
- participant confidentiality, transparent and well-mapped results, effective partnership, and validated approaches.

Practices applied in well-organized monitoring systems in different countries highlight the significance of simultaneous surveillance over a range and quantities of antimicrobials used both in people and animals. This is done by collecting data on sales on the national level, observations over use of medications at hospitals and animal farms as well as by direct control over their residues in forages and manufactured products [5, 13].

When a system is integrated in such a way, it fully corresponds to tasks set within "One Health" approach. Comparing data on resistance which come from different sources provides competent authorities with a whole number of opportunities to assess and manage risks at the national level. Among other things, this allows making correlations between data on antimicrobial use and resistance in different socioeconomic sectors, identifying emerging risks of antimicrobial resistance, prioritizing these risks along food chains (which sector? which bacteria? what resistance? which products?) and creating an authentic database for developing specific policies and effective measures.

The European antimicrobial resistance monitoring for zoonotic and indicator bacteria of animal, human, and food origin that started in 2005 is in line with most aforementioned principles. In 2017 a new action plan was adopted with its focus on fighting this resistance and its basic motto being "turning the EU into a region with best applied practices". The Action plan includes more than 75 specific tasks. The focus is on intensified research, development, and innovations, finding new solutions and instruments to prevent and treat infections as well as better diagnostics of resistance prevalence. A whole section is devoted to intensifying efforts on developing global measures and reducing risks related to resistance all over the world.

In 2019 the UN Secretary-General Antonio Gutterres made a statement stressing out that integration was crucially important in fighting against antimicrobial resistance. The statement was made on the 73rd session of the UN General Assembly summarizing all the efforts on implementing national action plans and measures taken to implement the political declarations made on the high-level meeting in 2015. It was said that "Along with the human health sector, the full engagement of the animal and plant health and environmental sectors through a "One Health" approach and a functional multisectoral coordination mechanism are urgently needed in each country; national action plans should be reviewed to reflect a comprehensive "One Health" approach" [14].

To sum up all these data, we can conclude that it is urgent to implement integral assessment of microbial resistance in Russia, not only in the clinical sphere but also in food production. To do that, legislative initiatives are required immediately; they should provide support for inter-brunch interactions by creating an interdepartmental structure with a coordination scientific-methodical center and a network comprising local monitoring centers.

Risk-based approach in global fighting against resistance in food production and distribution. In 2018 the second intergovernmental target group was created by Codex Alimentarius Commission as a response to growing attention paid to threats for public health imposed by antimicrobial resistance. Its major task was to develop science-based guidelines on coordinated management of antimicrobial resistance along the whole food chains [15]. The RF participates in both parts of this project which concentrate on revising the Code of practice to minimize and contain antimicrobial resistance in food products (CAC/RCP 61-2005) and developing the Guidelines on integrated monitoring and surveillance over food-borne antimicrobial resistance.

CAC/RCP 61-2005 is being actively revised by remote work teams with 41 EU countries and regions participating in the process. The document should provide grounds for developing measures aimed at reducing risks of resistance transmission with food. These measures can be implemented by any country within its national strategies on antimicrobial resistance taking its priority and capabilities into account and during a reasonable period of time. At present, 3 stages out of total 8 planned to be considered have been completed [16].

This code of practice is an integral part of risk analysis regarding foodborne antimicrobial resistance; it focuses on managing risks. All instructions on relevant measures and practices along food chains included into it are based on risk assessment and analysis [17]. These instructions cover such areas as responsible and reasonable production, registration, sale, deliveries, prescription, and use of antimicrobials in animal farming, aquaculture, plant growing as well as forages. They also provide guidance on how to contain development and spread of re-

sistant microorganisms, and how to identify resistance determinants in food processing, cooking, storage, transportation, selling, and consumption. The Code is interrelated with the Guidelines for risk analysis of food-borne microbial resistance (CAC/GL 77-2011) created in 2011 with its aim being to develop all components in analyzing risks of foodborne antimicrobial resistance, including science-based health risk assessment methodologies.

Peculiarities in assessing risks of foodborne antimicrobial resistance. CAC/GL 77-2011 describe how to assess health risks caused by presence of antimicrobial resistant microorganisms (AMRM), their determinants (AMRD) and/or residues of antimicrobial use (AMU) to which resistance is expressed in food products and animal forages and their transmission along food chains [17]. In Russia a similar guide covering these issues was introduced in 2012 and entitled MR 2.1.10.0067-12 "Assessment of health risks caused by exposure to microbial factors in food products"[10].

Negative outcomes for human health caused by resistant food isolates are not always urgent and can be even rather latent (in case of genetic determinants). Therefore it is more difficult to assess them than to assess risks related to clinical resistance or risks related to microbial contamination in food products. Such outcomes should be separated from all other obvious ones caused by microbial factors and assessment methodology in their case should be based on specific approaches.

In general, assessment of risks caused by resistance transmitted with food is not structurally different from the conventional microbial risk assessment (MRA) [18]. Initially a risk profile is created as a combination of a specific product with AMRM, AMRD or AMU. However, we should bear in mind much more information sources than it is stipulated by MRI for infectious agents which cause FBTIs. Usual information sources include monitoring programs, epidemiological analyses of outbreaks and sporadic cases caused by resistant microbes, clinical examinations and reports on incidence of foodborne infections, results produced by antimicrobial therapy and a correlation between resistance and frequency and severity of related diseases. But apart from that, we should take into consideration national or regional recommendations on FBTIs treatment, enhanced data on microbial properties (pathogenicity, virulence, survivability and growth in food products and the environment, resistance to selection and gene element transfer (in vitro, in vivo)) and resistance determinants (mechanisms, localization, cross resistance to other antimicrobials transmission between microbes and spread in the environment). It is important to have an insight into relations between resistance, virulence, and adaptability; to understand AMU pharmacokinetics and pharmacodynamics when such medications are used to treat humans and animals; to examine correlations between antimicrobial use and resistance of flora in animals and agricultural plants. It is also necessary to analyze data on food products bearing in mind their influence on risk management (how they are treated and processed prior to consumption, pH, A_w etc.), to describe factors and risks influencing how safe a given food product is on its way to ultimate consumers (primary production → processing → storage → processing → distribution → consumption)[10] [17].

Assessment of risks caused by foodborne resistance, just as in case with MRA, involves hazard identification, exposure estimation, hazard characteristics, and risk characteristics. But given all specificity of the issue, each stage unavoidably involves epidemiological monitoring which is not a traditional component in MRA[10]. This monitoring conducted at each stage in assessment allows spotting out a correlation with consumption of food which is not simply contaminated with pathogens or antibiotic residues but with consumption of food which contains such a harmful factor as

[10] MR 2.1.10.0067-12. Otsenka riska zdorov'yu naseleniya pri vozdeistvii faktorov mikrobnoi prirody, soderzhashchikhsya v pishchevykh produktakh. Metodicheskie osnovy, printsipy i kriterii otsenki: metodicheskie rekomendatsii [MR 2.1.10.0067-12. Assessment of health risks caused by exposure to microbial factors in food products. Methodical grounds, assessment principles and criteria: methodical guidelines]. Moscow, The Federal Center for Hygiene and Epidemiology of Rospotrebnadzor, 2012, 44 p. (in Russian).

antimicrobial resistance. Among other things, such assessments include additional steps which can't be found within simple MRA:

– hazard identification, apart from describing resistance of microbes and/or determinants in forages, aquaculture, or food matrices, involves examining the same features of sensitive strains belonging to the same or related taxa and/or them having determinants;

– exposure estimation involves calculating frequency and quantity of resistant microbes and/or determinants which result from AMU in all possible ranges, from food-producing animals to agricultural plants (from animal wastes) and in finished food products ready to be consumed after processing. And when resistance determinants are target hazards, including those in commensal bacteria, then it is advisable to consider rates of their transmission to human pathogens and symbionts which become resistant. Synthesis of data on frequency and quantities of target agents in food taking into account all factors which can influence these indicators and knowledge about structure of consumption determine exposure to AMRM, AMRD or AMU for a person, a group, or population as a whole.

– hazard characteristics involve estimating contagion probability, a number of disease cases and other outcomes as a response to exposure; the stage also involves identifying additional health outcomes (more frequent and severe pathologies, their longer duration, frequency of infections in blood flow, admissions to hospitals and mortality, failed treatments) caused by antimicrobial resistance. Similar to the 1st stage in MRA, reactions by sensitive microorganisms are also estimated;

– risk characteristics combines all conclusions made at the previous stages; it can be given using such indicators as an individual risk of a disease due to resistance in food, population health risk (risk for specific subgroups), risk caused by a single meal or annual consumption, or as calculated damage due to diseases. Validity of the ultimate estimation depends on changeability, uncertainty and assumptions accepted during MRA.

Ultimate assessment results are taken into account in giving grounds for systemic measures aimed at preventing diseases among population, implementing new technologies in agriculture, and making choices on new prospective research directions in science.

Another specific feature is the necessity to permanently reevaluate risks due to frequent changes in AMU range applied in agriculture or to new detected mechanisms of resistance[10].

Development of the risk-based approach within an integrated system for monitoring and surveillance. Although we are provided with the legitimate risk analysis methodology described in CAC/GL 77-2011, there still haven't been any etalon risk assessments performed either at national or global levels. Ideally, integrated systems for monitoring and surveillance which are outlined in the WHO-AGISAR guidelines should be developed taking into consideration all possible health risks related to foodborne antimicrobial resistance. Among other things, they should provide a solid basis for assessing population exposure to resistant microbes and/or determinants [5]. But such knowledge has turned out to be almost unavailable in most countries. This is primarily due to a very vague idea about scales in which preparations are used in agriculture and we should remember that scopes of occurring antimicrobial resistance depend on them. Another reason is that resistance profiles in people vary greatly depending on selected microorganisms and geographical regions [15]. This is confirmed by the fact that the overall global market of goods for animal health is estimated to be equal to 22 billion USD (in 2011) but only 22 % of all UN member countries have a full-fledged and operational system for collecting data on use of antimicrobials in animal farming. At present there is no any common database with data on global use of antimicrobials in farm animals [15].

To solve the aforementioned issues, experts have proposed draft Guidelines on Integral Monitoring and Surveillance (GLIS) of Foodborne Antimicrobial Resistance. The document conforms to the concept stated by the WHO-AGISAR but also envisages step-by-step implementation taking into account priorities, infrastructure, capabilities and resources in different countries [19]. The draft describes a procedure for coordinated systemic data collection and

sampling at all stages in food chains, their testing to determine AMRM, AMRD or AMU in them using harmonized methods for sampling, investigation, and reporting as well as complex analysis of relevant epidemiological data on humans, animals, food products, agricultural plants, and environments at food production.

All this indicates that GLIS data on AMRM, AMRD and AMU in food chains, including their transmission during food processing and spread in the environment, are not only useful for solving issues related to food safety but also provide important information for risk assessment and making decisions on managing risks caused by antimicrobial resistance for humans, animals, and plants. That is, these data are an integral, well-organized, and well-structured part of theoretical and practical risk assessment and a very important stage in risk analysis.

In this context a major issue in any country, Russia included, is how to provide proper management and coordination within GLIS systems and to support its legitimacy with political decisions made by the highest executive authorities and with a relevant legal and regulatory base. The Action plan on implementation of the Strategy for preventing spread of antimicrobial resistance in the Russian Federation for the period up to 2030[3] stipulated the responsibility borne by the RF Public Healthcare Ministry, Rospotrebnadzor, and other concerned federal executive authorities for developing relevant departmental documents in 2020[3]. These documents should cover such issues as organizing and conducting monitoring over antibiotic residues in food raw materials and food products and over antimicrobial resistance in bacteria isolated from animals, food raw materials and food products. Another important issue was to create and develop a common (interdepartmental) database on prevalence of antimicrobial resistance and to include this database into a state information system for providing chemical and biological safety which is being created at the moment. However, it is rather complicated to achieve relevant coordination in the process since public healthcare organizations and concerned federal executive authorities still participate in it independently from each other. It is also difficult to coordinate implementation of separate systems for monitoring over antimicrobials turnover (monitoring over turnover of preparations used in medicine and monitoring conducted by the federal state information system in veterinary medicine). Both points require certain adjustment and well-grounded initiatives, especially with respect to assigning a relevant authority responsible for their implementation.

But still, in 2018 monitoring over antibiotic residues in food raw materials and food products and antimicrobial resistance in food isolates was introduced within the aforementioned international project by Rospotrebnadzor and FAO[2]. This monitoring is well in line with all the concepts outlined in the new Guidelines. Full-fledged GLIS can be implemented on its basis; to do that, it is necessary to introduce the same monitoring process in other spheres in food chains including veterinary medicine, environments at production facilities, and consumers' health. The process will require certain adjustments made in the regulatory and legal documents.

Aspects of the risk-based approach in selecting GLIS directions and objects. This new progressive approach should be implemented as a risk-based one at each stage in conformity with CAC/RCP 61-2005 [16] and MR 2.1.10.0067-12[10] and take into account all available knowledge on risks related to food-borne resistance and accumulated international experience. It is also important to provide data compatibility at the global level.

At initial stage in monitoring a correct choice should be made on GLIS objects (AMRM, AMRD and AMU to which resistance in expressed in food chains). To do that, it is vital to analyze relevant legitimate data on types and quantities of antimicrobials sold in a country to be used in non-medical purposes and their shares used in agriculture as well as their significance for public healthcare.

In the RF the issue is hardly transparent at the moment although at least two State Strategies stipulate certain plans on how to track antimicrobials used in food production. One of them is the aforementioned federal state information system in veterinary medicine; another is the unified information system for food products tracking which is mentioned in the

Strategy for improving food quality in the RF for the period up to 2030[11]. This will make sources of imported foods more transparent and provide availability of knowledge on antibiotics used to produce them. But the system hasn't been fully developed and implemented yet.

It is also hardly reasonable to rely on a list of standardized antibiotics in food. In the RF they are controlled according to the principles of mandatory priority and voluntary application. It means that mandatory inspections are to be performed regarding residues of antibiotics which are widely used in animal farming (predominantly 1st–2nd generation preparations); other antibiotics are to be inspected only in case there is an application from a food manufacturer[12]. It is impossible to make any correct estimations of the whole range of preparations used in the country since the application procedure lacks credibility and integrity. Therefore, monitoring over AMU can't be equated with a system for goods conformity assessment. To sum up, we can state that it is advisable to use data from the register of veterinary preparations, results produced by veterinary and sanitary inspections which clarify their residues in food raw materials, monitoring results in other countries and scientific publications, especially those focusing on screening of raw materials using multi-residue detection and heat map creation[10] [17].

Medical significance of antimicrobials is an unconditional criterion which should be used when GLIS objects are selected[3] [20]. The Table provides data taken from the WHO list of critically important antimicrobials which are used in medicine, the 6th revision accomplished in 2018.

All antimicrobials in the List are divided into 3 groups according to their significance: critically important, highly important and important. Many of them or their analogues are used in food-producing animals. This leads to selection and spreading resistance to these antimicrobials in animal bacteria, induction of cross and co-resistance which are then transmitted to people with food[3] [11]. This undermines effective antimicrobial use in medicine which is especially dangerous in case of critically important preparations since they are the only available therapy or highly important drugs which are included into treatment standards for treating zoonoses and suppurative infections in people who are able to induce resistance to their agents in non-clinical conditions thus making these drugs completely non-productive and useless.

To reduce health risks caused by use of critically important and highly important antimicrobials in agriculture, the WHO developed recommendations on optimization and best available practices of using them in food-producing animals. These recommendations are based on evidence statistics and are included into the WHO Guidelines [2]. It is recommended to impose complete limitations on use of medically important antimicrobials in food-producing animals:

– all categories, not to be used to stimulate growth and prevent infections which are not diagnosed clinically;

– critically important, not to be used to control clinically diagnosed infections;

– critically important classified as top priority, not to be used to treat clinically diagnosed infections.

Accordingly, for example if chicken meat turns out to contain residues of fluoroquinolones or *E. coli* which are phenotypically resistant to them or DNA-gyrase genes which code resistance to these medications, it means that producers failed to adhere to recommendations on use of quinolones

[11] Strategiya povysheniya kachestva pishchevoi produktsii v Rossiiskoi Federatsii do 2030 g.: utv. rasporyazheniem Pravitel'stva RF ot 29.06.2016 № 1364-r [The Strategy for improving food quality in the Russian Federation for the period up to 2030: approved by the RF Government Order on June 29, 2016 No. 1364-p]. *KODEKS*. Available at: https://docs.cntd.ru/document/420363999?marker=6540IN (December 01, 2021) (in Russian).

[12] Edinye sanitarno-epidemiologicheskie i gigienicheskie trebovaniya k tovaram, podlezhashchim sanitarno-epidemiologicheskomu nadzoru (kontrolyu): utv. resheniem Komissii Tamozhennogo soyuza ot 28.05.2010 № 299 (v red. ot 08.12.2020) [The unified sanitary-epidemiological and hygienic requirements to goods which are subject to sanitary-epidemiological surveillance (control): approved by the Decision of the Customs Union Commission on May 28, 2010 No. 299 (last edited on December 8, 2020)]. *Rospotrebnadzor*. Available at: https://www.rospotrebnadzor.ru/deyatelnost/tsouz/doc/?ELEMENT_ID=922 (November 29, 2021) (in Russian).

Table

WHO list of Critically Important Antimicrobials for Human Medicine [20]

Medically Important Antimicrobials		Antimicrobial class	Criterion / Prioritization factor (Yes = ●)					
		CRITICALLY IMPORTANT ANTIMICROBIALS	**C1**	**C2**	**P1**	**P2**	**P3**	
	Critically important	***Highest priority***						**C1 – Criterion 1.** The antimicrobial class **is the sole, or one of limited available therapies**, to treat serious bacterial infections in people. **C2 – Criterion 2.** The antimicrobial class is used to treat infections in people caused by either: (1) bacteria that **may be transmitted to humans from nonhuman sources**, or (2) bacteria that may **acquire resistance genes from nonhuman sources.** **P1 – Prioritization factor 1.** Large number of people in the community or in certain high risk populations (e.g. patients with serious infections in health care settings), who are affected by diseases for which **there are very limited antimicrobial choices.** **P2 – Prioritization factor *2*. High frequency of use of the antimicrobial class for any indication in human medicine** or in certain high-risk groups (e.g. patients with serious infections in health care settings), since their use may favor selection of resistance. **P3 – Prioritization factor 3**. The antimicrobial class is used to treat infections in people for which there is already **extensive evidence of transmission of resistant bacteria** (e.g. nontyphoidal *Salmonella spp.* and *Campylobacter spp.*) or resistance genes (high for *E. coli* and *Enterococcus spp.*) **from non-human sources.**
		Cephalosporins (3rd, 4th and 5th generation)	●	●	●	●	●	
		Glycopeptides	●	●	●	●	●	
		Macrolides and ketolides	●	●	●	●	●	
		Polymyxins	●	●	●	●	●	
		Quinolones	●	●	●	●	●	
		High priority						
		Aminoglycosides	●	●		●	●	
		Ansamycins	●	●	●	●		
		Carbapenems and other penems	●	●	●	●		
		Glycylcyclines	●	●	●			
		Lipopeptides	●	●	●			
		Monobactams	●	●	●			
		Oxazolidinones	●	●	●			
		Penicillins (antipseudomonal)	●	●		●		
		Penicillins (aminopenicillins)	●	●		●	●	
		Penicillins (aminopenicillins with ß-lactamase inhibitors)	●	●		●	●	
		Phosphonic acid derivatives	●	●	●	●		
		Drugs used solely to treat tuberculosis / mycobacterial diseases	●	●	●	●		
	Highly important	**HIGHLY IMPORTANT ANTIMICROBIALS**	**C1**	**C2**	**P1**	**P2**	**P3**	
		Amphenicols		●	NA			
		Cephalosporins (1st and 2nd generation) and cephamycins		●				
		Lincosamides		●				
		Penicillins (amidinopenicillins)		●				
		Penicillins (anti-staphylococcal)		●				
		Penicillins (narrow spectrum)		●				
		Pseudomonic acids		●				
		Riminofenazines	●					
		Steroid antibacterials		●				
		Streptogramins		●				
		Sulfonamides, dihydrofolate reductase inhibitors and combinations		●				
		Sulfones	●					
		Tetracyclines	●					
	Important	**IMPORTANT ANTIMICROBIALS**	**C1**	**C2**	**P1**	**P2**	**P3**	
		Aminocyclitols			NA			
		Cyclic polypeptides						
		Nitrofuran derivatives						
		Nitroimidazoles						
		Pleuromutilins						

in agriculture thus creating an elevated risk of resistance to them in clinical settings. Therefore, recommendations outlined in these Guidelines should be treated as priority ones in examining all monitoring objects with the focus on products-carriers which are manufactured at relevant stages in food chains (when kettle and poultry are grown for meat, or milk is produced by cows which were treated with antimicrobials etc.).

When assessing risks within monitoring over foodborne antimicrobial resistance, it is also important to determine certain stages in food chains where its transmitters (ARMM, ARMD, or AMU) can occur, spread or be inhibited. The issue is being discussed due to many practical experts trying to confine monitoring solely to food raw materials thus avoiding methodological problems arising when processed foods are controlled including those with mixed compositions even if there are clear recommendations on the necessity to examine them [17].

But international experience shows that control over raw materials allows assessing food contamination with AMRM, AMRD and AMU and managing these risks only when it concerns agricultural producers. It doesn't prevent negative effects produced by these factors during food processing, storage, transportations, sales, imports included, and consumption [21]. Besides, certain technologies applied to process food raw materials (drying, jerking, thickening, or condensation) support AMU residue concentration and do not destroy AMRD. In particular, we were able to detect coliform bacteria resistant to four and eight antimicrobials simultaneously exactly in products ready for consumption (curds and pickle cheese) [9, 10]. Therefore, we can conclude that monitoring over such markers of foodborne antimicrobial resistance as AMRM, AMRD and AMU should cover all food chains up to actual consumption.

Conclusion. Implementation and further development of a system for integrated monitoring and surveillance will result in wider use of their results in assessing actual consumer exposure to such harmful factors as resistant microorganisms and genes, antibiotic residues and risks related to food products being contaminated with them. This can be especially useful for examining antimicrobial resistance, new impacts on food chains, changes in patterns of antibiotic residues in humans and animals, and new testing methodologies.

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References

1. WHO estimates of the global burden of foodborne diseases: foodborne disease burden epidemiology reference group 2007–2015. *WHO*, 2015, 265 p. Available at: https://apps.who.int/iris/bitstream/handle/10665/199350/9789241565165_eng.pdf (29.11.2021).

2. WHO guidelines on use of medically important antimicrobials in food-producing animals. Geneva, WHO, 2017, 68 p.

3. The FAO action plan on antimicrobial resistance 2016–2020. Rome, FAO, 2016, 17 p. Available at: https://www.fao.org/3/i5996e/i5996e.pdf (29.11.2021).

4. CX/MRL 2-2018. Maximum residue limits (MRLs) and risk management recommendations (RMRs) for residues of veterinary drugs in foods. *Codex Alimentarius. FAO/WHO*. Available at: https://www.fao.org/fao-who-codexalimentarius/sh-proxy/es/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCXM%2B2%252FMRL2e.pdf (27.11.2021).

5. Irwin R. WHO Guidance on Integrated Surveillance of Antimicrobial Resistance (WHO AGISAR). *WHO Department of Food Safety and Zoonoses*, 2016, 23 p. Available at: http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-804-05%252FSIDE%20EVENTS%252FCurrent_guidance_on_Integrated_Surveillance.pdf (29.11.2021).

6. Andremont A., Fleck F. What to do about resistant bacteria in the food-chain. *Bull. World Health Organ.*, 2015, vol. 93, no. 4, pp. 217–218. DOI: 10.2471/BLT.15.030415

7. Edelstein M.V., Skleenova E.Yu., Shevchenko O.V., Tapalskiy D.V., Azyzov I.S., D'souza J.W., Timokhova A.V., Sukhorukova M.V. [et al.]. Prevalence and molecular epidemiology of gram-negative

bacteria producing metallo-β-lactamases (MBLs) in Russia, Belarus and Kazakhstan. *Klinicheskaya mikrobiologiya i antimikrobnaya khimioterapiya*, 2012, vol. 14, no. 2, pp. 132–152 (in Russian).

8. Chebotar I.V. O deyatel'nosti Referens-tsentra Rospotrebnadzora po monitoringu ostatochnogo kolichestva antibiotikov v prodovol'stvennom syr'e i pishchevykh produktakh i antibiotikorezistentnosti bakterii [On the activities of the Reference Center of Rospotrebnadzor regarding monitoring over the residual amount of antibiotics in food raw materials and food products and antibiotic resistance of bacteria]. *Federal Service for Surveillance over Consumer Rights Protection and Human Well-being Central Research Institute of Epidemiology*, 2019. Available at: https://snipchi.ru/updoc/2019/Prezent/%D0%A7%D0%B5%D0%B1%D0%BE%D1%82%D0%B0%D1%80%D1%8C%20%D0%98%D0%92.pdf (29.11.2021) (in Russian).

9. Korotkevich Yu.V. Antibiotic resistance analysis of Enterococcus spp. and Enterobacteriaceae spp. isolated from food. *Voprosy pitaniya*, 2016, vol. 85, no. 2, pp. 5–13 (in Russian).

10. Stankevich A.A., Netyaga I.M., Bykova I.B., Efimochkina N.R. Frequency detection and antibiotic resistance of bacteria of the genus Klebsiella – contaminants of foodstuffs. *Trudy Vserossiiskogo NII eksperimental'noi veterinarii im. Ya.R. Kovalenko*, 2018, vol. 80, no. 2, pp. 347–350 (in Russian).

11. Sheveleva S.A. Antimicrobial-resistant microorganisms in food as a hygienic problem. *Gigiena i sanitariya*, 2018, vol. 97, no. 4, pp. 342–354. DOI: 10.18821/0016-9900-2018-97-4-342-354 (in Russian).

12. Karp B.E., Tate H., Plumblee J.R., Dessai U., Whichard J.M., Thacker E.L., Hale K.R., Wilson W. [et al.]. National antimicrobial resistance monitoring system: two decades of advancing public health through integrated surveillance of antimicrobial resistance. *Foodborne Pathog. Dis.*, 2017, vol. 14, no. 10, pp. 545–557. DOI: 10.1089/fpd.2017.2283

13. European Food Safety Authority, European Centre for Disease Prevention and Control. The European Union Summary Report on Antimicrobial Resistance in zoonotic and indicator bacteria from humans, animals and food in 2017/2018. *EFSA Journal*, 2020, vol. 18, no. 3, pp. e06007. DOI: 10.2903/j.efsa.2020.6007

14. Follow-up to the political declaration of the high-level meeting of the General Assembly on antimicrobial resistance: Report of the Secretary-General. *United Nations General Assembly*, 2019, 25 p. Available at: https://undocs.org/pdf?symbol=en/A/73/869 (28.11.2021).

15. Antimicrobial resistance. *Codex Alimentarius*, *FAO/WHO*. Available at: http://www.fao.org/fao-who-codexalimentarius/themes/antimicrobial-resistance (29.11.2021).

16. CAC/RCP 61-2005. Code of practice to minimize and contain antimicrobial resistance. *Codex Alimentarius*, 15 p. Available at: http://www.fsc.go.jp/senmon/sonota/amr_wg/amr_kanren.data/CXP_061e.pdf (29.11.2021).

17. CAC/GL 77-2011. Guidelines for risk analysis of foodborne antimicrobial resistance. *FAO/WHO*. Available at: http://www.fao.org/3/i4296t/i4296t.pdf (30.11.2021).

18. CAC/GL 30-1999. Principles and guidelines for the conduct of microbiological risk assessment (Adopted 1999. Amendments 2012, 2014). *Codex Alimentarius*, *FAO/WHO*. Available at: http://www.fao.org/input/download/standards/357/CXG_030e_2014.pdf (01.12.2021).

19. Ad Hoc Intergovernmental Task Force on Antimicrobial Resistance (TFAMR): U.S. Delegate's Report, 7th Session of the Codex Alimentarius. *USDA*. Pyeongchang, Republic of Korea, December 9–13, 2019, 8 p. Available at: https://www.usda.gov/sites/default/files/documents/tfamr-delegate-report.pdf (27.11.2021).

20. WHO list of Critically Important Antimicrobials for Human Medicine. WHO, 2019. Available at: https://apps.who.int/iris/bitstream/handle/10665/325036/WHO-NMH-FOS-FZD-19.1-eng.pdf?ua=1 (29.11.2021).

21. CAC/GL 71-2009. Guidelines for the design and implementation of national regulatory food safety assurance programme associated with the use of veterinary drugs in food producing animals. *FAO/WHO Joint Publications*. Available at: https://www-pub.iaea.org/iaeameetings/cn222pn/SatelliteEvent/12Montes.pdf (30.11.2021).

Sheveleva S.A., Smotrina Yu.V., Bykova I.B. Contemporary aspects in control over resistant to antibiotics microbial contaminants of food, taking into account peculiarities of related health risk assessment. Part 1. Health Risk Analysis, 2022, no. 1, pp. 58–71. DOI: 10.21668/health.risk/2022.1.06.eng

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Scientific review

HOW TO MINIMIZE INFECTIOUS HEALTH RISKS FOR ELDERLY PEOPLE (BASED ON FOCUS GROUP DATA)

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This literature review focuses on practices aimed at mitigating infectious health risks for elderly people in acute care inpatient hospitals with multiple specializations. We revealed a necessity to create medical information centers; common reference centers for PCR diagnostics, sequencing, plasmid analysis, and MULDI-TOF; as well as to provide support and further development of bacteriological and hygienic service in medical and preventive organizations. Our review also dwells on theoretical solutions to issues related to minimizing infection risks in nursing homes and prospective approaches to providing infectious safety at home. A focus group was organized on May 20, 2021 at the E.A. Wagner's Perm State Medical University of the RF Public Healthcare Ministry with its aim being to implement theoretical approaches into practices of minimizing infectious health risks for elderly people in Perm region within the "aging in place" paradigm. The sociological explication made it possible to fix the regional agenda on minimizing infectious heath risks for elderly people as per three basic directions: by improving living conditions, by improving care provided for elderly people at home, and by making elderly people's lives more active as a way to support their immunity.

All the discussion participants unanimously agreed both on assigning the primary role to the strengthened immunity as a way to minimize infectious health risks and on obvious absence of any drugs which would be able to resolve the issue. Experts believe adherence to conventional recommendations on how to improve elderly people's immunity to be fundamental for infection risk mitigation. We should remember that some elderly people live in improper housing which should be renovated and adapted to basic needs of an elderly person. It is also important to develop the city environment taking into account elderly people's habits and needs (they should be provided with a special place in the yard where they can communicate with each other, play board games or do physical exercises). Financial support should be given to "Inpatient hospital at home" program and to developing tools used to promptly minimize infection risks, for example, telemedicine which allows detecting certain alerting symptoms typical for communicable diseases (fever, complaining about cough and running nose, pains in the lumbar spine, decreased diuresis etc.)

Key words: *sociology of medicine, infection risks, infectious safety, stereotypes of medical care, elderly patients, transmission routes of hospital acquired infections, vaccination, immunity.*

Today there are hardly any doubts that issues related to viral and bacterial infections are top priority since their prevalence is growing persistently every year. Elderly people are a specific population group exposed to high risks of infections. A combination of an infection and an old age is unfavorable for health and has some peculiarities.

Firstly, infections tend to have atypical clinical course in elderly people, that is, they are often afebrile and their symptoms are vague due to concomitant diseases; as a result infections are diagnosed too late and are not treated properly. As a rule, infections in elderly people are concomitant diseases, not primary ones. But if they are not treated, they can become a major health issue and even result in a patient's death.

Secondly, elderly people are a population group who has higher risks of developing sepsis. According to some research data, lethality of bacteremia amounts to 49 % among elderly people during the following 3 years after diagnosis [1, 2]. Sepsis also has some remote ef-

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fects including metastatic infection foci (recurrent sepsis), people becoming carriers of highly pathogenic strains and fungal invasion agents, and antibiotic-associated diarrhea. Bacteremia in clinical case history has its negative influence on life quality and cognitive functions in future. Experts generalized data on 637,867 elderly patients (older than 65 years) focusing on their functional and cognitive abilities after sepsis over the following 3 years. As a result, it was established that 476,311 people had functional disorders and 106,311 people had cognitive ones [3].

Thirdly, comorbidity in elderly patients creates favorable conditions for infectious processes developing more actively. Mild or even asymptomatic infections in an elderly person can cause severe complications: pneumococcal infection can develop together with viral pneumonia and cause otitis, meningitis and sepsis as well [4]. It was established that bacterial intestinal infections, salmonellosis and shigellosis had certain clinical peculiarities in patients who were older than 60 years and their clinical course was usually more severe in such patients than in those aged 20–40 years [5].

Fourthly, infection health risks grow considerably during the present COVID-19 pandemic since the disease is the direct cause of mortality among elderly people. According to data provided by the WHO, a half of lethal outcomes due to COVID-19 in Europe were registered in nursing homes [6]. 89 % of deaths due to COVID-19 in Great Britain occurred among people who were older than 65 years [7]. Outbreaks of the new coronavirus infection were analyzed in 4 nursing homes in Great Britain with their total number of inhabitants being 394 people. The analysis revealed that 26 % of elderly people in these nursing homes died during the first 2 months since an outbreak started [8]. However, according to the US CDC, in December 2021 the total vaccination among people older than 65 years reduced risks of hospitalization by 17 times in the country and vaccination with an additional dose or a buster reduced these risks by 50 times against non-vaccinated people [9].

Fifthly, the immunity, in particular, T-cells activity, becomes weaker with age. Such changes mean that as people get older their bodies gradually lose the ability to react to new infections and vaccines. This phenomenon is known as the immune system aging [10].

In our research, we didn't consider a risk as something resulting from threats which occur due to a direct presence of a person in a certain group. Instead, we examined it as a certain contact with a danger, as a combination of factors which increase or reduce this danger. "That is, risk prevention involves not observing one particular person but rather probable occurrence of diseases, anomalies and deviant behavior in order to minimize them and, conversely, to maximize healthy behavior prevalence" [11]. In other words, you are in a risk zone not due to being who you are but due to doing what you do and certain practices you adhere to can even be lethal. Let us note that the pandemic development directly depends on people's behavior.

The issue of minimizing infection health risks for elderly people has been studied by expert society with its major focus being on examining causes and clinical course of healthcare-associated infections (HAIs). The issue is closely related to different levels of medical aid provided for elderly patients (polyclinic, diagnostic center or in-patient hospital), hygiene, dynamics of infection processes influenced by a number of elderly patients, etc.

Medical aid provision for elderly patients at different levels is regulated by international[1], federal[2] and regional legal

[1] Rhodes A., Evans L.E., Alhazzani W., Levy M.M., Antonelli M., Ferrer R., Kumar A., Sevransky J.E. [et al.]. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Critical Care Medicine*, 2017, vol. 45, no. 3, pp. 486–552. DOI: 10.1097/CCM.0000000000002255

[2] Ob utverzhdenii Poryadka okazaniya meditsinskoi pomoshchi po profilyu «geriatriya»: prikaz Ministerstva zdravookhraneniya RF ot 29.01.2016 № 38n [On Approval of the procedure for medical aid provision as per "geriatrics" profile: the Order by the RF Healthcare Ministry issued on January 29, 2016 No. 38n (last amended on February 21, 2020)]. *KODEKS: the electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/420339190 (August 18, 2021) (in Russian).

acts[3]. Though we can admit that these documented recommendations are effective, we still can't fail to notice that it is rather difficult to implement them in reality since differential diagnostics of sepsis with systemic diseases of the connective tissue, infectious pathology (meningococcal infection, hemorrhagic fever with renal syndrome, and tuberculosis), leucosis, and oncologic diseases is rather complicated. Minimization of infection risks for elderly people involves accepting the fact that such strains exist practically in every in-patient hospital.

An optimal solution to the HAIs-related issues would be to implement express-diagnostics of highly pathogenic strains (MALDI–TOF mass spectrometry, PCR-analysis, sequencing, plasmid analysis) on the basis of common reference centers or to develop bacteriological services in medical and prevention organizations.

Some authors believe failure to put a correct diagnosis to be the major cause for severe clinical course of infections in elderly people. For example, according to Big and others [12] patients older than 80 years who had bacteremia caused by *St. Aureus* didn't have echocardiography in 45 % cases. Failure to prescribe echocardiography to elderly patients results in a failure to diagnose "Infectious endocarditis" and rational antibiotic treatment is not provided for them in due time [13, 14].

High-tech medical treatment procedures improve health and make life expectancy longer; they also facilitate surgeries on elderly patients which were previously considered impossible. However, certain involutive and pathological processes in elderly people's bodies can aggravate a post-surgery period and create health problems during it. A growing range of facultative normal flora in all locuses is among such potentially hazardous aspects [15]. The situation is further aggravated by lower production of local (lysozyme, complement) and acquired (secretory immunoglobulins A) immunity factors together with antibacterial treatments a patient has been prescribed to have during the whole lifespan. There is a growing risk that a body would be colonized by poly-resistant microflora with elevated pathogenic potential. Susceptibility of elderly people's bodies to such flora is only growing in clinical settings (directly depending on a period of time spent in a hospital), especially in a post-surgery period [16]. It was proved that septic shock was much more likely to develop in elderly patients and acute kidney failure developed two times more frequently in them than in middle-aged people [17]. According to some research works, infections are suspected in 51 % of patients in intensive care units [18]. Inflammatory processes become more severe with age, they occur more frequently and last longer thus inducing specific changes in the body which suppress immune reactions and create favorable conditions for developing inflammations and lesions in the lungs. Therefore, it is completely reasonable to try and minimize a period of hospitalization for elderly patients since this helps mitigate infection risks considerably.

The most acute issue in elimination of hospital-acquired infections is active use of catheters. Use of a urine catheter to treat patients with neurological or cognitive disorders results in 3–7 % higher risks of developing infections in the urinary system. In case of pyelonephritis risks related to bacteremia become even higher. Vascular catheters cause bacteremia in 1–10 % cases. "Long-term usage of a catheter results in a higher risk of developing catheter-associated urinary tract infections (CAUTI)." [19].

In our opinion, when we discuss alternative approaches to using catheters bearing in mind infection risk minimization [20–22], we

[3] Ob organizatsii meditsinskoi evakuatsii bol'nykh i postradavshikh v Permskom gorodskom okruge (s izmeneniyami na 30.06.2021): Prikaz Ministerstva zdravookhraneniya Permskogo kraya ot 14.09.2018 № SED-34-01-06-786 [On organizing medical evacuation of diseased and injured in Perm city (last amended on June 30, 2021): the Order by the Healthcare Ministry of Perm region issued on September 14, 2018 No. SED-34-01-06-786]. *KODEKS: the electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/550193670/titles/1A9QHU6 (August 18, 2021) (in Russian).

should focus from the very beginning on a differential approach to two different groups of patients: those who require hourly diuresis control and those who don't need it so critically. This approach allows avoiding excessive, too long and groundless use of catheters. Undoubtedly, any catheter should be replaced immediately in case its integrity or working capacity is lost. However, the basic challenge which should be overcome here is violated septic and antiseptic rules when medical workers don't want to work in sterile gloves or use non-sterile glycerin, etc. Systemic review of reasons for weak control over infections in nursing homes also revealed that personnel were rather incompetent with respect to providing infection safety and necessity to eliminate infections [23].

An idea to support basic treatment procedures provided for elderly people with some hygienic ones has been accepted as a very effective way to minimize infection risks. These hygienic procedures include oral cavity, skin, body, and feet hygiene [24]. Immune functions performed by skin deteriorate in elderly people and this is accompanied with greater frequency of bacterial (streptococcal and staphylococcal cellulite) and fungal (most frequently candidosis) infections and also makes a contribution to more frequent cases of malignant neoplasms of skin [25, 26].

Proper oral cavity hygiene is an integral part of fighting against infections. Dentists discuss how to minimize infection health risks within a new discipline which is called gerontostomatology [27]. Oral cavity hygiene is included into national healthcare programs in most countries since prevalence of dental problems among elderly people varies from 42 % in low income countries to 29 % in high income ones [28]. Major oral health issues, such as dry mouth or caries, are caused by weaker salivation [29]. Acinar tissue atrophies with age, proliferation of duct elements occurs and there are some degenerative changes in major and small salivary glands. Accordingly, salivation reduces gradually and the process can be influenced by frequent use of multiple medications. There are some ways recommended to prevent and treat dry mouth in older age. They include installing air humidifiers which regulate air humidity automatically; having drinking water available all the time; avoiding spicy, salty or too sweet food, carbonated drinks and coffee; drinking herbal teas or drinks made of cranberries, sea-buckthorn berries, or cowberries. It is also effective to use chewing gums and lollypops with xylite and prebiotics. Training sessions on proper oral cavity hygiene provided for patients in inpatient hospitals are aimed at teaching them how to properly clean the teeth and tongue, removable and non-removable dental prostheses and how to choose personal hygiene means correctly.

When discussing where elderly people live, we should pay attention to the fact established by international social studies performed in many countries, Russia included. The fact is that only 5 % of respondents would like to live in alternative housing such as nursing homes, various specialized boarding houses, or other social housing instead of their own home [30].

The national guide on infection control contains comprehensive recommendations on how to minimize infection risks in nursing homes for elderly people [31]. Long-term staying in nursing homes is considered a factor that can cause contamination with resistant agents. According to these recommendations, patients carrying some strains should be placed in such ways so that cross contamination would be prevented. However, elderly patients carry pathogenic and opportunistic bacteria and fungi so frequently that any attempts to place them in accordance with carrying this or that microorganism are hardly effective. Any placement can't prevent contacts and interactions between different cohorts of patients. Therefore it is more important to create barriers "inside" elderly patients, that is, maintain their immunity rather than to try and create protection "around" them.

Obviously, elderly people spend most their time at home. In 2021 the RF Government announced that a new expert long-term system of permanent care would be developed

in the country and would have permanent funding sources. The accomplished steps include creating roadmaps on implementation of hospital-replacing technologies for elderly people; training nurses or caregivers; in some regions mobile inter-branch teams are created to bring medications or foods to elderly people's homes. In 2007 the WHO issued the report "Cities comfortable for elderly people" where the accent was made on creating an environment which stimulates active aging. There are some research works concentrating on assessing how well a city is adapted to its elderly citizens [32]. A lot of support is given to an idea to develop clubs for elderly people (retired freelancers) where they, on one hand, can develop some new skills, for example, computer ones, or become more physically active, but on the other hand, they can help other people doing what is within their power and getting paid for it. There are works in literature where their authors state that it is advisable to develop city infrastructure for leisure, labor, and social activities of elderly people; it is important to preserve social capital of elderly people (including their neighbors) [33]. Some experts established a correlation between social isolation and poor health [34, 35], examined peculiarities of communicative therapy applied to treat dementia, rules and standards of talking to elderly people [36], and described attitudes towards aging prevention [37]. There are a lot of publications focusing on up-to-date ways to develop medical aid provided for elderly people at home using artificial intellect [38] and peculiarities of immune prevention for them [39, 40].

In theory, all these aforementioned approaches should minimize infection health risks for elderly people at home. The question is how to implement them into everyday routines of elderly people living in Perm region. A tendency to neglect banal solutions makes people's life quality poorer because when we consider obvious and vital things to be simply banal, we exclude basic statements which represent the reality in the best possible way from our social discourse thus allowing ourselves not to think about the essentials (for example, we stop talking to our old relatives, etc.). It is well known that "ignoring banalities comes at the highest price" (I. Kant).

Our research goal was to explicate managerial decisions aimed at minimizing infection risks for elderly people in a given region. Perm region was chosen as a research object. Sociological methods give an opportunity to find an answer to the question what known instruments aren't still used properly to achieve the major target, an increase in life expectancy in the region. These methods also help determine peculiarities of hygienic culture necessary for elderly patients who are involved into an epidemic process in their families. "A sociological approach, rather than a scientific one, is required to analyze all the roles played by all the concerned parties in decision making." [41].

Practical significance. Expert estimates produced by focus groups can be used both in implementation of the Order by the RF Public Healthcare Ministry issued on January 29, 2016 No. 38n "On Approval of the procedure for medical aid provision as per "geriatrics" profile" and the State Programs adopted in Perm region including "Social support for Perm region citizens" and "Qualitative healthcare", the regional project "Development and implementation of the program for systemic support and improving life quality of elderly people (Perm region)".

Research technique. Focus groups as a research technique differ from a formalized expert questioning or depth interviews since they are better focused on key issues. In our research, there were three key issues:

1. How to minimize infection risks for elderly people by improving their living conditions in Perm region;
2. Relevant practices which can be implemented in the region to improve care provided for elderly people at home;
3. How to make elderly people's lives more active as a way to support the immunity.

Our focus group was created as per the following principles: a team should include experts from multiple spheres; experts

should be personally involved into practical activities aimed at providing infection safety for elderly people in the region. Participation in the focus group was voluntary, and experts were representatives of all age groups; the group included scientific experts from higher educational establishments, practical healthcare and business, and from various occupational groups such as administrative staff, doctors with various specialties, postgraduate students, and independent experts (a microbiologist, a philosopher, a businessman, and a volunteer).

The focus group was created as per objective and subjective criteria. The objective approach meant that experts were chosen based on documentary data (higher education, work experience in the sphere relevant to the discussion, an academic degree, title, position, a number of published papers, and participation in international conferences). The subjective approach involved choosing experts bearing in mind their knowledge on details, subtle points and difficulties in providing infection safety for elderly patients.

The ultimate goal was to stimulate the participants in the discussion to share their perception of practical results achieved in mitigating infection risks for elderly people in Perm region. To achieve this, the following focus group was formed in full conformity with the principles which should be followed when an expert pool is created; all the participants fully corresponded to the definition of a "true expert".

1. L.A. – the moderator, a postgraduate student at the Department of Microbiology and Virology, epidemiologist;

2. N.A. – Doctor of Medical Sciences, Professor at the Department for Polyclinic Therapy, the Chief Free-lance Therapist of the Perm Regional Public Healthcare Ministry;

3. Yu.N. – Doctor of Medical Sciences, Professor, Leading researcher at the Central Scientific Research Laboratory of E.A. Wagner's Perm State Medical University, Professor at the Department of Microbiology and Virology;

4. K.S. – The Head of the social service "The Social Welfare Center";

5. A.R. – the medical supervisor at the Perm regional department of the All-Russian Youth Social Organization "Russian Student Groups";

6. T.A.– a dermatovenerologist, Candidate of Medical Sciences;

7. I.A.– Doctor of Philosophy, Professor;

8. A.Yu.– an infectiologist and therapist, Candidate of Medical Sciences;

9. N.E. – a postgraduate student at the Department for Neurology and Medical Genetics, neurologist;

10. A.V. – a postgraduate student at the Department for Anesthesiology, and Critical Care Medicine, anesthesiologist and resuscitator;

11. S.V. – the director of "Liniya ulybki" LLC (a dental clinic).

Results and discussion. The participants in the discussion were guided by the central idea in the European social policy developed in the second half of the 20th century. According to this idea, a possibility to live at one's own home is believed to be the fundamental principle and value for an elderly person [42]. Living at home preserves one's dignity and gives an opportunity to pursue a lifestyle a person is accustomed to. But still, to make aging at home safe for elderly people, it is necessary to implement active social strategies when attention of all the relevant authorities is concentrated on improving care, providing maximum possible comfort for elderly people at their homes, as well as on considering elderly people to be productive participants in social life [43].

New risks occurred during the COVID-19 pandemic with respect to an issue how to organize safe living environment for elderly people. When there are a lot of elderly people at one place, this leads to high lethality due to elevated infection risks. All the discussion participants estimated people's wishes to get old at their homes, in their settlements, "age in place", and to remain at home in case of a disease in order to recover sooner [44] as evidence that elderly people were quite reasonable in this respect.

The discussion on the issue "How to minimize infection risks for elderly people by

improving their living conditions" advanced by searching for up-to-date markers of proper housing. These markers primarily include the access to basic communal services such as safe drinking water, energy to cook food, heating, lighting, safe food storage, waste utilization, and proper sanitary conditions [45]. The discussion participants mentioned a social survey which was performed in spring 2020 among retired people in Russia. According to the results, more than 30 % of retired people who live in private houses don't have permanent access to hot water and warm toilet; 30 % of respondents also complained that they didn't have elevators or comfortable bathrooms and toilets in their houses [30]. The moderator also mentioned another study focusing on sanitary-epidemiological determinants of life expectancy growth in Perm region. These determinants include providing people with qualitative drinking water and raising safety of certain foods (meat, milk, fish, and bread) [46]. A correlation between the aforementioned housing-related and other everyday problems and growing infection risks is obvious for experts. I.A. outlined a promising administrative trend in risk minimization, namely housing renovation provided for elderly people; another suggestion was to supplement widely used subsidies provided to elderly people to help them with payments for communal services with funding provided for repairing living spaces and making them more suitable to satisfy elderly people's needs. This means making doorways wider, removing high thresholds, probable installment of shower cabins in bathrooms, making solariums on balconies, as well as subsidizing elderly people's expenses on transport and communication.

The moderator drew the participants' attention to solitary elderly people and their needs since they don't feel safe and are often afraid of falling or a sudden disease [47]. According to N.E.'s opinion, "Installing an alarm button is the first step in helping a solitary person". N.A. mentioned systems which were aimed at providing a so called "in-patient hospital" at home. They make medicine an integral part of a person's life due to constant monitoring over his or her health, either by constant wearing of artificial intellect devices or by consulting and partnership with medical workers (immunization, therapeutic exercises, detection of untreated diseases, and improved drug therapies). A.Yu. noted that telemedicine devices detect alerting symptoms typical for communicable diseases (fever, saturation, complaints about cough, running nose, pains in the lumbar spine, reduced diuresis etc.) in online mode and give an opportunity to minimize infection risks promptly and effectively.

When discussing the issue "Relevant practices which can be implemented in the region to improve care provided for elderly people at home", the experts mentioned a positive trend related to developing partnership between private and state participants in finding solutions to the problem. The social service supervisor drew the participants' attention to the fact that elderly people could be provided with professional care at home if they applied to the Social Welfare Center; they could hire a nurse at a reasonable price for the service; there was a service of transportation provided for bed-ridden patients, escort for wheelchair-bound people, and consultations on how to care for a bed-ridden patient. "We are also ready to work in close contacts and joint projects with the Pension fund, social security fund, medical organizations, and to participate in medical and social expertise" K.S. concluded.

I.A. believed that effective rehabilitation of elderly people at home after treatment in in-patient hospital was considerably hampered by practices adopted by social services when they solely react to citizens' applications asking for help. A medical organization should be obliged to provide a relevant social service with all the necessary data on a patient who need professional care. In Great Britain, the public healthcare system includes special information centers which are responsible for finding optimal solutions to variable challenges patients have to face. Such information centers would be quite useful for elderly patients since they can answer not only the question "What hurts?" but also

"What to do?" or "Where to get help most effectively?" For example, hardly many people know that the Social Welfare Center provides hygienic services for bed-ridden patients at home: washing in a bath, shaving, nail care, and hairdresser's services. Also very few people know that cognitive disorders require help by relatives and it is recommended to use diapers instead of catheters since it helps minimize infection risks etc.

When discussing peculiarities of immune prevention among elderly people, the participants expressed an opinion that people older than 65 years should be the target audience for vaccination against pneumococcal infection. Patients aged 65–85 years are recommended to get the first vaccination with pneumococcal vaccine 13; then, after a year, pneumococcal vaccine 23. Patients who accidentally got vaccinated with pneumococcal vaccine 23 should get vaccinated with pneumococcal vaccine 13 during the year from the first vaccination, not later. Revaccination with pneumococcal vaccine 23 is recommended every 5 years [48]. The participants discussed two probable attitudes towards estimating remote effects produced by elderly people's vaccination against opportunistic pathogens. A.Yu. thought that vaccination against pneumococcal infection probably resulted in more aggressive microorganisms, such as *St. Aureus*, *Acinetobacter baumani*, *Klebsiella pneuminiae* etc., starting to dominate in the body. Yu.N. stated that "Since it is pneumococcus which is called "elderly people's friend", that is, the direct cause of deaths among them, vaccination with pneumococcal vaccines is the best way to preserve their health".

A.Yu. was still not fully convinced that vaccination of elderly people against influenza is effective. Yu.N. believed that according to the reports on effectiveness of up-to-date subunit and split influenza vaccines they are effective and optimal exactly for elderly people. There was also no unambiguous attitude towards vaccination against Type III herpes virus. Yu.N. believed that this vaccine was primarily aimed at preventing chicken pox in children; moreover, in some countries it is recommended not to use it in old people since there were cases of herpes zoster among people who got immunized with it.

When the discussion moved to the issue how to make elderly people's life more active in order to minimize infection risks, the Moderator shared some results produced by a social survey according to which people didn't trust geroprotectors as an effective way to optimize their immunity [37] and they faced certain problems when trying to stick to "Don't stay at home!" appeal, the effective recommendation on how to support their immunity. We can't fail to notice that yards are now much more suitable for young people and elderly people lost some territories which they once considered theirs. There are no wooden benches in the yards where elderly women can sit and socialize; there are no tables with benches around them where old men used to sit and play dominos, checkers, backgammon and even chess or just socialize; there are no chin-up bars for adults. City development has led to elderly people losing a space which was significant for them and a number of people who spend all their time indoors has grown drastically.

I.A. thought that a massive mass media campaign aimed at promoting use of therapeutic exercises for various age groups and for elderly patients with different pathologies would make elderly people do them more actively; they could also be persuaded to do basic muscle-strengthening exercises to prevent muscle weakness, go dancing or attend choral singing sessions. In this respect, experts remembered Item 9 in the Order by the RF Public healthcare Ministry issued on January 29, 2016 No. 38n where it is stated that "medical aid as per "geriatry" profile is rendered by a geriatrist who should interact with medical workers with non-medical higher education (speech therapists, medical psychologists, and therapeutic training instructors) in order to assess and correct the psychoemotional state of a patient, communicative disorders, limitations on physical activity, any disorders in using one's common and occupational skills". In I.A.'s opinion, today it is necessary to

make young people understand that talking to an elderly person is the most universal and available care he or she can be given. Unfortunately, this banality has lost its meaning as a cultural pattern; therefore, social advertising of home safety for elderly is priceless since "banalities exist simply because they are the truth in the essence" (Margaret Thatcher). This social advertising can cover some topics described on the relevant web-site [49]:

– Don't warn you parents that you're going to visit and come to them suddenly. This will help you to understand how your parents really get on.

– Watch over an elderly person when the weather is too hot or too cold (this creates elevated risks of heat strokes or frostbites).

– Encourage your beloved elders to wear a necklace with an alarm button since this will help them to call for help in case of emergency (for example, if they fall).

– Teach your elders to move slower since there are often no reasons to hurry.

– Recommend your elders to always ask for your help instead of doing all the cleaning or repairing themselves.

All the participants agreed that making elderly people stronger and raising their vital capacity would involve not only doing physical exercises at home, on sport grounds, in parks or sport clubs, participating in volunteering activities, interesting leisure and travelling, but also caring about beauty and strength of one's body. T.A. stated that "Skin elasticity reduces with age due to decreasing volume of liquid in the body, hydrolipid cellular mantle becomes thinner, skins becomes drier and loses one of its basic functions, namely, acting as a barrier preventing adverse exposures. To minimize infection risks, people should adhere to several very simple rules of skin care at an older age: they should not use spirit-containing skin care products as well as means for skin hygiene which contain antibacterial components; they should avoid using stiff loofas when washing and blot the body with a towel, not rub it. The most important thing is to use wetting cosmetics after bathing as well as during a day in case of necessity".

Research works accomplished in many countries indicate that in most cases dental status of elderly people is unsatisfactory. But at the same time, dentists manage to effectively treat pathologies of hard tissues in elderly patients who regularly visit them at least twice a year to get primary and secondary prevention of dental diseases and who are also committed to proper dental care. Inflammatory pathology in periodontium is usually in remission in such patients and oral cavity hygiene is quite satisfactory which has positive effects on their life quality [50]. S.V. stated that poor awareness about adverse effects produced by periodontal pathogens and low incomes of elderly people prevented them from going to a dentist at least every 6 months to have their oral cavity to be cleaned by an expert. And it's a pity since it is well proven that dental tartar and bacterial plaque removal reduces infection risks considerably. We should also note that oral cavity sanitation not only prevents HAIs in elderly patients but also helps prevent caries in their children and grandchildren. A smile showing some teeth missing is ugly and stimulates developing inferiority complex; missing teeth also make people eat only high caloric foods with very small quantities of useful nutrients (vitamins minerals, or dietary fiber) which have been cooked with excessive mechanical and thermal processing. All this combined leads to failures of various systems in the body, including the immune system. A beautiful smile which can be provided by a proper prosthesis technology is a unique way to raise one's spirits and to start eating foods which are useful for immunity (sour cabbage, carrots, nuts, or celery).

I.A. suggested developing a bit paradox recreational concept which once existed but eventually lost its drive. The concept was entitled "Perm is a territory of ravines". The idea is to make elderly people's life more interesting due to organizing safe tobogganing for them in winter, rock climbing or bicycle races in summer, and creating special grounds for walking with dogs. Infection risks for elderly people should be minimized by creating safe routes for health walks, benches where they can meditate etc.

Conclusion. Risk management is improving everyday practices in elderly people's lives at their homes; this improvement should be aimed at strengthening the immunity since it helps minimize health risks caused by infections. Subjects who participate in the process are relevant authorities, medical and social workers and elderly people themselves. The active long life paradigm makes it possible to minimize infection risks as it changes behavioral attitudes adopted by all the concerned parties:

– authorities should be responsible for creating not only a long-term care system but also adequate infrastructure which helps elderly people to realize their human potential in everyday life, communication, labor and leisure thereby supporting their immunity. They should also provide funding for renovating elderly people's homes so that their specific needs are satisfied and create special places in yards where elderly people can spend their time outdoors. Elderly people should be encouraged to render mutual aid to each other but the state should eliminate poverty among them, at least, by providing social benefits to cover expenses on transport and communication. A number of social workers who get paid by the government should also be increased;

– managing health risks for elderly people involves introducing stricter preventive measures with respect to this population group due to active social and medical aid provided at home;

– medical and social workers should return to providing elderly people with care at home or in close proximity to places where they live. This can be done, first of all, be developing "in-patient hospital at home" which makes medicine an integral part of a person's everyday life due to constant health monitoring, either with artificial intellectual devices worn constantly by a person or by consulting and partner relations with medical workers (immunization, therapeutic exercises, detection of diseases which haven't been treated, improved drug therapies). We have already noted that telemedicine devices detect alerting symptoms typical for communicable diseases (fever, saturation, complaints about cough, running nose, pains in the lumbar spine, reduced diuresis etc.) in online mode and give an opportunity to minimize infection risks promptly and effectively. The discussion participants believe that the immunity of elderly people is to a great extent a derivative from improved interactions between medical personnel and relevant workers without medical education (speech therapists, psychologists, IT-specialists, social workers, city-managers, and paid workers who render assistance to those in need in specific situations);

– any considerations on how to minimize health risks caused by infections for elderly people are based on eliminating despondency by taking care of oneself. Unfortunately, a simple talk with an elderly person as the most universal and available care and way to relieve stress is a non-banal banality which requires social advertising and pedagogical innovations. Elderly people's communities organized near their places of residence are a powerful resource for health risk mitigation which, regrettably, has been forgotten. If supported by local authorities, elderly people's communities are able to raise resistance to stress, safety, stability, and self-confidence due to mutual support. Complex care which elderly people take of themselves is the most effective practice to minimize infection risks.

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References

1. Leibovici L., Samra Z., Konigsberger H., Drucker M., Ashkenazi S., Pitlik S.D. Long-term survival following bacteremia or fungemia. *JAMA*, 1995, vol. 274, no. 10, pp. 807–812.

2. Lilie P.J., Allen J., Hall C., Walsh C., Adams K., Thaker H., Moss P., Barlow G.D. Long-term mortality following bloodstream infection. *Clin. Microbiol. Infect.*, 2013, vol. 19, no. 10, pp. 955–960. DOI: 10.1111/1469-0691.12101

3. Iwashyna T.J., Cooke C.R., Wunsch H., Kahn J.M. The population burden of long-term survivorship after severe sepsis among older Americans. *J. Am. Geriatr. Soc.*, 2012, vol. 60, no. 6, pp. 1070–1077. DOI: 10.1111/j.1532-5415.2012.03989.x

4. Fatenkov O.V., Kuzmina T.M., Rubanenko O.A., Svetlova G.N., Djubailo A.V. Community acquired bacterial pneumonia and comorbidity in elderly patients. *Uspekhi gerontologii*, 2017, vol. 30, no. 3, pp. 394–397 (in Russian).

5. Utenkova E.O., Lyubeznova O.N., Noskova E.V., Noskova V.V. Features of intestinal infections in elderly patients. *Uspekhi gerontologii*, 2018, vol. 31, no. 2, pp. 246–249 (in Russian).

6. Birnbaum M., Booth W. Nursing homes linked to up to half of coronavirus deaths in Europe, WHO says. *The Washington Post*, 2020. Available at: https://www.washingtonpost.com/world/europe/nursing-homes-coronavirus-deaths-europe/2020/04/23/d635619c-8561-11ea-81a3-9690c9881111_story.html (30.07.2021).

7. Coronavirus (COVID-19) latest insights. *Office for National Statistics*. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/articles/coronaviruscovid19roundup/2020-03-26 (30.07.2021).

8. Graham_N.S.N., Junghans C., Downes R., Sendall C., Lai H., McKirdy A., Elliott P., Howard R. [et al.]. SARS-CoV-2 infection, clinical features and outcome of COVID-19 in United Kingdom nursing homes. *J. Infect.*, 2020, vol. 81, no. 3, pp. 411–419. DOI: 10.1016/j.jinf.2020.05.073

9. COVID Data Tracker. *CDC*. Available at: https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination (22.02.2022).

10. Castelo-Branco C., Soveral I. The immune system and aging: a review. *Gynecol. Endocrinol.*, 2014, vol. 30, no. 1, pp. 16–22. DOI: 10.3109/09513590.2013.852531

11. Rabinow P. Sociobiology and Biosociality. In: G.B. Yudin translation. *Chelovek*, 2019, vol. 30, no. 6, pp. 8–26 (in Russian).

12. Big C., Malani P.N. Staphylococcus aureus bloodstream infections in older adults: clinical outcomes and risk factors for in-hospital mortality. *J. Am. Geriatr. Soc.*, 2010, vol. 58, no. 2, pp. 300–305. DOI: 10.1111/j.1532-5415.2009.02666.x

13. Ratsional'naya antibiotikoterapiya: vzglyad i kommentarii spetsialistov [Rational antibiotic therapy: view and comments of specialists]. *Effektivnaya farmakoterapiya*, 2017, no. 3, pp. 60–66 (in Russian).

14. Ratsional'naya antibiotikoterapiya: effektivnaya i adekvatnaya [Rational antibiotic therapy: effective and adequate]. *Effektivnaya farmakoterapiya*, 2017, no. 15, pp. 24–35 (in Russian).

15. Bokeriya L.A., Beloborodova N.V. Infektsiya v kardiokhirurgii [Infection in cardiac surgery]. Moscow, NTsSSKh im. A.N. Bakuleva RAMN Publ., 2007, 572 p. (in Russian).

16. Popov D.A. Postoperative infectious complications in cardiosurgery: the frequency of development, risk factors, etiology, peculiarities of pathogenesis, diagnosis optimization. *Annaly khirurgii*, 2011, no. 5, pp. 10–14 (in Russian).

17. Yahav D., Schlesinger A., Daitch V., Akayzen Y., Farbman L., Abu-Ghanem Y., Paul M., Leibovici L. Presentation of infection in older patients – a prospective study. *Ann. Med.*, 2015, vol. 47, no. 4, pp. 354–358. DOI: 10.3109/07853890.2015.1019915

18. Hermandez C., Fehér C., Soriano A., Marco F., Almela M., Cobos-Trigueros N., De La Calle C., Morata L. [et al.]. Clinical characteristics and outcome of elderly patients with community-onset bacteremia. *J. Infect.*, 2015, vol. 70, no. 2, pp. 135–143. DOI: 10.1016/j.jinf.2014.09.00

19. Mladenovic J., Veljovic M., Udovicic I., Lazic S., Segrt Z., Ristic P., Suljagić V. Catheter-associated urinary tract infection in a surgical intensive care unit. *Vojnosanit. Pregl.*, 2015, vol. 72, no. 10, pp. 883–888. DOI: 10.2298/vsp140624078m

20. Priefer B.A., Duthie E.H. Jr., Gambert S.R. Frequency of urinary catheter change and clinical urinary tract infection. Study in hospital-based, skilled nursing home. *Urology*, 1982, vol. 20, no. 2, pp. 141–142. DOI: 10.1016/0090-4295(82)90343-0

21. Firestein M., Mendelson G., Gronich D., Granot E., Ben-Israel J., Raz R. Can antibiotic use during routine replacement of long-term urinary catheter prevent bacteriuria? *Infectious Diseases in Clinical Practice*, 2001, vol. 10, no. 3, pp. 133–135. DOI: 10.1097/00019048-200103000-00003

22. Cheung K., Leung P., Wong Y., To O., Yeung Y., Chan M., Yip Y., Kwok C. Water versus antiseptic periurethral cleansing before catheterization among home care patients: a randomized controlled trial. *Am. J. Infect. Control*, 2008, vol. 36, no. 5, pp. 375–380. DOI: 10.1016/j.ajic.2007.03.004

23. Lee M.H., Lee G.A., Lee S.H., Park Y.-H. Effectiveness and core components of infection prevention and control programmers in long-term care facilities: a systematic review. *J. Hosp. Infect.*, 2019, vol. 102, no. 4, pp. 377–393. DOI: 10.1016/j.jhin.2019.02.008

24. Markelova E.V., Yutskovskaya Ya.A., Birko O.N., Baibarina E.V., Chepurnova N.S. The immune system of the skin: the age peculiarities. *Klinicheskaya dermatologiya i venerologiya*, 2016, vol. 15, no. 6, pp. 4–10. DOI: 10.17116/klinderma20161564-10 (in Russian).

25. Laube S. Skin infections and ageing. *Ageing Res. Rev.*, 2004, vol. 3, no. 1, pp. 69–89. DOI: 10.1016/j.arr.2003.08.003

26. Bazarnyi V.V. Immunnaya sistema kozhi [The immune system of the skin]. *Mezoterapiya*, 2014, no. 2, pp. 52–56 (in Russian).

27. Kuznetsov S.V. Klinicheskaya gerontostomatologiya [Clinical gerontostomatology]. Moscow, MIA, 2018, 240 p.

28. Petersen P.E., Yamamoto T. Improving the oral health of older people: the approach of the WHO Global Oral Health Programme. *Community Dent. Oral Epidemiol.*, 2005, vol. 33, no. 2, pp. 81–92. DOI: 10.1111/j.1600-0528.2004.00219.x

29. Vissink A., Spijkervet F.K., Amerongen A.V.N. Aging and saliva: a review of the literature. *Spec. Care Dentist.*, 1996, vol. 16, no. 3, pp. 95–103. DOI: 10.1111/j.1754-4505.1996.tb00842.x

30. Griaznova O.S., Manuilskaya K.M. Housing-related needs assessment of older people in Russia and worldwide. *Chelovek*, 2020, vol. 31, no. 3, pp. 45–70. DOI: 10.31857/S023620070010036-6 (in Russian).

31. Infection prevention and control manual for older people and adult care homes. *National Services Scotland*. Available at: https://www.nipcm.scot.nhs.uk/infection-prevention-and-control-manual-for-older-people-and-adult-care-homes/ (22.02.2022).

32. Expósito Miralles S., Martínez Sánchez J., Munteanu Munteanu A.D., Caballer Miedes A. Evaluación diagnóstica del grado de adaptación de la ciudad de Castellón a las personas mayors. *Àgora de Salut*, 2017, vol. 4, pp. 93–98. DOI: 10.6035/AgoraSalut.2017.4.10

33. Rogozin D.M. The British School of Social Gerontology: A Bibliographical Review of a Publication Project. *Chelovek*, 2020, no. 3, pp. 173–183. DOI: 10.31857/S023620070010041-2 (in Russian).

34. Dickens A.P., Richards S.H., Greaves C.J., Campbell J.L. Interventions targeting social isolation in older people: a systematic review. *BMC Public Health*, 2011, vol. 11, pp. 647. DOI: 10.1186/1471-2458-11-647

35. Polishchuk Yu.I., Baranskaya I.V., Gurvich V.B. Mediko-sotsial'naya pomoshch' litsam pozdnego vozrasta s reaktsiyami gorya i sostoyaniyami odinochestva [Medical and social assistance to elderly people with grief reactions and loneliness]. *Gerontologiya i geriatriya*, 2001, no. 1, pp. 312–315 (in Russian).

36. Killick J. Communication and the care of people with dementia. UK, Open University Press, 2001, 338 p.

37. Smol'kin A.A., Zhigareva P.A., Makarova E.A., Kiryukhina A.A., Milova E.A., Khaltourina D.A. Attitudes toward aging prevention: results of a focus groups study. *Uspekhi gerontologii*, 2017, vol. 30, no. 4, pp. 609–617 (in Russian).

38. Bryzgalina E.P. Medicine in the optics of artificial intelligence: the philosophical context of the future. *Chelovek*, 2019, vol. 30, no. 6, pp. 54–71. DOI: 10.31857/S023620070007669-2 (in Russian).

39. Cameron K. How Older Adults Can Stay Protected During the Omicron Surge. *NCOA's Center for Healthy Aging*, 2022. Available at: https://www.ncoa.org/article/how-older-adults-can-stay-protected-during-the-omicron-surge (19.02.2022).

40. Agapova E.G., Pritulina Yu.G., Donika A.D. Medical and sociological aspects of prevention of influenza and acute respiratory infections of aged people on the model group of military retirees. *Zdorov'e i obrazovanie v 21 veke*, 2017, vol. 19, no. 2, pp. 47–52 (in Russian).

41. Reis J., Zaitseva N.V., Spencer P.S. Understanding the perception and hierarchy of risks: an environmental medico-scientific perspective with COVID-19 in mind. *Health Risk Analysis*, 2020, no. 3, pp. 5–18. DOI: 10.21668/health.risk/2020.3.01.eng

42. Wiles J.L., Leibing A., Guberman N., Reeve J., Allen R.E. The meaning of "aging in place" to older people. *Gerontologist*, 2012, vol. 52, no. 3, pp. 357–366. DOI: 10.1093/geront/gnr098

43. Morley J.E. Aging in place. *J. Am. Med. Dir. Assoc.*, 2012, vol. 13, no. 6, pp. 489–492. DOI: 10.1016/j.jamda.2012.04.011

44. Wagner S.L., Shubair M.M., Michalos A.C. Surveying Older Adults' Opinions on Housing: Recommendations for Policy. *Social Indicators Research*, 2010, vol. 99, no. 3, pp. 405–412. DOI: 10.1007/s11205-010-9588-5

45. World report on ageing and health. *WHO*, 2016. Available at: https://apps.who.int/iris/bitstream/handle/10665/186463/9789240694811_eng.pdf?sequence=1&isAllowed=y (15.12.2021).

46. Popova A.Yu., Zaitseva N.V., Onishchenko G.G., Kleyn S.V., Glukhikh M.V., Kamaltdinov M.R. Sanitary-epidemiologic determinants and potential for growth in life expectancy of the population in the Russian Federation taking into account regional differentiation. *Health Risk Analysis*, 2020, no. 1, pp. 4–17. DOI: 10.21668/health.risk/2020.1.01.eng

47. World Well-Being Project. Available at: https://wwbp.org (15.08.2021).

48. Esposito S., Bonanni P., Maggi S., Tan L., Ansaldi F., Lopalco P.L., Dagan R., Michel J.-P. [et al.]. Recommended immunization schedules for adults: Clinical practice guidelines by the Escmid Vaccine Study Group (EVASG), European Geriatric Medicine Society (EUGMS) and the World Association for Infectious Diseases and Immunological Disorders (WAidid). *Hum. Vaccin. Immunother.*, 2016, vol. 12, no. 7, pp. 1777–1794. DOI: 10.1080/21645515.2016.1150396

49. Tip Sheet: Home safety tips for older adults. *AGS Health in Aging Foundation*. Available at: https://www.healthinaging.org/tools-and-tips/tip-sheet-home-safety-tips-older-adults#:~:text=Safety%2Dproof%20your%20home,when%20you%20walk%20on%20them (22.02.2022).

50. Iordanishvili A.K. Domestic prophylactic agents in maintaining the dental health of the elderly. *Meditsinskii alfavit*, 2020, no. 35, pp. 5–9. DOI: 10.33667/2078-5631-2020-35-5-9 (in Russian).

Yagodina A., Serova I., Maslov U., Korotin S. How to minimize infectious health risks for elderly people (based on focus group data). Health Risk Analysis, 2022, no. 1, pp. 72–84. DOI: 10.21668/health.risk/2022.1.08.eng

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Research article

ASSESSMENT OF BACTERIAL FILTRATION AND AIR PERMEABILITY OF FACE MASKS USED BY PEOPLE DURING THE COVID-19 PANDEMIC

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The pandemic caused by SARS-CoV-2 remains a serious threat to human health. Non-specific protection measures including face masks are an effective way to reduce risks of the infection spread. Face masks have different protective capacities and their effectiveness depends on an extent to which a material a mask is made of can retain droplets and aerosol particles containing the virus. Bacterial filtration can be used an as indicator showing how effectively a mask protects from contagion and air permeability can be used to estimate how comfortable it is to wear it.

Our research aim was to comparatively assess effectiveness and comfort in wearing provided by masks which were most frequently used by people during the pandemic.

We examined medical, cotton, and neoprene masks. Bacterial filtration was determined in accordance with the procedure stipulated in the State Standard GOST 12.4.136-84. Air permeability was estimated by determining how thin air was with VTPM-2 device produced by "Metroteks" LLC. All the data were statistically analyzed with StatTech v. 2.4.1 software package. We calculated quantitative indicators (M ± SD, 95 % CI for normal distribution), Fischer's test (comparison between groups as per quantitative indicators) and Spearman's rank correlation coefficient (directions and intensity of correlations). We developed our predictive model using linear regression.

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The research results indicate that the neoprene mask tends to have the highest bacterial filtration; the cotton mask, the highest air permeability. We detected a correlation between bacterial filtration and air permeability.

All masks are quite comparable to a medical one as per all their combined examined characteristics and can be used as a barrier for mitigating risks of droplet infections spread. It is advisable to further investigate face masks with concentrating on more characteristics of their effectiveness, comfort in wearing and safety.

Key words: *face mask, COVID-19, bacterial filtration, air permeability, cotton mask, neoprene mask, medical mask, statistical analysis.*

The COVID-19 pandemic caused by SARS-CoV-2 virus which started in December 2019 still remains a threat to human health all over the world [1]. Despite newly developed and quite effective immunobiological medications and wide-scale vaccination the COVID-19 incidence is growing at the moment due to new occurring SARS-CoV-2 virus strains. Therefore, non-drug approaches to COVID-19 prevention, face masks included, are still considered a simple and effective way to reduce risks of the infection spread [2–5].

In different countries there are different approaches to regulation of mask wearing during the COVID-19 pandemic. Primarily, all these approaches take into account epidemiological significance and barrier functions of a mask but they are not usually based on its hygienic assessment. The WHO recommends people in general and those who work in closed spaces or in close proximity from each other (or clients) to use non-medical (woven) masks consisting of 3 layers[1]. The US Centers for Disease Control and Prevention recommend using woven masks made of at least 2 layers of materials with good air permeability[2] whereas the European Center for Disease Prevention and Control recommends both medical and non-medical masks which meet the requirements on effective filtration and air permeability[3]. In China it is recommended to wear non-reusable medical masks in places where contagion risks are relatively low and non-medical masks in places where these risks are low[4]. In the Russian Federation, just as in some other countries, administrative, organizational, technical, sanitary and hygienic measures were introduced step by step. All these measures were aimed at preventing COVID-19 spread [6]. At present, it is mandatory to wear hygienic masks in public places and public transport[5]; employers are obliged to provide their workers with non-reusable masks to be worn at workplaces[6].

Effectiveness of protection provided by a mask depends on a material it is made of; to be

[1] Mask use in the context of COVID-19: interim guidance. Geneva, Switzerland, World health organization, December 1, 2020, 22 p.; Preventing and mitigating transmission of COVID-19 at work: policy brief, 19 May 2021. *WHO, ILO*, 2021, 23 p.

[2] Masks. *Centers for Disease Control and Prevention*, 2020. Available at: https://www.cdc.gov/coronavirus/2019-ncov/prevent-getting-sick/diy-cloth-face-coverings.html (November 09, 2021).

[3] Using face masks in the community: first update. Effectiveness in reducing transmission of COVID-19. Stockholm, European Centre for Disease Prevention and Control, 15 February 2021. Available at: https://www.ecdc.europa.eu/sites/default/files/documents/covid-19-face-masks-community-first-update.pdf (November 09, 2021).

[4] China Guidelines for the selection and use of different types of masks for preventing new coronavirus infection in different populations. *The State Council. The People's Republic of China*, February 5, 2020. Available at: http://www.gov.cn/xinwen/2020-02/05/content_5474774.htm (November 09, 2021) (in Chinese).

[5] O dopolnitel'nykh merakh po snizheniyu riskov rasprostraneniya COVID-19 v period sezonnogo pod"ema zabolevaemosti ostrymi respiratornymi virusnymi infektsiyami i grippom: Postanovlenie glavnogo gosudarstvennogo sanitarnogo vracha RF ot 16.10.2020 № 31 [On additional activities aimed at reducing risks of COVID-19 spread during a seasonal rise in morbidity with acute respiratory virus infections and flu: The Order by the RF Chief Sanitary Inspector issued on October 16, 2020 No. 31]. *The official Internet portal of legal information*. Available at: http://publication.pravo.gov.ru/Document/View/0001202010270001 (November 09, 2021) (in Russian).

[6] O merakh po profilaktike novoi koronavirusnoi infektsii (COVID-19): Pis'mo Rospotrebnadzora ot 10.03.2020 № 02/3853-2020-27 [On prevention measures against the new coronavirus infection (COVID-19): The Letter by Rospotrebnadzor issued on March 10, 2020 No. 02/3853-2020-27]. *The Federal Service for Surveillance over Consumer Rights protection and Human Wellbeing*. Available at: https://www.rospotrebnadzor.ru/deyatelnost/epidemiological-surveillance/?ELEMENT_ID=13955 (November 09, 2021) (in Russian).

more exact, it depends on how well this material retains droplets and aerosol particles which contain viruses. Although the size of SARS-CoV-2 virus is about 1 μm, virus particles attach to water droplets which are released into the air by sick people when they she breathe, sneeze, cough, or talk. Therefore, the total size of a single infecting virus particle together with water becomes larger and varies from 5 to 15 μm [7, 8]. According to some other data, when a person breathes, water particles which are released in the process vary from 0.1 to 1000 μm [9]. Pore size in a medical mask varies from 0.3 to 10 μm and is quite comparable to sizes of various bacteria. For example, *Staphylococcus aureaus* is 0.8–1 μm in diameter; this bacterial culture is often used to determine bacterial permeability of personal protective equipment (GOST 12.4.136-84[7]). Therefore, masks which are recommended to be worn by people for protection make contagion with coronaviruses less probable and bacterial filtration can be used as an indirect indicator showing how effectively a mask protects from respiratory viral infections, COVID-19 included.

Comfort in wearing is primarily determined by air permeability of a material a mask it made from [10–14]. This property determines how easy it is for a person to breathe through a mask; it also determines if there is a probability of various adverse effects produced by wearing it such as breathing discomfort, headache, and local skin reactions.

Our research aim was to comparatively assess effectiveness and comfort in wearing provided by masks which were used by population during the pandemic.

To achieve it, it was necessary to solve the following tasks:

1. To determine effectiveness of bacterial filtration provided by the most frequently used types of masks as an indicator showing effectiveness.

2. To determine air permeability of the most frequently used masks as an indicator showing comfort in wearing.

3. To comparatively assess effectiveness and comfort provided by different types of masks.

Materials and methods. We selected 3 types of masks to be examined bearing in mind our accomplished market analysis which focused on sales of respiratory protective equipment applied during this pandemic [15] as well as recommendations on mask wearing developed in different countries (Table 1).

Examined masks of each type were bought from the same manufacturer.

Bacterial filtration was determined as per the conventional procedure stipulated in the State Standard GOST 12.4.136-84 "Personal protective means. Method for determination of microorganism permeability"[7]. The procedure involves comparing a number of grown *Staphylococcus aureus* colonies which penetrated through a tested mask with a number of colonies grown on control plates. We calculated the bacterial filtration coefficient as $1 - (M \div M_1) \cdot 100$ where M was a simple mean of a number of colonies for each sample and M1 was a simple mean of a number of colonies

Table 1

Examined types of masks

Type	Description
Medical	Disposable medical non-woven 3-layer (spunbond / metlblown) mask with noise clip and ear straps
Cotton	Reusable non-medical cotton 2-layer mask with behind-the-ear loops, without nose clip and exhalation valve
Neoprene	Reusable non-medical neoprene one-layer mask with behind-the-ear loops, without nose clip and exhalation valve

[7] The State Standard GOST 12.4.136-84. System of safety standards. Personal protective means. Method for determination of microorganism permeability: approved and validated by the Order of the USSR State Committee on standards issued on March 23, 1984 No. 896. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200012741 (November 09, 2021) (in Russian).

in control. All the tests were conducted by an accredited testing laboratory.

Air permeability was determined as per how thin the air was using VTPM-2 device manufactured by "Metroteks" LLC (Russia). Pressure difference at air passage through a sample was kept at the same level equal to 49 Pa. We estimated air output in l/sec through the preset cross-sectional area of a mask. Ten measurements were accomplished for each sample. The results were checked with Q-test to identify and reject outliers.

We statistically analyzed all the data using StatTech v. 2.4.1 software package ("StatTech" LLC, Russia). Quantitative indicators were checked to determine whether they were distributed normally using Shapiro – Wilk test. Quantitative indicators which were distributed normally were described with simple means (*M*) and standard deviations (*SD*) as well as boundaries of the 95 % confidence interval (95 % CI). Fischer's test was applied to compare the analyzed groups as per quantitative indicators. We applied Spearman's rank correlation coefficient to determine direction and intensity of correlations between two quantitative indicators. We developed our predictive model which characterized dependence between a quantitative variable and various factors by using linear regression.

Results and discussion. Table 2 provides results produced by examining bacterial filtration.

All the examined masks had comparable bacterial filtration. Bacterial filtration of the examined medical masks didn't conform to the standard value. We established that the cotton mask had the lowest bacterial filtration out of all three examined types. The neoprene mask turned out to be less permeable for bacteria than the medical mask made of spunbond / meltblown.

There are multiple research works with its basic focus being on aerosol filtration effectiveness of masks. The authors established that medical masks protected from the COVID-19 agent better than cotton ones and were inferior only to respirators [14, 16–19]. According to Brazilian researchers, neoprene masks provide as good filtration as medical ones do [20].

We compared air permeability of different masks (Table 3 and Figure).

Having analyzed air permeability depending on a type of a mask, we revealed that there were statistically significant differences ($p < 0.001$, the applied procedure was Fischer's test).

According to the requirements[10] materials which contact human skin directly should have air permeability being not lower than 100 dm^3/m^2sec. Air permeability of all the examined masks conformed to these requirements. The cotton mask was established to have the highest air permeability.

Our results produced by estimating air permeability are similar to those described by other authors. For example, cotton masks were established to have air permeability which was approximately by 2 times higher than that of medical masks made from spunbond / meltblown [13]. However, Brazilian experts also showed that neoprene masks had extremely

[8] GOST 58396-2019. Medical face masks. Requirements and test methods: approved and introduced by the Order of the Federal Agency on Technical Regulation and Metrology on March 28, 2019 No. 115-st. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200163559 (November 12, 2021) (in Russian).

[9] AFNOR SPEC S76-001. Masque barrière. Guide d'exigenceminimales, de méthoded'essais, de confection etd'usage [Barrier masks. Guide to minimum requirements, methods of testing, making and use]. *AFNOR*, 2020. Available at: https://www.snof.org/sites/default/files/AFNORSpec-S76-001-MasquesBarrieres.pdf (November 12, 2021) (in French).

[10] TR TS 017/2011. O bezopasnosti tovarov legkoi promyshlenosti (s izmeneniyami na 9 avgusta 2016 goda): utv. Resheniem Komissii Tamozhennogo soyuza ot 09.12.2011 № 876 [CU TR 017/2011. On safety of goods manufactured by light industries (last amended on August 9, 2016): approved by the Decision of the Customs Union Commission on December 9, 2011 No. 876]. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/902320564 (November 09, 2021) (in Russian).

Table 2

Bacterial filtration provided by different types of masks

Type	Bacterial filtration coefficient, %	
	Research results	Standard value
Medical	85.00	≥ 95[8]
Cotton	62.50	≥ 50[9]
Neoprene	93.75	≥ 70[5]

Table 3

Analysis of air permeability depending on a type of a mask

Type	Air permeability (dm^3/m^2sec)			p
	$M \pm SD$	95 % CI	n	
Medical	209.28 ± 8.75	198.42–220.14	10	$p_{medical-cotton} = 0.001$ $p_{neoprene-cotton} = 0.001$
Cotton	397.85 ± 22.99	369.31–426.39	10	
Neoprene	248.69 ± 52.73	183.22–314.17	10	

N o t e : n is a number of samples.

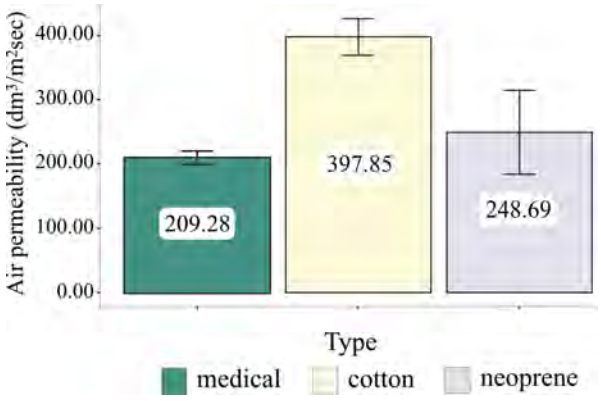

Figure. Analysis of air permeability depending on a type of a mask

Table 4

Analysis of the correlation between bacterial filtration and air permeability

Indicator	Correlation characteristics		
	r_{xy}	Correlation intensity as per Chaddock scale	p
Bacterial filtration – Air permeability	–0.889	High	0.303

low air permeability and didn't conform to safety standards [20].

We analyzed the correlation between bacterial filtration and air permeability (Table 4).

The expected dependence of bacterial filtration from air permeability is given by the following pair linear regression equation:

$$y = –0.144x + 121.491,$$

where y is bacterial filtration and x is air permeability.

When air permeability goes down by 1 dm^3/m^2sec, we should expect a rise in bacterial filtration by 0.144. This model explains 79.0 % of the observed dispersion of bacterial filtration.

Our research results prove there is dependence between air permeability of a material a mask is made from and its bacterial filtration coefficient. Thus, the neoprene mask had the highest bacterial filtration but its air permeability was average. This can be due to neoprene being more hydrophobic that cotton and this prevents microorganisms which spread in the air together with water droplets from penetrating through the mask.

Research limitations. We didn't examine respirators since the WHO recommends them only for medical personnel who work with patients in an environment where virus aerosol can occur in the air and not for the general public. Besides, qualitative respirators which conform to all international standards and are registered in the Russian State Medical Equipment and Organizations Register are rather expensive and therefore rather rarely used by population.

In future it is necessary to examine each type of masks produced by different manufac-

turers. It is also advisable to examine other properties of face masks influencing their effectiveness, comfort in wearing and safe everyday use. These properties are absorbability, chemical structure, changes in skin temperature and humidity behind a mask etc.

Conclusions. The neoprene mask turned out to have the highest bacterial filtration (93.75 %); the cotton mask, the highest air permeability (397.85 ± 22.99 dm^3/m^2sec).

We established and described the correlation between bacterial filtration and air permeability ($r = 0.889$, $p = 0.3$).

All the examined masks were comparable with a medical one as per all their combined examined characteristics and can be used as a barrier for mitigating risks of droplet infections spread.

It is necessary to conduct further research focusing on more properties of face masks which allow estimating their effectiveness, comfort, and safety.

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References

1. Coronavirus disease (COVID-19) Weekly Epidemiological update and weekly operational update. *World health organization*, 2021. Available at: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports (09.11.2021).

2. Clapham H.E., Cook A.R. Face masks help control transmission of COVID-19. *Lancet Digit. Health*, 2021, vol. 3, no. 3, pp. e136–e137. DOI: 10.1016/S2589-7500(21)00003-0

3. Chu D.K., Akl E.A., Duda S., Solo K., Yaacoub S., Schünemann H.J. COVID-19 Systematic Urgent Review Group Effort (SURGE) study authors. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. *Lancet*, 2020, vol. 395, no. 10242, pp. 1973–1987. DOI: 10.1016/S0140-6736(20)31142-9

4. Talic S., Shah S., Wild H., Gasevic D., Maharaj A., Ademi Z., Li X.,. Xu W. [et al.]. Effectiveness of public health measures in reducing the incidence of COVID-19, SARS-CoV-2 transmission, and COVID-19 mortality: systematic review and meta-analysis. *BMJ*, 2021, vol. 375, pp. e068302. DOI: 10.1136/bmj-2021-068302

5. Howard J., Huang A., Lid Z., Tufekci Z., Zdimal V., van der Westhuizen H.-M., von Delft A., Price A. [et al.]. An evidence review of face masks against COVID-19. *Proc. Natl Acad. Sci. USA*, 2021, vol. 118, no. 4, pp. e2014564118. DOI: 10.1073/pnas.2014564118

6. Reshetnikov V., Mitrokhin O., Shepetovskaya N., Belova E., Jakovljevic M. Organizational measures aiming to combat COVID-19 in the Russian Federation: the first experience. *Expert Rev. Pharmacoec. Outcomes Res.*, 2020, vol. 20, no. 6, pp. 571–576. DOI: 10.1080/14737167.2020.1823221

7. Tellier R., Li Y., Cowling B.J., Tang W.J. Recognition of aerosol transmission of infectious agents: a commentary. *BMC Infect. Dis.,* 2019, vol. 19, no. 1, pp. 101. DOI: 10.1186/s12879-019-3707-y

8. Stadnytskyi V., Bax C.E., Bax A., Anfinrud P. The airborne lifetime of small speech droplets and their potential importance in SARS-CoV-2 transmission. *Proc. Natl Acad. Sci. USA*, 2020, vol. 117, no. 22, pp. 11875–11877. DOI: 10.1073/pnas.2006874117

9. Prather K.A., Wang C.C., Schooley R.T. Reducing transmission of SARS-CoV-2: Masks and testing are necessary to combat asymptomatic spread in aerosols and droplets. *Science*, 2020, vol. 368, no. 6498, pp. 1422–1424. DOI: 10.1126/science.abc6197

10. Schilling K., Gentner D.R., Wilen L., Medina A., Buehler C., Perez-Lorenzo L.J., Pollitt K.J.G., Bergemann R. [et al.]. An accessible method for screening aerosol filtration identifies poor-performing commercial masks and respirators. *J. Expo. Sci. Environ. Epidemiol.*, 2020, vol. 31, no. 6, pp. 943–952. DOI: 10.1038/s41370-020-0258-7

11. Kähler C.J., Hain R. Fundamental protective mechanisms of face masks against droplet infections. *J. Aerosol Sci.,* 2020, vol. 148, pp. 105617. DOI: 10.1016/j.jaerosci.2020.105617

12. Parlin A.F., Stratton S.M., Culley T.M., Guerra P.A. A laboratory-based study examining the properties of silk fabric to evaluate its potential as a protective barrier for personal protective equipment and as a functional material for face coverings during the COVID-19 pandemic. *PLoS One*, 2020, vol. 15, no. 9, pp. e0239531. DOI: 10.1371/journal.pone.0239531

13. Aydin O., Emon B., Cheng S., Hong L., Chamorro L.P., Saif M.T.A. Performance of fabrics for home-made masks against the spread of COVID-19 through droplets: A quantitative mechanistic study. *Extreme Mech. Lett.*, 2020, vol. 40, pp. 100924. DOI: 10.1016/j.eml.2020.100924

14.Xi J., Si X.A., Nagarajan R. Effects of mask-wearing on the inhalability and deposition of airborne SARS-CoV-2 aerosols in human upper airway. *Phys. Fluids*, 1994, 2020, vol. 32, no. 12, pp. 123312. DOI: 10.1063/5.0034580

15.Shashina E.A., Isiutina-Fedotkova T.S., Makarova V.V., Gruzdeva O.A., Mitrokhin O.V. Approaches to analyzing efficiency of respiratory protective equipment as a way to reduce health risks during COVID-19 pandemic. *Health Risk Analysis*, 2021, no. 1, pp. 151–158. DOI: 10.21668/health.risk/2021.1.16.eng

16. Clapp P.W., Sickbert-Bennett E.E., Samet J.M., Berntsen J., Zeman K.L., Anderson D.J., Weber D.J., Bennett W.D. US Centers for Disease Control and Prevention Epicenters Program. Evaluation of Cloth Masks and Modified Procedure Masks as Personal Protective Equipment for the Public during the COVID-19 Pandemic. *JAMA Intern. Med.*, 2021, vol. 181, no. 4, pp. 463–469. DOI: 10.1001/jamainternmed.2020.8168

17. Zhao M., Liao L., Xiao W., Yu X., Wang H., Wang Q., Lin Y.L., Kilinc-Balci F.S. [et al.]. Household Materials Selection for Homemade Cloth Face Coverings and Their Filtration Efficiency Enhancement with Triboelectric Charging. *Nano Lett.*, 2020, vol. 20, no. 7, pp. 5544–5552. DOI: 10.1021/acs.nanolett.0c02211

18. Ngonghala C.N., Iboi E., Eikenberry S., Scotch M., MacIntyre C.R., Bonds M.H., Gumel A.B. Mathematical assessment of the impact of non-pharmaceutical interventions on curtailing the 2019 novel Coronavirus. *Math. Biosci.*, 2020, vol. 325, pp. 108364. DOI: 10.1016/j.mbs.2020.108364

19. Kim M.N. What Type of Face Mask Is Appropriate for Everyone-Mask-Wearing Policy amidst COVID-19 Pandemic? *J. Korean Med. Sci.*, 2020, vol. 35, no. 20, pp. e186. DOI: 10.3346/jkms.2020.35.e186

20. Morais F.G., Sakano V.K., de Lima L.N., Franco M.A., Reis D.C., Zanchetta L.M., Jorge F., Landulfo E. [et al.]. Filtration efficiency of a large set of COVID-19 face masks commonly used in Brazil. *Aerosol Science and Technology*, 2021, vol. 55, no. 9, pp. 1–15. DOI: 10.1080/02786826.2021.1915466

Shashina E.A., Belova E.V., Gruzdeva O.A., Skopin A.Y., Andreev S.V., Zhernov Y.V., Zhukova A.V., Isiutina-Fedotkova T.S., Makarova V.V., Mitrokhin O.V. Assessment of bacterial filtration and air permeability of face masks used by people during the COVID-19 pandemic. Health Risk Analysis, 2022, no. 1, pp. 85–91. DOI: 10.21668/health.risk/2022.1.09.eng

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Research article

SCHISTOSOMA HAEMATOBIUM BILHARZIASIS DURING OVERWINTERING IN ADELIE LAND: HEALTH AND OPERATIONAL RISK IN ANTARCTICA

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While serving from December 1970 to January 1972 as a medical doctor of the 21st French Polar Expedition in Adelie Land, Antarctica, at Dumont d'Urville Station, the author diagnosed Schistosoma haematobiumurinary bilharziasis in a winterer who suffered from pain in the right iliac fossa, at the beginning of the overwintering. The patient had participated in a bush investigation in West Africa, but, despite his complaints, the illness had not been diagnosed prior to the Antarctic expedition. Microscopic examination revealed Schistosoma haematobium eggs in the urine centrifugation deposit. In the absence of anti-bilharziasis medication, the patient was treated symptomatically with urinary antiseptic or antibiotic, hemostatic and antihistamine medications to palliate the egg deposition in the bladder wall and the subsequent induction of inflammatory reactions. Nine months later, a US Navy plane landed on the continent in the vicinity of the French Station and delivered the specific parasiticidal niridazole tablets. The patient received three niridazole tablets per day during one week. He returned to Paris in March 1972. Exploratory medical tests did not reveal any bladder or urinary tract alteration. He never since complained of any related problem. Recommendations are provided to avoid personal and / or operational risks due to such tropical infectious diseases during Antarctic expeditions.

Key words: *Adelie Land, Antarctic, overwintering, Schistosoma haematobium, niridazole, medical risks.*

Introduction to the case study. Polar expeditions offer unique medical challenges when medical emergencies or peculiarities arise. The latter may endanger individual and/or overwintering groups, particularly if these occur after the so-called summer campaign, during the actual winter-over. Outside access is then out of the question and evacuation of medical emergencies may reveal impossible. Besides, medications are in limited supplies reinforcing the medical challenge and risk. The author wishes to present the exceptional and 'exotic' case of *Schistosoma haematobium* bilharziasis that occurred while he served as a medical doctor on the 21st French Polar Expedition in Adelie Land at Dumont d'Urville Station or DDU Station (66° 40' South, 140° 01' East, Figure) between December 1970 and January 1972 [1].

On January 16, 1971, the author received, for the statutory monthly consult, a 29-year-old mechanic. He was meant to winter-over at DDU until the end of December 1971 and to participate in the following January and February 1972 summer campaign. His polar expertise had been acquired previously in 1967, as a member of the second International Glaciological Expedition to Greenland. As a volunteer for the 1971 overwintering, he had followed the enrolment procedure including a medical consultation at the Paris Val-de-Grâce military hospital (March 19, 1970) that only revealed a slight blood eosinophilic polymorphonuclear cell count (222/ml). He was

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Figure. Watercolor sketch of Dumont d'Urville Station built on Petrel Island in Adelie Land, Antarctica, during the overwintering between December 1970 and March 1972

selected and underwent a voluntary "preventive" appendectomy in October 1970 in Paris. Such a recommendation had been issued by French Polar Medical Services after the 1961 Leonid Rogozov's self-operated appendectomy while overwintering at the Antarctic Novolazarevskaya Soviet base [2].

Over several months since summer 1969, the patient had occasionally noticed red traces in his urines, associated with slight perineal pain and itch, and frequent urinations. Nevertheless, he had not worried about it. On February 16, 1971, he complained about perineal itch, associated with pollakiuria and dull pain in the right iliac fossa. The symptoms had recently become exaggerated. On examination of the patient, the author did not observe any pathological signs, and the symptoms were attributed to the hard outside physical work in preparation for the Antarctic overwintering.

Diagnosis of bilharziasis. On March 1st, the patient mentioned casually to the author that he had worked eight months in West Africa between October 1968 and May 1969. He had been hired as a mechanic and driver to serve in a field trial organized by the French National Institute of Geography (French acronym IGN) at the Senegal-Mali border. He was notably in charge of the safety of the IGN trucks in fording across the Falémé River. The author himself had spent several years in Africa and had recently completed courses to familiarize in tropical diseases at the Marseilles "Pharo" Institute of Tropical Medicine. He became suspicious of a potential contamination of the patient by *Schistosoma haematobium*.

The author summoned the patient to the infirmary and requested a urine sample. After centrifugation of the urine sample for 5 min at 4,000 revolutions/min using the old hand centrifuge that equipped the laboratory, a microscopic examination of the centrifuged deposit revealed numerous *Schistosoma haematobium* eggs, with their characteristic apical spine. Egg vitality was tested under the microscope by adding a drop of lukewarm water, which provoked immediately the exit of miracidia easily visible by light refraction. The author concluded that the patient was at the second egg laying stage of urinary schistosomiasis. He

called the patient, showed him the eggs and performed a demonstrative water test. Small pelvis radiography did not reveal any bladder wall thickening or calcifications. No specific treatment could be undertaken, as the DDU Station pharmacy did not contain any specific antiparasitic medication, such as niridazole, nor any other parasitical product (praziquantel had not yet been approved for humans), to treat parasitosis.

The Thala Dan ship, operated then by the French Polar Expeditions to support DDU Station, arrived on March 2, 1971 to transfer the members of the summer campaign back to Hobart (Tasmania). The Chief Medical Officer of the French Polar Expeditions was on board for a three-day inspection. The author presented the patient's case and identified the potential risk of inflammatory granulomatosis susceptible of evolving towards carcinogenesis.

Symptomatic palliative treatment during overwintering. Pressure was exerted by the summer campaign field authorities to allow the patient to remain in Antarctica due to his polar field expertise, especially in operating the M29 Weasel Half Tracks of the French Polar Expeditions. It was decided that the patient would winter-over at DDU Station. A symptomatic treatment was undertaken after reception of an informative telegram from the Director of the Marseilles Pharo Institute. Diverse medications present in the DDU pharmacy stock were used to palliate oviposition in the bladder wall: urinary antiseptics or antibiotics (sulfamethizole, tetracyclins), hemostatics and antihistamines. By the end of the overwintering, this medication stock was almost worn out [3]. Urinary *Schistosoma haematobium* eggs were counted weekly using the laboratory microscope to verify that the bladder wall was permeable for the eggs.

During the overwintering, the symptoms diminished progressively, except for a dull pain at the right iliac fossa that gradually subsided by mid-April. Acute short pain episodes supervened occasionally. Blood eosinophilia persisted at around 400 cells/ml. After the patient himself interrupted his treatment during one month in June, he complained of right iliac fossa pains and presented a slight hematuria with tiny blood clots in the urine. Viable eggs (lukewarm water test) were present. Symptomatic treatment was resumed in July 1971, but was again interrupted by the patient in August. He was consulted on September 7, 1971 to resume symptomatic treatment because he had been concerned by post-defecation hematuria. Hematuria decreased under symptomatic treatment over a period of three weeks.

Specific parasiticidal treatment and cure. On November 1st, 1971, a US Navy Lockheed LC-130 Hercules plane landed an International Antarctic Glaciological Project French team on the D10 continental plateau landing strip, at 10 km from DDU [4]. The team conveyed the niridazole medication to treat the patient. The niridazole treatment session was undertaken on November 18, 1971 with three tablets administered daily, still accompanied by the symptomatic treatment [5].

On November 25, a small basin radiography test showed an enlargement of vesical and right ureteral walls. No undesirable neuropsychological or cardiac side effects were noted [6]. The iliac fossa pain and hematuria disappeared in two weeks. On December 7, 1971, the patient still didn't have any symptoms and *Schistosoma haematobium* eggs were not detectable in his urine samples.

The author left DDU Station at the beginning of January 1972 to return to France and was replaced by a new medical doctor. The patient continued to work at DDU Station during the summer campaign that ended at the beginning of March 1972. Being symptomless, he did not consult the new DDU medical doctor.

After he returned to France, the patient reported to the Paris Medical Services of the French Polar Expeditions in April 1972. He underwent a medical check-up at the Paris Pitié-Salpétrière Hospital [7]. His urine did not contain any *Schistosoma haematobium*

eggs, and eosinophilia had decreased to 2 % of white blood cells. Specific serologic tests showed residual antibody levels. Cystoscopy and intravenous urography did not reveal any lesions.

The patient has never experienced any related problems since then [8], especially, no sequelae due to oviposition, such as bladder wall calcifications, bladder masses, small capacity scarred bladder, bladder stones, bladder neck sclerosis, stenosis of ureteral orifices, ureteral stones, ureteral wall calcifications, hydro ureter or bladder cancerization. This may have been helped by the maintenance of urinary bladder wall permeability during the several months-long symptomatic treatments, which palliated any egg deposition.

Conclusion and learning points on health and operational risk. The author chose to report this unique case of *Schistosoma haematobium* bilharziasis as it constitutes an historical 'exotic' medical case in Antarctica, along with a personal risk for the patient as well as an operational risk for the expedition team.

Key points concerning the health and operational risk of such a disease occurring in a small human group isolated in Antarctica are as follows:

- The parasite is encountered principally in African and South or Oriental Mediterranean areas. Except for the present case, schistosomiasis has never been observed in Antarctica. The present case surfaced after the patient's sojourn in West Africa.
- Health risk assessment for tropical diseases at the recruitment medical visit should be sought by simply asking all candidates preparing to sojourn in Antarctica or Sub-Antarctic territories if they have ever worked or lived in areas where tropical diseases are prevalent.
- The decision to use of symptomatic palliative treatment during several months seemed to help cure the disease with specific parasiticidal treatment.The patient never suffered from any specific treatment adverse effect.
- On the patient's point of view, the decisions taken in Antarctica, regarding his maintenance as a member of the expedition while receiving symptomatic treatment followed by specific anti-bilharziasis treatment when available, allowed the patient to complete his winter-over, and permitted his professional carrier development.
- This case study illustrates unique unexpected risks that may confront medicine in isolated small groups separated from broader medical assistance.

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References

1. International Antarctic Glaciological Project. *Polar Record*, 1971, vol. 15, no. 98, pp. 829–833. DOI: 10.1017/S0032247400062033

2. Rogozov V., Bermel N. Auto-appendectomy in the Antarctic: case report. *BMJ*, 2009, vol. 339, pp. b4965. DOI: 10.1136/bmj.b4965

3. Buguet A. Rapport d'activité médicale de la 21e expédition polaire française, 1972 (in French).

4. Evans S., Drewry D.J., Robin G. de Q. Radio-echo sounding in Antarctica, 1971-72. *Polar Record*, 1972, vol. 16, no. 101, pp. 207–212. DOI: 10.1017/S003224740006280X

5. Wolfe H.L. Treatment of urinary schistosomiasis with niridazole (Ambilhar) in 576 African schoolchildren. *Lancet*, 1967, vol. 289, no. 7486, pp. 350–354. DOI: 10.1016/S0140-6736(67)92894-2

6. McMahon J.E. A report on the side effects of ambilhar (niridazole) and the effect of antihistamines and aspirin on these reactions. *Trans. Roy. Soc. Trop. Med. Hyg*., 1967, vol. 61, no. 5, pp. 648–652. DOI: 10.1016/0035-9203(67)90127-7

7. Fall B., Sow Y., Traoré A., Ondo C.Z., Diagana M., Sarr A., Sine B., Faye S.T. [et al.]. Clinical and pathological aspects of the sequelae of urogenital schistosomiasis: findings regarding 43 cases. *Int. J. Clin. Urol*., 2019, vol. 3, no. 1, pp. 10–14. DOI: 10.11648/j.ijcu.20190301.13

Buguet A. Schistosoma haematobium bilharziasis during overwintering in Adelie Land: health and operational risk in Antarctica. Health Risk Analysis, 2022, no. 1, pp. 92–96. DOI: 10.21668/health.risk/2022.1.10.eng

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ARTIFICIAL VENTILATION AS A RISK FACTOR CAUSING HOSPITAL-ACQUIRED PNEUMONIA (HAP) IN PATIENTS TREATED IN THE INTENSIVE CARE UNIT OF A CARDIAC SURGERY HOSPITAL

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Hospital-acquired pneumonia (HAP) is the most common purulent septic infection among patients treated in intensive care units (ICUs) at cardiac surgery hospitals. Risk factors that can cause HAP, in particular, contribution made by artificial ventilation (AV) have not been studied enough. Our objective was to examine an epidemiological role played by AV in HAP occurrence among children and adults treated in the intensive care unit at a cardiac surgery hospital. We examined health records of 5318 patients (503 children and 4815 adults) who had a cardiac surgery due to congenital heart diseases or acquired cardiovascular disorders over 1 year. HAP was identified according to the epidemiological standards for case definition. Besides, we took into account pre-nosologic HAP cases, that is, patients already having certain pathological symptoms typical for purulent septic infections, but still, even combined, these symptoms were not enough to diagnose a typical HAP case in accordance with the standard case definition. Data were statistically analyzed by calculating the χ^2 goodness-of-fit test. We established that most HAP cases occurred among patients of a cardiac surgery hospital who were being treated in the intensive care unit after a surgery. We proved AV to be the leading risk factor causing HAP. Higher incidence rates of HAP were detected among children in comparison with adults. We showed that Klebsiella pneumoniae was the primary infectious agent that caused HAP. Particularly, background respiratory diseases and diseases of the central nervous system were proven to be endogenous risk factors of developing HAP among patients treated in the ICU at a cardiac surgery hospital.

Key words: *cardiac surgery hospital, intensive care unit, hospital-acquired pneumonia, risk groups, etiology, role played by artificial ventilation.*

Intensive care units (ICUs) are those divisions in medical organizations where there are the highest risks of hospital acquired purulent septic infections [1, 2]. Hospital acquired pneumonia (HAP) is the most common infection among patients treated in them [3, 4]. HAP occurs in 9–65 % patients in intensive care units [5–7], *Klebsiella pneumoniae* [8] being the leading infectious agent.

HAP in intensive care units often occurs in patients who have to undergo artificial ventilation (AV). In this case it is conventional to call it AV-associated or ventilator-associated pneumonia (VAP) [2, 7, 9]. Artificial airways created with an AV device are assumed to make swallowing less efficient. Bacteria can penetrate the lower airways either directly or through a split between tracheal tube walls and

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the airways thus causing an infection. Besides, long-term ventilation creates elevated risks of infections in the airways due to humidifiers and ventilation circuits [7].

Incidence of ventilator-associated pneumonia varies from 5 to 80 % (depending on a population of patients, severity of their cases, and AV duration) [10]. Frequency of occurring HAP is close to 80–100 % after a two-week AV period. Stratified incidence rate of HAP varies from 9.1 to 52.7 per 1000 AV-days spent in an ICU [10–12].

There are some works that dwell on results produced by comparative assessment of HAP incidence among children and adults. Some authors state that adults, especially those who are older than 60 years, have ventilator-associated pneumonia more often than children [13]. But at the same time others note there are no differences in incidence rate of the disease among children and adults [14].

There are available literature data on frequency of ventilator-associated pneumonia and risk factors that cause the disease in ICUs of surgical, oncologic, neurological, therapeutic and pediatric in-patient hospitals [5, 15]. But the issue hasn't been given proper attention with respect to an intensive care unit of a cardiac surgery hospital.

Our objective was to examine an epidemiological role played by artificial ventilation in occurrence of hospital acquired pneumonia among children and adults treated in an intensive care unit of a cardiac surgery hospital.

Materials and methods. Our study was accomplished in a specialized cardiac surgery hospital for children and adults where open heart surgeries and endovascular invasions on the heart and vessels are performed. Surgeries are performed in equipped operating rooms; then, patients are moved into an ICU where they can spent some time, starting from 1 day and for a longer period, depending on their clinical condition. After that patients are moved into cardiac surgery units. Patients who have undergone an endovascular invasion can be moved directly into an ordinary surgery unit without any time spent in an ICU.

We examined health records of 5318 patients (503 children and 4815 adults) who were treated in a cardiac surgery hospital and who had a heart surgery due to congenital heart diseases or acquired cardiovascular disorders over the last year. HAP was identified in accordance with the epidemiologic standard for the case definition [16]. Besides, we took into account pre-nosologic HAP, that is, cases when patients already had certain pathological symptoms typical for pneumonia but all these symptoms combined still were not enough to diagnose typical pneumonia according to the standard case definition [17]. Incidence rates of typical and prenosological HAP were calculated per 1000 patients. Our analysis included only patients who had HAP as a monoinfection. We considered a period during which a postoperative patient was ventilated starting from intubation and up to the first clinical signs of HAP as well as AV duration in case the first clinical HAP signs appeared after extubation. And in case a patient was ventilated several times during his or her period in the ICU, we took only a period of time from the next intubation and up to the first clinical signs of HAP. Ventilator-associated pneumonia was a HAP case when the disease occurred after a patient spent 48 hours ventilated [15]. HAP incidence density was calculated as per 1000 AV days.

We considered microorganisms to be isolated from patients with HAP only if they were identified at appearance of the first clinical HAP signs. Repeated cases of infectious agents' identification were neglected.

All materials were statistically analyzed by calculating χ^2 goodness-of-fit test. We determined confidence intervals for calculated rates (0.95 % CI) using WinPepi software package, Version 11.65 (created by Professor Joe Abramson, Israel). Differences between the rates were considered statistically significant at $\chi^2 \geq 3.8$ ($p < 0.05$). Assessment of risk factors involved calculating relative risk (*RR*) and respective 95 % confidence intervals.

Results and discussion. Overall, over the last year 503 children and 4815 adults

were operated in the examined cardiac surgery hospital. 246 children and 1567 adults were moved to the ICU after surgery. Data in Table 1 show that there were only sporadic HAP cases among patients who didn't spend any time in the ICU after surgery. Conversely, almost all HAP cases occurred among patients who were sent to the ICU after surgery and spent some time ventilated. A number of typical and prenosological HAP among patients treated in the ICU was greater among children (31.5 and 111.9 per 1000 accordingly) than among adults (16.6 and 47.2) (χ^2 = 7.5 and 40.3; p = 0.007 and 0.001 accordingly). Overall, incidence with both typical and prenosological HAP turned out to be by 2.2 times higher among children (143.4 per 1000) than among adults (63.8) (χ^2 = 219.9, p = 0.001).

Data in Table 2 indicate that incidence of typical and prenosological HAP turned out to be higher among children and adults who had a long AV period (632.7 and 301.6 per 1000 accordingly) than among those who had a shorter one (42.2 and 53.9 per 1000 accordingly), by 15.0 and 5.6 times (χ^2 = 12.2 and 62.1 accordingly, p = 0.001 in both cases). *RR* amounted to 14.9 (7.8–28.5) and 5.6 (3.6–8.6) accordingly. In case AV duration was shorter than 48 hours, there was no difference in incidence between children and adults (χ^2 = 0.6, p = 0.5); but if it was longer than 48 hours, than incidence among children was by 2.1 times higher than among adults (χ^2 = 21.8, p = 0.001). All these data indicate there is an epidemiological contribution made by AV into developing HAP in an ICU of a cardiac surgery hospital, especially among children.

Table 1

Incidence of hospital acquired pneumonia among patients in cardiac surgery hospital after heart surgery; both treated in the ICU and those who didn't spend any time there, cases/1000

Patients' group	Age	A number of patients	Typical HAP		Prenosological HAP cases		Total	
			Number of cases	cases/1000	Number of cases	cases/1000	Number of cases	cases/1000
Not treated in the ICU	children	217	0	0	0	0	0	0
	adults	3248	1	0.3 [0.01–1.7]	5	1.5 [0.5–3.5]	6	1.8 [0.7–4.0]
	total	3465	1	0.3 [0.01–1.6]	5	1.4 [0.5–5.3]	6	1.7 [0.6–3.7]
Treated in the ICU with some time spent on AV	children	286	9	31.5 [14.5–58.9]	32	111.9 [77.8–154.2]	41	143.4 [104.9–189.2]
	adults	1567	26	16.6 [10.9–24.2]	74	47.2 [37.3–58.9]	100	63.8 [52.2–77.1]
	total	1853	35	18.9 [13.2–26.1]	106	57.2 [47.1–68.7]	141	76.1 [64.4–89.1]

Table 2

Incidence of hospital acquired pneumonia among patients in cardiac surgery hospital after heart surgery who were treated in the ICU and had a short period (up to 48 hours) and longer period (more than 48 hours) spent on artificial ventilation, cases/1000

Age group	AV for less than 48 hours			AV for more than 48 hours		
	A number of patients	A number of HAP cases	per 1000	A number of patients	A number of HAP cases	per 1000
Children	237	10	42.2 [20.4–76.2]	49	31	632.7 [482.8–765.8]
Adults	1503	81	53.9 [43.0–66.5]	63	19	301.6 [192.3–430.2]
Total	1740	91	52.3 [44.5–67.1]	112	50	446.4 [355.9–547.7]

Table 3

The incidence density of typical and prenosological HAP among patients treated in the ICU (per 1000 AV days)

HAP clinical form	The incidence density	
	children	adults
Typical	45.0 [20.8–83.7]	24.8 [16.3–36.3]
Prenosological	108.1 [120.8–234.1]	68.7 [54.3–85.4]
Total	80.1 [58.3–107.4]	47.7 [38.5–57.0]

Having calculated stratified incidence rates, we established (Table 3) that the incidence density of typical and prenosological HAP per 1000 patient-days was by 1.8 and 1.6 times higher accordingly among children (45.0 and 108.1 accordingly) than among adults (24.8 and 68.7 accordingly) (χ^2 = 6.6 and 6.3 accordingly, p = 0.01 in both cases). Summated incidence of typical and prenosological HAP was by 1.5 times higher among children than among adults (χ^2 = 9.1, p = 0.003).

Sex-adjusted incidence assessment (Table 4) revealed that the epidemic process regarding all HAP forms was more intense among men than among women after a short period spent on AV (χ^2 = 15.9, p = 0.001). But in case AV was performed for more than 48 hours, incidence grew by 6.1 times among men and by 16.6 times among women (χ^2 = 95.5 and 13.3 accordingly, p = 0.001 in both cases). Ultimately incidence rates among men (432.8 per 1000) matched to those among women (466.6 per 1000) (χ^2 = 0.1, p = 0.7).

K. pneumoniae and fungi from *Candida* genus (Table 5) were most frequently isolated from phlegm of patients with typical or prenosological HAP. Detection rates for these microorganisms amounted to 17.7 and 15.5 per 100 examined patients accordingly. *S. aureus* и *P. aeruginosa* were detected less frequently, each microorganism in 7.3 % cases. There were no statistically significant differences in how often most agents were isolated from patients after either short-term or long-term AV, except *P. aeruginosa* and *K. pneumoniae*. We also detected a trend for increasing frequency of isolating *P. aeruginosa,* from 4.4 to 12.0 (χ^2 = 2.8, p = 0.1) and statistically significant growing in occurrence of *K. pneumoniae,* from 12.1 to 28.0 per 100 examined patients (χ^2 = 5.6, p = 0.02). Therefore, patients who spend less than 48 hours on AV are likely to get infected with *K. pneumoniae* due to endogenous reasons, and patients who spend more than 48 hours on AV, due to exogenous reasons. And just as we noted earlier [18], extensively drug-resistant strains (XDR-strains) and pandrug-resistant strains (PDR) were detected in 11.1 % and 3.7 % cases accordingly among *K. pneumoniae* isolated from patients treated in the examined cardiac surgery hospital. Moreover, *K. pneumoniae* strains produced beta-lactamases with a wider action spectrum in 92.6 % cases. Presence of HAP agents with polyresistance to antibiotics indicates that hospital clones of microorganisms causing group incidence might occur among them.

Patients with HAP had various background somatic pathologies as well; respiratory diseases, diseases of the endocrine and central nervous system were the most frequent

Table 4

Frequency of typical and prenosological hospital acquired pneumonia among patients, sex-dependent distribution

Sex	AV for less than 48 hours			AV for more than 48 hours		
	A number of patients	HAP cases		A number of patients	HAP cases	
		abs.	per 1000		abs.	per 1000
Men	968	69	71.2 [58.9–89.3]	67	29	432.8 [312.2–556.6]
Women	772	22	28.5 [17.9–42.8]	45	21	466.6 [316–621.2]

Table 5

Microorganisms isolated from children and adults with typical and prenosological hospital acquired pneumonia (per 100 examined patients)

Microorganisms	AV for less than 48 hours (n = 91)		AV for more than 48 hours (n = 50)		Total (n = 141)	
	Number of strains	per 100 examined patients	Number of strains	per 100 examined patients	Number of strains	per 100 examined patients
Staphylcoccus aureus	6	6.5 [2.5–13.8]	4	8.0 [2.2–19.2]	10	7.1 [3.3–12.6]
Staphylcoccus epidermidis	4	4.4 [1.2–10.8]	1	2.0 [0.1–10.6]	5	3.5 [1.2–8.1]
Streptococcus pneumoniae	2	2.2 [0.3–7.7]	1	2.0 [0.1–10.6]	3	2.7 [0.4–6.1]
Enterococcus faecalis	2	2.2 [0.3–7.7]	0	0	2	1.4 [0.2–5.0]
Enterococcus faecium	1	1.1 [0.03–7.7]	1	2.0 [0.1–10.6]	2	1.4 [0.2–5.0]
Acinetobacter baumannii	2	2.2 [0.3–7.7]	1	2.0 [0.1–10.6]	3	2.7 [0.4–6.1]
Pseudomonas aeruginosa	4	4.4 [1.2–10.8]	6	12.0 [4.5–24.1]	10	7.1 [3.5–12.6]
Escherichia coli	4	4.4 [1.2–10.8]	3	6.0 [1.3–16.5]	7	4.9 [2.0–9.9]
Klebsiella pneumoniae	11	12.1 [6.2–20.6]	14	28.0 [16.2–42.4]	25	17.7 [11.8–25.1]
Morganella morganii	2	2.2 [0.3–7.7]	0	0	2	1.4 [0.2–5.0]
Candida	15	16.5 [9.5–25.2]	7	14.0 [5.8–26.7]	22	15.6 [10.4–22.6]

Table 6

Frequency of background somatic pathology among patients with typical and prenosological hospital acquired pneumonia (%)

Background somatic pathology	A number of patients with background somatic pathology among those who spent some time on AV					
	Less than 48 hours (n = 91)		More than 48 hours (n = 50)		Total (n = 141)	
	abs.	%	abs.	%	abs.	%
Respiratory diseases (COPD, bronchitis, bronchial asthma, emphysema, lung infarction)	24	26.4 [17.7–36.6]	22	44.0 [29.9–58.7]	46	32.6 [24.9–41.0]
Endocrine diseases (diabetes mellitus, obesity)	30	32.9 [23.5–43.6]	9	18.0 [8.6–31.4]	39	27.6 [20.5–35.8]
Acute cerebrovascular accident (stroke)	7	7.7 [3.2–15.2]	5	10.0 [3.3–21.8]	12	8.5 [4.5–14.4]
Diseases of the genitourinary system (urolithiasis, pyelonephritis, kidney masses, prostate adenoma)	2	2.2 [0.3–7.7]	2	4.0 [0.5–13.7]	4	2.8 [0.8–7.1]
Perinatal CNS lesions	6	6.6 [2.5–13.8]	16	32.0 [19.5–46.7]	22	15.6 [10.4–22.6]
Previous heart surgery due to congenital heart diseases	3	3.3 [0.7–9.3]	2	4.0 [0.5–13.7]	5	3.5 [1.2–8.1]

(in 32.6, 27.6 and 15.6 % cases accordingly). Others were not so frequent, including acute disorders of cerebral circulation, previous heart surgery due to congenital heart diseases and diseases of the genitourinary system (in 8.5, 3.5 and 2.8 % cases accordingly) (Table 6). We established a statistically significant growth in frequency of respiratory diseases and diseases of the central nervous system among patients with HAP who spent more than 48 hours on AV than among those who spent less than 48 hours on it: from 26.4 to 44.0 and from 6.6 to 32.0 % accordingly ($\chi^2 = 4.6$ and 15.8, $p = 0.03$ and 0.001 accordingly). *RR* amounted to 1.7 (1.0–2.6) and 4.8 (2.0–11.6) accordingly. Therefore, respiratory diseases and diseases of the central nervous system are risk factors of HAP; this might be due to non-specific resistance being suppressed in such patients [13, 19].

We have established earlier that children and adults who are treated in cardiac surgery hospitals after all kinds of open and closed heart surgery may face the risk of hospital acquired purulent septic infections (PSIs) [20, 21]. HAP is more frequent but there can also be infections in areas of surgical interventions, infections of the urinary tracts, and sepsis. We have shown that hospital acquired PSIs, HAP in particular, primarily occur among children and adults being treated in cardiac surgery hospitals not due to an operation itself but due to consequent treatment in ICUs with its duration depending on a type of a performed operation. We have also revealed that the more time patients spend in ICUs, the longer such an epidemiologically significant procedure as AV lasts. The present work highlights a special role played by AV as a risk factor of developing HAP in patients treated in a cardiac surgery hospital.

Conclusions:

1. Most cases of hospital acquired pneumonia occur in patients who are treated in an intensive care unit at a cardiac surgery hospital after heart surgery. We have proven the role played by artificial ventilation as a leading risk factor that can cause pneumonia.

2. We have detected higher incidence rates among children treated in an intensive care unit at a cardiac surgery hospital than among adults. *Klebsiella pneumoniae* is established to be the primary infectious agent that causes pneumonia.

3. Background respiratory diseases and diseases of the central nervous systems are endogenous risk factors of developing hospital acquired pneumonia among patients treated in an intensive care unit at a cardiac surgery hospital.

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References

1. Svetlichnaya Y.S., Kolosovskaya E.N., Kaftireva L.A., Zueva L.P., Daryina M.G., Zakhvatova A.S. Hospital infection epidemic in the intensive care unit of a general hospital. *VICh-infektsiya i immunosupressii*, 2016, vol. 8, no. 4, pp. 60–65. DOI: 10.22328/2077-9828-2016-8-4-60-65 (in Russian).

2. Abdelrazik O.A., Salah Abdelazim M. Ventilator-associated pneumonia in adult intensive care unit prevalence and complications. *Egypt. J. Crit. Care Med.*, 2017, vol. 5, no. 2, pp. 61–63. DOI: 10.1016/j.ejccm.2017.06.001

3. Arefyeva L.I., Gorskaya E.M., Savostiyanova O.A., Senchenko O.R., Gabrieliyan N.I. The infectious complications of bacterial nature in cardio-vascular surgery. *Rossiiskii meditsinskii zhurnal*, 2013, no. 3, pp. 36–42 (in Russian).

4. Gelijns A.C., Moskowitz A.J., Acker M.A., Argenziano M., Geller N.L., Puskas J.D., Perrault L.P., Smith P.K. [et al.]. Management practices and major infections after cardiac surgery. *J. Am. Coll. Cardiol.*, 2014, vol. 64, no. 4, pp. 372–381. DOI: 10.1016/j.jacc.2014.04.052

5. Orlova O.A., Akimkin V.G., Chistova A.V., Efremova N.P. Epidemiological characteristics of infections associated with delivery of health care in surgical departments. *Epidemiologiya i infektsionnye bolezni*, 2014, vol. 19, no. 6, pp. 20–27 (in Russian).

6. Gelfand B.R., Belotserkovskiy B.Z., Milukova I.A., Gelfand E.B. Epidemiology and nosological structure of nosocomial infections in intensive care unit of multitype hospital. *Infektsii v khirurgii*, 2014, vol. 12, no. 4, pp. 24–36 (in Russian).

7. Ding C., Zhang Y., Yang Z., Wang J., Jin A., Wang W., Chen R., Zhan S. Incidence, temporal trend and factors associated with ventilator-associated pneumonia in mainland China: a systematic review and meta-analysis. *BMC Infect. Dis.*, 2017, vol. 17, no. 1, pp. 468. DOI: 10.1186/s12879-017-2566-7

8. Lobacheva G.V., Popov D.A., Rakhimov A.A., Kolesnikova E.A. IVL-assotsiirovannye pnevmonii v kardioreanimatsionnom otdelenii [Ventilator-associated pneumonia in the cardiac intensive care unit]. *Klinicheskaya fiziologiya krovoobrashcheniya*, 2014, no. 3, pp. 71–75 (in Russian).

9. O'Keefe S., Williams K., Legare J.-F. Hospital-acquired infections after cardiac surgery and current physician practices: a retrospective cohort study. *J. Clin. Med. Res.*, 2017, vol. 9, no. 1, pp. 10–16. DOI: 10.14740/jocmr2637w

10. Chiurazzi C., Motos-Galera A., Torres A. Early identification of ventilator-associated pneumonia causative pathogens: focus on the value of gram-stain examination. *Annual update in Intensive Care and Emergency Medicine 2015*. Springer, Charm, 2015, pp. 3–14. DOI: 10.1007/978-3-319-13761-2_1

11. Vijay G., Mandal A., Sankar J., Kapil A., Lodha R., Kabra S.K. Ventilator associated pneumonia in pediatric intensive care unit: incidence, risk factors and etiological agents. *Indian J. Pediatr.*, 2018, vol. 85, no. 10, pp. 861–866. DOI: 10.1007/s12098-018-2662-8

12. Papazian L., Klompas M., Luyt C.-E. Ventilator-associated pneumonia in adults: a narrative review. *Intensive Care Med.*, 2020, vol. 46, no. 5, pp. 888–906. DOI: 10.1007/s00134-020-05980-0

13. Chang L., Dong Y., Zhou P. Investigation on risk factors of ventilator-associated pneumonia in acute cerebral hemorrhage patients in intensive care unit. *Can. Respir. J.*, 2017, vol. 2017, pp. 7272080. DOI: 10.1155/2017/7272080

14. Zubair S., Ali H., Raza S.F., Warind J.A., Beg A.E., Bushra R. Assessment of frequency and transience rate for ventilator-associated pneumonia (VAP) in geriatric patients in tertiary care settings of Karachi, Pakistan. *J. Coll. Physicians Surg. Pak.*, 2018, vol. 28, no. 7, pp. 536–540. DOI: 10.29271/jcpsp.2018.07.536

15. Nozokomial'naya pnevmoniya u vzroslykh: Rossiiskie natsional'nye rekomendatsii [Hospital-acquired pneumonia in adults: Russian national guidelines]. In: Academician B.R. Gelfand ed. Moscow, MIA, 2016, 176 p. (in Russian).

16. Reilly J.S., Price L., Godwin J., Cairns S., Hopkins S., Cookson B., Malcolm B., Hughes G.J. [et al.]. Point prevalence survey of healthcare associated infections and antimicrobial use in European acute care hospitals – protocol version 4.3. *European Centre for Disease Prevention and Control*, 2012, Chapter 3, pp. 1–108.

17. Sergevnin V.I., Klyucharyova N.M. Pre-epidemic diagnosis of hospital-acquired purulent-septic infections morbidity. *Zdorov'e naseleniya i sreda obitaniya*, 2018, vol. 298, no. 1, pp. 27−29. DOI: 10.35627/2219-5238/2018-298-1-27-29 (in Russian).

18. Sergevnin V.I., Kudryavtseva L.G., Pegyshina O.G., Volkova E.O., Reshetnikova N.I. Group Incidence by Purulent-Septic Infections of Clebsiellous Etiology in Cardiosurgical Patients. *Epidemiologiya i vaktsinoprofilaktika*, 2020, vol. 19, no. 1, pp. 90–98. DOI: 10.31631/2073-3046-2020-19-1-90-98 (in Russian).

19. Jimenez-Trujillo I., Jimenez-Garcia R., de Miguel-Diez J., de Miguel-Yanes J.M., Hernandez-Barrera V., Mendez-Bailon M., Pérez-Farinós N., Salinero-Fort M.-Á. [et al.]. Incidence, characteristic and outcomes of ventilator-associated pneumonia among type 2 diabetes patients: an observational population-based study in Spain. *Eur. J. Intern. Med.*, 2017, no. 40, pp. 72–78. DOI: 10.1016/j.ejim.2017.01.019

20. Sergevnin V.I., Kudryavtseva L.G., Zolotukhina A.I. Frequency and Risk Factors of Purulent Septic Infection among Adults after Different Types of an Open Heart Operations. *Epidemiologiya i vaktsinoprofilaktika*, 2020, vol. 19, no. 5, pp. 34–40. DOI: 10.31631/2073-3046-2020-19-5-34-41 (in Russian).

Sergevnin V.I., Kudryavtseva L.G., Lazarkov P.V. Artificial ventilation as a risk factor causing hospital-acquired pneumonia (HAP) in patients treated in the intensive care unit of a cardiac surgery hospital. Health Risk Analysis, 2022, no. 1, pp. 97–103. DOI: 10.21668/health.risk/2022.1.11.eng

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Research article

ON ASSESSING RISKS OF DEVELOPING AND PROGRESSING NON-ALCOHOLIC FATTY LIVER DISEASE USING TNF-A, IL6, AND VEGF FACTORS AND POLYMORPHISMS OF THEIR GENES

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Our research aim was to develop a system for calculating risks of development and progression of non-alcoholic fatty liver disease (NAFLD). The system would be based on interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), vascular endothelial growth factor (VEGF) and TNF-α gene polymorphism in the region -308G/A (rs1800629), IL-6 in the region –174G/C (rs1800795), and VEGFA in the region –634G/C (rs2010963).

We examined 52 patients with NAFLD and 65 healthy donors. The examination involved estimating levels of cytokines TNF-α, IL-6 and VEGF in blood serum. We also studied the polymorphism of the TNF-α genes in the -308G/A region, IL-6 in the -174G/C region, and VEGFA in the -634G/C region.

Women aged from 32 to 54 years prevailed among patients with NAFLD (67 %). We established in this research that concentrations of the pro-inflammatory cytokines TNF-α, IL-6 and the level of VEGF in the blood serum were significantly higher in patients with NAFLD than in the reference group ($p = 0.03$; $p = 0.00003$ and $p = 0.001$ accordingly). This confirms an occurring inflammatory syndrome and endothelial dysfunction that are typical for this pathology. Patients with NAFLD tended to have the AA genotype of the TNF-α -308G/A gene (rs1800629) significantly more frequently than healthy donors ($p = 0.04$). Homozygote CC and allele C of the VEGFA gene (G-634C) in the position rs2010963 were significantly more often detected in the test group (patients with NAFLD) than in the reference one ($p = 0.02$ and $p = 0.01$ respectively). We didn't detect any statistically significant differences in the IL-6 gene polymorphism in the -174G/C (rs1800795) region in the analyzed groups. TNF-α -308G/A gene polymorphism correlated with activating production of TNF-α and IL-6 cytokines ($Ki = 0.588$; $p = 0.043$ and $Ki = 0.597$; $p = 0.04$, respectively), which can lead to developing immune-inflammatory syndrome in its carriers. When determining genetic profiles, we established that 51 % donors had low risks of NAFLD development whereas the risk was high for 75 % of patients with the disease.

The risk of developing NASP is associated with carrying the AA genotype of the TNF-α -308G/A gene and the CC genotype of the VEGFA -634G/C gene. Assessment of a genetic profile using these markers provides an opportunity to assess risks of developing NAFLD in healthy people and to predict its progression in patients with the disease.

Key words: *non-alcoholic fatty liver disease, cytokines, tumor necrosis factor alpha, interleukin-6, vascular endothelial growth factor, gene polymorphism.*

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Non-alcoholic fatty liver disease (NAFLD) holds the first rank place among liver pathologies [1]. The All-Russian study DIREG 2 established than more than a half adult population in the country had NAFLD and the disease was diagnosed in 80 % of them. According to some researchers, NAFLD is associated with metabolic syndrome in 95 % cases, most frequently as fatty hepatosis [2]. Some patients also suffer from developing inflammation in the liver as a complication of the disease (non-alcoholic steatohepatitis). Chronic inflammation leads to developing fibrosis and cirrhosis and makes for occurrence of liver cancer as well. All this calls for more profound examination of how NAFLD develops in order to determine risk factors causing the disease, including genetic ones.

According to some data, NAFLD is more frequently detected among women aged 40–50 years and men to women ratio is 1:3, though the disease can occur in any age group [3][1]. All-Russian study DIREG 1 with 30,754 people participating in it produced the following results: women with NAFLD accounted for 56 %. According to this study there were several prevailing risk factors that caused NAFLD including dyslipidemia (type II as per Fredrikson classification) detected in 75.9 % patients; hypertension, 69.9 %; and hypercholesterolemia, 68.8 % [4]. Some other studies discovered such risk factors causing NAFLD as male sex, age from 30 to 59, overweight and obesity (body mass index being higher than 25 kg/m^2), hyperglycemia, hypertriglyceridemia, and hypercholesterolemia [5].

There is no unified and well-explored mechanism of NAFLD development. The disease has multifactorial pathogenesis which includes the following processes: the main component is resistance to insulin and changes in the hormonal profile regarding hormones that regulate lipid metabolism, occurring hyperinsulinemia, activation of lipolysis in fat tissue, an increase in contents of free fatty acids, activated gluconeogenesis in the liver resulting in hyperglycemia, increased production of very low density lipoproteins and decreasing seizure of triglycerides with developing dyslipidemia, pro-inflammatory cytokines and free radicals becoming more active with developing inflammation in the liver. Ultimately all this leads to steatosis progressing into steatohepatitis and liver fibrosis which can later turn into cirrhosis [6].

Inflammation is a component in complicated pathogenesis of NAFLD development and progress. Its basic mediators are cytokines, the key ones being interleukin-6 (IL6) and tumor necrosis factor alpha (TNF-α). Apart from stimulating inflammation, these cytokines regulate apoptosis and necrosis of hepatocytes, exacerbate resistance to insulin and induce fibrosis as well [7].

According to several research works, TNF-α correlates with a degree of liver fat dystrophy and activates adhesive properties of endothelial cells [8–10]. Several authors established higher IL6 contents in blood of patients with NAFLD [11–13]. IL6 concentration in the liver correlated directly with inflammation and fibrosis intensity and contents of this cytokine in blood, especially when NAFLD was progressing [14].

Vascular endothelial growth factor (VEGF) activates production of collagen by astrocytes in the liver and neoangiogenesis mechanisms in case of inflammation. There were several examinations on rats with NAFLD and metabolic syndrome which established that endothelial dysfunction occurs prior to inflammation and developing fibrosis in the liver [15–18].

Recently, a lot of attention has been given to hereditary predisposition to NAFLD. A significant aspect here is polymorphism of genes

[1] Nealkogol'naya zhirovaya bolezn' pecheni: metodicheskie rekomendatsii [Non-alcoholic fatty liver disease: methodical guidelines]. In: G.I., Storozhakov ed. Moscow, N.I. Pirogov's Russian National Research Medical University Publ., 2015, 42 p.

that regulate immune inflammatory processes [19]. Cytokine genes are highly polymorphic. Nevertheless, there are still rather few studies focusing on examining an association between polymorphism of TNF-α and IL6 genes and developing NAFLD and they tend to produce somewhat controversial results. It can probably be due to certain peculiarities related to how frequencies of alleles and genotypes are distributed in a population; there could be differences explained by a region, race, or a different methodical approach.

For example, a ratio of allele frequencies (A to G) as per -308G>A polymorphic marker of TNF gene amounts to 1.2–7 % among people living in the Asian-Pacific region; about 3.3 %, among healthy people in China; and it varies from 12 to 24 % in some other populations. AA genotype as per this gene doesn't occur in people living in the Asian-Pacific region whereas it is usually detected in 1.2–7.9 % cases among people from other populations [20].

There were some research works focusing on determining a contribution made by mutations in the promoter part of IL6 gene to developing liver pathologies; however, they produced rather controversial results. According to data available in literature, frequency of allele C as per -174G>C marker of IL6 gene was significantly higher among Europeans suffering from non-alcoholic steatohepatitis and hepatocellular carcinoma than among healthy people [21, 22]. It was also discovered that having allele C as per -174G>C polymorphism of IL6 gene was associated with developing non-alcoholic steatohepatitis in the Russian population [23]. However, another research didn't establish any correlation between this polymorphism and developing pathology in the liver [24].

Our research aim was to develop a system for calculating risks of developing and progressing non-alcoholic fatty liver disease (NAFLD) based on interleukin-6 (IL6), tumor necrosis factor alpha (TNF-α), vascular endothelial growth factor (VEGF), and polymorphism of TNF-α gene in -308G/A (rs1800629) region, IL6 gene in -174G/C (rs1800795) region, and VEGFA gene in -634G/C (rs2010963) region.

Materials and methods. We examined 52 patients with non-alcoholic fatty liver disease (NAFLD) in its clinical form; 35 of them were women (67 %) and 17 were men (33 %). Patients' average age amounted to 43.0 ± 11.1 years. Liver steatosis was established by an ultrasound examination. We excluded patients with alcoholic or drug-induced fatty liver disease confirmed by data taken from their clinical case histories; we also excluded patients with non-alcoholic steatohepatitis that was diagnosed by estimating transaminase levels. The analyzed samplings were similarly susceptible to factors that could cause NAFLD development. Prevalence of women in our random sampling made up of people with NAFLD living in Perm region is comparable with data obtained in much larger All-Russian studies [3, 4][1].

Our reference group consisted of 65 practically healthy people that were comparable with the test group as per sex and age; they didn't have either liver pathology or any other pathology associated with metabolic syndrome. All participants were provided with the comprehensive information about the study and they all gave their voluntary informed written consent to take part in it.

We determined contents of TNF-α, IL6 and VEGF cytokines in blood serum of 15 practically healthy people and 40 patients with NAFLD by ELISA tests using "Stat-Fax-2100" microplate reader (USA) and reagent sets produced by "Vector-Best" LLC (Novosibirsk).

We examined polymorphism of TNF-α gene in -308G/A region, IL6 gene in -174G/C region, and VEGFA gene in -634G/C region in 52 patients with NAFLD and 65 healthy donors using "CFX-96" real-time PCR detection system (Bio-Rad Laboratories, Inc., USA) and "SNP-Screen" allele-specific PCR (Syntol LLC, Moscow).

To determine risks of NAFLD development and progression, we estimated genetic profiles of

patients and donors depending on frequencies of genotypes and alleles of examined gene polymorphisms according to a score estimate scale developed specifically for this study.

Score estimates:

0 means that a patient is homozygous as per protective alleles regarding all three polymorphisms;

1 means a patient is heterozygous as per one of two genes;

2 means a patient is heterozygous as per two genes;

3 means a participant has two risk alleles as per one gene and is homozygous as per protective alleles in another gene;

4 means that a participant has both risk alleles as per one gene but he or she is heterozygous as per another gene;

5 means a participant is homozygous as per risk alleles of TNF-α (AA) / VEGFA (CC) regarding both genes.

According to this scale, when healthy donors scored 0–1, risk of developing NAFLD was low; 2–3 scores, moderate; 4–5 scores, high. When patients with NAFLD scored 0–1, it meant a risk of the disease progression was low; 2–3 scores, moderate; 4–5 scores, high.

All the data were statistically analyzed using Statistica 7.0 software package. Quantitative parameters were given as median and interquartile range (Q1–Q3). Significance of difference between two independent groups was estimated using Mann – Whitney test. We applied Spearman's correlation coefficient (r) with determining the significance level to estimate correlations. We applied χ^2 technique to describe frequency ratios for genotypes and alleles of the examined gene polymorphisms. Contingency tables and Pearson contingency coefficients $(Ki)^2$ were used to establish any dependence between examined qualitative attributes. Differences between the samplings were considered to be authentic at $p < 0.05$.

Results and discussion. We established that patients with NAFLD had significantly higher concentrations of TNF-α and IL6 and VEGF level in their blood serum than their counterparts from the reference group ($p = 0.03$, $p = 0.00003$, and $p = 0.001$, respectively) (Table 1).

Higher contents of the examined pro-inflammatory cytokines in blood of patients with NAFLD mean that inflammation is already developing and it was also mentioned as a typical NAFLD sign by some other authors [8, 11–13]. TNF-α authentically correlated with IL6 concentration ($r = 0.54$; $p = 0.0001$).

Growing VEGF concentration in blood of patients with NAFLD can indicate that endothelial dysfunction is developing against this pathology. Our data are well in line with results produced by several other studies that confirmed occurring endothelial dysfunction against liver steatosis by not only biochemical but also functional techniques [25, 26].

Table 1

Concentrations of TNF-α, IL6 and VEGF cytokines in the reference group and in patients with NAFLD (*Me*, 25 and 75 percentiles)

Parameter	Reference group ($n = 15$)	Patients with NAFLD ($n = 40$)	p
TNF-α, pg/ml	0 (0; 0.02)	1.1 (0; 3.15)	0.03*
IL6, pg/ml	0 (0; 0)	0.9 (0; 2.2)	0.0003*
VEGF, pg/ml	86.65 (10.7; 132.4)	184.6 (94.7; 291.6)	0.001*

Note: p is significance of differences, * means differences are statistically significant.

[2] Shelud'ko V.S., Podluzhnaya M.Ya. Teoreticheskie osnovy meditsinskoi statistiki: metodicheskie rekomendatsii [Theoretical grounds of medical statistics: methodical guidelines]. Perm, 2001, 36 p. (in Russian).

Table 2

Frequency of allele types of TNF-α gene in -308G/A (rs1800629) region, IL6 gene in -174G/C (rs1800795) region, and VEGFA gene in -634G/C (rs2010963) region in patients with NAFLD and healthy donors

Genotype / gene alleles		Donors (n = 65) % ± m	NAFLD (n = 52) % ± m	*OR*	p
TNF-α -308G/A	GG, %	21.54 ± 5.1	13.46 ± 4.73	0.57	0.25
	GA, %	78.46 ± 5.1	78.85 ± 5.66	1.02	0.96
	AA, %	0 ± 0	7.69 ± 3.69	1.76	0.04*
Alleles	G-allele, %	58.46 ± 4.32	52.88 ± 4.89	0.72	0.58
	A-allele, %	39.23 ± 4.28	47.12 ± 4.89	1.38	0.58
IL6 -174G/C	GG, %	32.31 ± 5.8	28.85 ± 6.28	0.85	0.69
	GC, %	52.31 ± 6.2	51.92 ± 6.93	0.98	0.97
	CC, %	15.38 ± 4.47	19.23 ± 5.47	1.31	0.59
Alleles	G-allele, %	58.46 ± 4.32	54.81 ± 4.88	0.86	0.58
	C-allele, %	41.54 ± 4.32	45.19 ± 4.88	1.16	0.58
VEGFA -634G/C	GG, %	35.38 ± 5.93	19.23 ± 5.47	0.43	0.04*
	GC, %	53.85 ± 6.18	51.92 ± 6.93	0.93	0.84
	CC, %	10.77 ± 3.85	28.85 ± 6.28	3.36	0.02*
Alleles	G-allele, %	62.31 ± 4.25	45.19 ± 4.88	0.50	0.01*
	C-allele, %	37.69 ± 4.25	54.81 ± 4.88	2.00	0.01*

Note: *OR* is odds ratio, p is significance of differences, * means differences are statistically significant.

52 patients with NAFLD and 65 healthy donors had practically the same frequency of GG genotype of TNF-α gene, 13.46 % and 21.54 % respectively (χ^2 = 3.23; p = 0.25; *OR* = 0.57) and GA genotype, 78.85 % and 78.46 % respectively (χ^2 = 1.28; p = 0.96; *OR* = 1.02), of TNF-α gene polymorphism in rs1800629 region. We didn't detect any significant differences regarding distribution of alleles G and A of TNF-α gene in -308G/A region between the examined groups (p = 0.58 and p = 0.58, respectively) (Table 2).

However, AA genotype of TNF-α gene in -308G/A region was detected significantly more frequently in patients with NAFLD than among healthy people (7.69 % and 0 % respectively; χ^2 = 6.05; p = 0.04; *OR* = 1.76) and similar results were also discovered by other researchers among people living in the Asian-Pacific region [20]. Probably, carrying AA genotype of TNF-α gene (rs1800629) plays a certain role in hereditary predisposition to NAFLD.

We didn't detect any significant differences as per IL6 gene polymorphism in -174G/C (rs1800795) region. GC genotype prevailed in both groups and was detected in 52.31 % and 51.92 % respectively (χ^2 = 0.36; p = 0.97; *OR* = 0.98). Alleles G and C also occurred with the same frequency (p = 0.58 and p = 0.50 respectively) (Table 3). Other researchers also pointed out that there was no correlation between this polymorphism and developing NAFLD [24].

When examining allele variants of VEGFA (G-634C) gene in rs2010963 region, we established GC genotype in 35.38 % of healthy people (χ^2 = 7.71; p = 0.04). However, CC homozygote was detected among patients with NAFLD significantly more frequently since it was highly probable in 28.85 % cases (*OR* = 3.36) whereas it was detected only in 10.77 % of healthy people (χ^2 = 6.18; p = 0.02). Allele C of VEGFA gene in -634G/C region was detected in 54.81 % cases among patients with NAFLD and this was significantly higher than among healthy

Table 3

Genetic profiles of healthy donors and patients with NAFLD

Groups / scores	0	1	2	3	4	5
Donors, % (*n*)	9 % (6)	42 % (27)	35 % (23)	3 % (2)	11 % (7)	–
NAFLD, % (*n*)	2 % (1)	23 % (12)	40 % (21)	4 % (2)	29 % (15)	2 % (1)

donors (χ^2 = 6.83; p = 0.01; OR = 2.00) (see Table 2).

We didn't detect any significant differences between men and women with NAFLD regarding frequencies of genes. Since the examined genes are located in autosomes (and not in the sex ones) and are inherited regardless of a sex, we assume that sex as a factor doesn't produce any significant effects on risks of developing NAFLD.

Therefore, we can assume allele C in the locus of VEGFA (G-634C) gene to be a predictor of developing NAFLD. We showed its significance in the process of viral liver diseases becoming chronic in our previous works [27].

Consequently, a risk of developing NAFLD is associated with carrying AA genotype of TNF-α -308G/A gene and CC genotype of VEGFA -634G/C gene.

When estimating dependences with contingency tables, we discovered a correlation between polymorphism of TNF-α in -308G/A region and activated production of TNF-α and IL6 cytokines in patients with NAFLD (Ki = 0.558; p = 0.043 and Ki = 0.597; p = 0.042, respectively). This can result in progressing immune-inflammatory syndrome in its carriers.

To determine risks of NAFLD development and progressing, we estimated genetic profiles of healthy donors and patients with the disease depending on frequencies of genotypes and alleles of TNF-α gene in -308G/A region and VEGFA gene in -634G/C region. Score estimates were given using our own scale. According to this scale, if healthy donors scored 0–1, then a risk of developing NAFLD was low; 2–3 scores, a risk was moderate; 4–5 scores meant a high risk. When patients with NAFLD scored 0–1, a risk that the disease would progress further was low; 2–3 scores meant a moderate risk; 4–5 scores meant a risk was high.

More than a half donors (51 %) had low risks of developing NAFLD (0–1 scores); 38 %, moderate (2–3 scores); 11 %, high (4 scores) (Table 3).

25 % of patients had low risks that NAFLD would progress further (0–1 scores); almost half of them (44 %) had moderate risks (2–3 scores), and one third (31 %) had high risks (4–5 scores) accordingly to the scale.

Conclusion. Women aged from 32 to 54 years prevail among patients with NAFLD (67 %). Patients with NAFLD have high concentrations of pro-inflammatory cytokines TNF-A and IL6, as well as elevated concentrations of VEGF which means there is inflammation and endothelial dysfunction developing against the pathology.

Homozygote AA in -308G/A region of TNF-α gene was significantly more frequently detected among patients with NAFLD than among healthy donors.

Having examined combinations of allele variants in -634G/C VEGFA gene in rs2010963 region, we established that homozygote CC b allele C were detected significantly more frequently in patients with NAFLD than in practically healthy people.

We didn't detect any authentic differences with respect to genotypes and alleles of IL6 gene polymorphism in -174G/C (rs1800795) region.

Consequently, a risk of developing NAFLD is associated with carrying AA genotype of TNF-α-308G/A gene and CC genotype of VEGFA -634G/C gene, especially when it is combined with high contents of pro-inflammatory cytokines.

The suggested approaches which involve analyzing genetic profiles as per TNF-α gene in -308G/A region and VEGFA gene in -634G/C region provide an opportunity to perform early non-invasive diagnostics and to determine whether there are any risks of developing NAFLD for healthy people (risks are considered to be high if the score estimate is 4–5) and risks of probable further NAFLD progressing for patients with the disease (score estimates equal to 4–5 men that risks of the disease progressing are high). These approaches can be applied in medical practice.

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References

1. Chalasani N., Younossi Z., Lavine J.W., Diehl A.M., Brunt E.M., Cusi K., Charlton M., Sanyal A.J. The diagnosis and management of non-alcoholic fatty liver disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and American Gastroenterological Association. *Hepatology*, 2012, vol. 55, no. 6, pp. 2005–2023. DOI: 10.1002/hep.25762

2. Kurskaya A.G., Tchesnokova L.V., Troshina I.A., Goncharova M.N., Petrov I.M. The structure of the liver lesions in patients with obesity and metabolic syndrome. *Meditsinskaya nauka i obrazovanie Urala*, 2013, vol. 14, no. 1 (73), pp. 34–37 (in Russian).

3. Pavlov Ch., Bakulin I. Nealkogol'nyi steatogepatit: klinicheskie osobennosti i printsipy lecheniya [Non-alcoholic steatohepatitis: clinical features and treatment principles]. *Vrach*, 2007, no. 10, pp. 24–28 (in Russian).

4. Drapkina O.M., Ivashkin V.T. Epidemiologicheskie osobennosti nealkogol'noi zhirovoi bolezni pecheni v Rossii (rezul'taty otkrytogo mnogotsentrovogo prospektivnogo issledovaniya-nablyudeniya DIREG L 01903) [Epidemiologic features of non-alcoholic fatty liver disease in Russia (Results of open multicenter prospective follow-up study DIREG L 01903)]. *RZhGGK*, 2014, vol. 24, no. 4, pp. 32–38 (in Russian).

5. Komova A.G., Maevskaya M.V., Ivashkin V.T. Printsipy effektivnoi diagnostiki diffuznykh zabolevanii pecheni na ambulatornom etape [Principles of effective diagnostics of diffuse liver diseases at out-patient stage]. *RZhGGK*, 2014, vol. 24, no. 5, pp. 36–41 (in Russian).

6. Ivashkin V.T., Maevskaya M.V., Pavlov Ch.S., Tikhonov I.N., Shirokova E.N., Bueverov A.O., Drapkina O.M., Shul'pekova Yu.O. [et al.]. Klinicheskie rekomendatsii po diagnostike i lecheniyu nealkogol'noi zhirovoi bolezni pecheni Rossiiskogo obshchestva po izucheniyu pecheni i Rossiiskoi gastroenterologicheskoi assotsiatsii [Clinical guidelines for the diagnosis and treatment of non-alcoholic fatty liver disease of the Russian Society for the Study of the Liver and the Russian Gastroenterological Association]. *RZhGGK*, 2016, vol. 26, no. 2, pp. 24–42 (in Russian).

7. Braunesreuther V., Viviani G.L., Mach F., Montecucco F. Role of cytokines and chemokines in non-alcoholic fatty liver disease. *World J. Gastroenterol.*, 2012, vol. 18, no. 8, pp. 727–735. DOI: 10.3748/wjg.v18.i8.727

8. Khan R., Quaiser S., Haque S.F., Ahmad A. TNF-α is an inflammatory marker of cardiovascular risks in non-alcoholic fatty liver disease. *JCDR*, 2011, vol. 5, no. 6, pp. 1237–1240.

9. Yubitskaya N.S., Antonyuk M.V., Veremchuk L.V., Khodosova K.K. Role of tumor necrosis factor in the development of metabolic syndrome. *Terapevticheskii arkhiv*, 2009, vol. 81, no. 11, pp. 59–63 (in Russian).

10. Sanyal A.J., Banas C., Sargeant C., Luketic V.A., Sterling R.K., Stravitz R.T., Shiffman M.L., Heuman D. [et al.]. Similarities and differences in outcomes of cirrhosis due to nonalcoholic steatohepatitis and hepatitis C. *Hepatology*, 2006, vol. 43, no. 4, pp. 682–689. DOI: 10.1002/hep.21103

11. Haukeland J.W., Damås J.K., Konopski Z., Løberg E.M., Haaland T., Goverud I., Torjesen P.A., Birkeland K. [et al.]. Systemic inflammation in nonalcoholic fatty liver disease is characterized by elevated levels of CCL2. *J. Hepatol.*, 2006, vol. 44, no. 6, pp. 1167–1174. DOI: 10.1016/j.jhep.2006.02.011

12. Kugelmas M., Hill D.B., Vivian B., Marsano L., McClain C.J. Cytokines and NASH: a pilot study of the effects of lifestyle modification and vitamin E. *Hepatology*, 2003, vol. 38, no. 2, pp. 413–419. DOI: 10.1053/jhep.2003.50316

13. Abiru S., Migita K., Maeda Y., Daikoku M., Ito M., Ohata K., Nagaoka S., Matsumoto T. [et al.]. Serum cytokine and soluble cytokine receptor levels in patients with nonalcoholic steatohepatitis. *Liver Int.*, 2006, vol. 26, no. 1, pp. 39–45. DOI: 10.1111/j.1478-3231.2005.01191.x

14. Wieckowska A., Papouchado B.G., Li Z., Lopez R., Zein N.N., Feldstein A.E. Increased hepatic and circulating interleukin-6 levels in human nonalcoholic steatohepatitis. *Am. J. Gastroenterol.*, 2008, vol. 103, no. 6, pp. 1372–1379. DOI: 10.1111/j.1572-0241.2007.01774.x

15. LeCouter J., Moritz D.R., Li B., Phillips G.L., Liang X.H., Gerber H.P., Hillan K.J., Ferrara N. Angiogenesis-independent endothelial protection of liver: role of VEGF. *Science*, 2003, vol. 299, no. 5608, pp. 890–893. DOI: 10.1126/science.1079562

16. Yang L., Kwon J., Popov Y., Gajdos G.B., Ordog T., Brekken R.A., Mukhopadhyay D., Schuppan D. [et al.]. Vascular endothelial growth factor promotes fibrosis resolution and repair in mice. *Gastroenterology*, 2014, vol. 146, no. 5, pp. 1339–1350.e1. DOI: 10.1053/j.gastro.2014.01.061

17. Drapkina O.M., Deeva T.A., Ivashkin V.T. Evaluation of endothelial function and estimation of the degree of apoptosis in patients with metabolic syndrome and non-alcoholic fatty liver disease. *Terapevticheskii arkhiv*, 2015, vol. 87, no. 5, pp. 76–83. DOI: 10.17116/terarkh201587576-83 (in Russian).

18. Bosch J., Abraldes J.G., Fernández M., García-Pagán J.C. Hepatic endothelial dysfunction and abnormal angiogenesis: New targets in the treatment of portal hypertension. *J. Hepatol.*, 2010, vol. 53, no. 3, pp. 558–567. DOI: 10.1016/j.jhep.2010.03.021

19. Lewis J.R., Mohanty S.R. Nonalcoholic fatty liver disease: a review and update. *Dig. Dis. Sci.*, 2010, vol. 55, no. 3, pp. 560–578. DOI: 10.1007/s10620-009-1081-0

20. Zhou Y.-J., Li Y.-Y., Nie Y.-Q., Yang H., Zhan Q., Huang J., Shi S.-L., Lai X.-B., Huang H.-L. Influence of polygenetic polymorphisms on the susceptibility to nonalcoholic fatty liver disease of Chinese people. *J. Gastroenterol. Hepatol.*, 2010, vol. 25, no. 4, pp. 772–777. DOI: 10.1111/j.1440-1746.2009.06144x

21. Carulli L., Canedi I., Rondinella S., Lombardini S., Ganazzi D., Fargion S., De Palma M., Lonardo A. [et al.]. Genetic polymorphisms in non-alcoholic fatty liver disease: interleukin-6-174G/C polymorphismis associated with non-alcoholic steatohepatitis. *Dig. Liver Dis.*, 2009, vol. 41, no. 11, pp. 823–828. DOI: 10.1016/j.dld.2009.03.005

22. Giannitrapani L., Soresi M., Giacalone A., Campagna M.E., Marasà M., Cervello M., Marasà S., Montalto G. IL-6-174G/C polymorphism and IL-6 serum levels in patients with liver cirrhosis and hepatocellular carcinoma. *OMICS*, 2011, vol. 15, no. 3, pp. 183–186. DOI: 10.1089/omi.2010.0093

23. Kurbatova I.V., Dudanova O.P., Topchieva L.V. Rol' polimorfizma rs4537545 (C>T) gena IL6R v razvitii nealkogol'nogo steatogepatita [The role of the rs4537545 (C>T) polymorphism of the IL6R gene in the development of non-alcoholic fatty liver disease]. *Meditsinskii akademicheskii zhurnal*, 2016, vol. 16, no. 4, pp. 59–61 (in Russian).

24. Cengiz M., Yasar D.G., Ergun M.A., Akyol G., Ozenirler S. The role of interleukin-6 and interleukin-8 gene polymorphisms in non-alcoholic steatohepatitis. *Hepat. Mon.*, 2014, vol. 14, no. 12, pp. e24635. DOI: 10.5812/hepatmon.24635

25. Pivtorak E.V. Narusheniya funktsii endoteliya u bol'nykh nealkogol'noi zhirovoi bolezn'yu pecheni [Endothelial dysfunction in patients with non-alcoholic fatty liver disease]. *Eksperimental'naya i klinicheskaya gastroenterologiya*, 2014, vol. 102, no. 2, pp. 63a (in Russian).

26. Cetindaglı I., Kara M., Tanoglu A., Ozalper V., Aribal S., Hancerli Y., Unal M., Ozarı O. [et al.]. Evaluation of endothelial dysfunction in patients with nonalcoholic fatty liver disease: Association of selenoprotein P with carotid intima-media thickness and endothelium-dependent vasodilation. *Clin. Res. Hepatol. Gastroenterol.*, 2017, vol. 41, no. 5, pp. 516–524. DOI: 10.1016/j.clinre.2017.01.005

27. Bulatova I.A. Vaskuloendotelial'nyi faktor rosta i polimorfizm gena VEGF (rs2010963) v patogeneze khronicheskogo virusnogo gepatita C [Vasculoendothelial growth factor and VEGF gene polymorphism (rs2010963) in the pathogenesis of chronic viral hepatitis C]. *Sovremennye problemy nauki i obrazovaniya*, 2013, no. 6. Available at: http://www.science-education.ru/113-11340 (07.02.2021) (in Russian).

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Research article

ON DETECTING OMIC-MARKERS OF NEGATIVE EFFECTS ASSOCIATED WITH COMBINED AEROGENIC EXPOSURE TO ALUMINUM AND FLUORIDE COMPOUNDS

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At present, it is relevant to study simultaneous combined impacts exerted by chemicals on developing adverse health effects. It is also becoming vital to search for molecular indicators of adverse effects with the altered expression level. This alteration makes it possible to determine peculiarities of molecular and cellular pathogenesis mechanisms regarding a number of non-communicable diseases under exposure to a mixture of chemicals.

Our research goal was to comparatively analyze and identify identical omic-markers of adverse effects under experimental and actual combined aerogenic exposure to aluminum and fluoride compounds. We substantiated molecular markers of prenosological changes by sequential implementation of an algorithm which included identifying altered proteins and peptides in blood plasma which were identical both under experimental and actual exposure; detecting and quantifying cause-effect relations between identical proteins and peptides and concentrations of aluminum and fluoride ion in urine.

The research results indicate that long-term combined aerogenic exposure to aluminum and fluoride compounds in low average daily doses (0.0005 mg/(kg·day) and 0.002 mg/(kg·day) accordingly) causes elevated concentrations of aluminum (by 2.8 times higher) and fluoride-ion (by 1.8 times higher) in exposed children's urine. This fact is verified by experimental research with its focus on combined exposure to the examined chemicals. We were able to substantiate identical omic-markers, J-chain of immunoglobulin and Kelch-like protein 4 (KLHL4 gene), under simultaneous exposure to aluminum and fluoride compounds both under experimental and actual combined aerogenic exposure. We proved a cause-effect relation between levels of identical proteins and concentrations of aluminum and fluoride ion in urine under simultaneous exposure to the mixture of the

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examined chemicals. Identified protein markers in blood plasma give an opportunity to predict future adverse effects including developing immunoglobulins A and M deficiency with subsequent humoral immunity failure when J-chain of immunoglobulin is expressed; occurring sclerotic and inflammatory changes in vascular walls when Kelch-like protein 4 is expressed. These predicted adverse effects can be estimated as resulting from simple summated (additive) toxic impacts exerted by aluminum and fluoride under simultaneous combined aerogenic exposure to both chemicals

Key words: *aluminum and fluoride ion in urine, risk of adverse effects, isolated and combined exposure, blood plasma proteomic profile, immune system, cardiovascular system, immunoglobulin J-chain and Kelch-like protein 4.*

At present, there is a significant trend in providing chemical safety in the Russian Federation and all over the world as well. This trend involves assessing adverse health effects produced by combined exposure to a mixture of contaminants even if each of them is hardly toxic when introduced separately. This aspect is outlined in guidelines issued by the World Health Organization (WHO) and the International Program on Chemical Safety (IPCS) [1, 2]. Nowadays people are often exposed to combined impacts exerted by a wide range of chemicals occurring in all media, ambient air included [3]. According to data provided by the WHO, ambient air pollution is a basic risk factor causing some non-communicable diseases, primarily, respiratory diseases, diseases of the cardiovascular and nervous systems [4]. A major contribution to ambient air pollution is made by industries, especially in places where a lot of industrial enterprises are concentrated. In some regions large metallurgical enterprises are located which mostly deal with aluminum production. In such regions ambient air contamination primarily occurs due to aluminum and fluoride compounds typical for such productions being introduced into the atmosphere, predominantly in gas and dust emissions. Long-term environmental aerogenic exposure to these compounds can result in damage to cellular membranes increasing their permeability; these chemicals can bind to proteins in blood and inhibit many enzyme systems and this can ultimately lead to various pathological changes in mechanisms which support homeostasis [5–7].

Examination of a proteomic blood plasma profile is a promising trend in research which provides an opportunity to effectively identify molecular and cellular mechanisms of changes in homeostasis caused by exposure to adverse risk factors. Identification, quantification and changes in levels of proteins (omic-markers) expressed in cellular and tissue structures under exposure to adverse risk factors, chemical ones included, are vital challenges in examining development of certain respiratory diseases, circulatory diseases, diseases of the nervous system etc. [8, 9]. Experimental research conducted on biological test models is a significant trend in molecular profiling aimed at searching for protein markers of negative effects, determining mechanisms and nature of interactions between chemical exposure factors which produce these negative effects both under separate and combined exposure [10]. Any changes in protein profiles which were determined by experiments should be verified with results produced by full-scale observations. This secures greater precision and objectivity of substantiated molecular protein markers. Foreign and domestic scientific data on alterations in peptides and genes coding their expression under exposure to a mixture of chemicals are rather controversial. Results produced by several experimental research works indicate that fluoride, when introduced separately, inhibits metal-containing enzymes and aluminum, in its turn, inhibits enzymes which are involved into energy metabolism in a cell [11]. Exposure to a mixture of these two chemicals makes the damage reverse and the chemicals inhibit each other's enzymes; this indicates that their toxic effects are antagonistic. Results produced by some other foreign studies show that mixed aluminum and fluoride act in the same way as they interact with the bilipid layer in cellular membranes, interfere with ion transportation, and induce conformation changes in guanosine triphosphate (GTP) which results in artificial activation of

guanosine diphosphate (GDP) and related Ras-proteins[1] [12–14]. These proteins are responsible for transferring signals from the extracellular space and participate in regulation of cellular proliferation[1].

Bearing in mind these controversial data on examining simultaneous combined exposure to different chemicals and its effects on the body, it seems advisable to search for molecular targets (proteins). Changes in their expression can be used as a tool for early prenosologic detection of non-communicable diseases. We can state that it is vital to establish relevant changes in proteins and peptides in a proteomic blood plasma profile in order to predict risks of developing adverse health effects produced by combined aerogenic exposure to chemical risk factors, including fluoride and aluminum compounds, both in experimental and actual conditions.

Our research goal was to comparatively analyze and identify identical omic-markers of negative effects both under experimental and actual combined aerogenic exposure to aluminum and fluoride compounds simultaneously.

Materials and methods. Our research objects were proteomic blood plasma profiles and protein peptides in children and experimental animals under combined exposure to aluminum and fluoride compounds.

We conducted our experiments on female Wistar rats, 12 animals overall. They were divided into 4 groups, 3 animals in each. Group No. 1 (test) was exposed separately to a standard sample (SS) of fluoride-ion in a dose equal to 20 mg/kg of body weight; Group No. 2 (test) was exposed separately to aluminum suspension based on isotonic sodium chloride solution in a dose equal to 1.67 mg/kg of body weight; Group No. 3 (test) was under combined exposure to a mixture of fluoride-ion and aluminum in doses outlined above; Group No. 4 was a control, animals were kept under the same conditions as three other groups but they were not exposed to the examined chemicals. The experimental exposures were one-time and intraperitoneal. Chemical doses introduced into experimental animals were equivalent to an actual aerogenic exposure allowing for the duration of exposure to chemicals, body weight, a period of exposure averaging, and species-related peculiarities.. Blood samples of the experimental animals were taken 24 hours after the exposure from the sublingual vein in a volume equal to 3 cm^3; urine samples were taken 24 hours after the exposure during one day in a DXL-D metabolic cage (3W Fengshi, China).

All the experiments conformed to 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.

We performed profound screening examinations of 35 children aged 4–7 years. 25 children who underwent long-term combined aerogenic exposure to aluminum compounds (in a concentration equal to 0.0005 mg/(kg·day)) and fluoride compounds (0.002 mg/(kg·day)) were included into the test group. Other 10 children were not exposed to the examined chemicals and were included into the reference group. Children were included into the test group as per such a criterion as elevated aluminum and fluoride-ion concentrations in urine; children in the reference group had the examined chemicals in their urine in concentrations corresponding to minimal or reference values[2].

All the children were examined in conformity with the ethical principles stated in the WMA Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, 2013) and the examinations were approved by the Committee on the biomedical ethics of the Federal Scientific Center for

[1] Heterotrimeric G-Protein Signaling at Atomic Resolution. *Handbook of Cell Signaling, Three-Volume Set*. In: R. Bradshaw, E. Dennis eds., 2009, 2nd ed., chapter 198, pp. 165–1619.

[2] Tits N.U. Klinicheskoe rukovodstvo po laboratornym testam [Clinical Guide on laboratory tests]. Moscow, YuNIMED-press, 2003, 960 p. (in Russian).

Medical and Preventive Health Risk Management Technologies. Legal representatives of all the participating children gave their informed voluntary consent to this participation. The conducted study didn't infringe on the rights of participating human subjects, didn't put their welfare in any danger and didn't cause any harm to their health.

Urine was analyzed to determine aluminum and fluoride-ion in it according to the methodical guidelines[3] using an ion-selective electrode with I-160M laboratory ionometer ("Antech" LLC, Belarus) and Agilent 7500cx mass spectrometer (Agilent Technologies Inc., USA) (by T.S. Ulanova, Doctor of Biological Sciences and Head of the Department for Chemical and Analytical Research Techniques).

An algorithm which we applied to examine proteomic blood plasma profiles of children and experimental animals included several stages: taking samples; two-dimensional gel electrophoresis in polyacrylamide gel[4]; analysis of two-deminsional electrophoresis charts; spotting out significant protein stains as per their intensity. The subsequent mass-spectrometry analysis performed with UltiMate 3000 chromatographer (Germany) and ABSciex 4000 QTRAP tandem mass spectrometer with Nanospray 3 ion source (Canada) involved determining amino acid sequences of individual protein fragments, protein identification, and analysis of UniProt database with sampling as per Homo Sapience and Rattus norvegicus taxon. We determined genes which identified proteins corresponded to using HGNC database of human gene name[5].

Indicator values established in exposed children were comparatively estimated against the same indicators in non-exposed children; indicator values established in experimental animals in test groups were comparatively analyzed against the same values in the control. The research results are given as a simple mean ($\bar{X}$), standard error of mean (*SEM*) and standard deviation (*SD*). We applied Mann – Whitney test ($U \leq U_{cr}$) to check whether intergroup differences in variables were statistically significant with the significance level fixed as $p \leq 0.05$. All the data were statistically analyzed using Statistica 10 software package.

Omic-markers of negative effects in children which were associated with combined exposure to the examined chemicals were substantiated by the step-by-step implementation of an algorithm including the following: identifying identical proteins and peptides in blood plasma profiles under experimental and actual exposure; determining and quantifying cause-effect relations between identical proteins and peptides and aluminum and fluoride-ion concentrations in urine; predicting adverse effects based on analyzing data on molecular functions and biological roles played by identified peptides. We tested whether the resulting models were authentic and relevant using Fischer's test ($F \geq 3.96$) and determination coefficient (R^2) with the statistical significance being $p \leq 0.05$.

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[3] MUK 4.1.773-99. Kolichestvennoe opredelenie ionov ftora v moche s ispol'zovaniem ionselektivnogo elektroda: utv. Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii G.G. Onishchenko 06.07.1999 [Quantitative determination of fluoride ions in urine using ion-selective electrode: approved by G.G. Onishchnko, the RF Chief Sanitary Inspector on July 06, 1999]. Moscow, The Federal Center for State Sanitary Epidemiologic Surveillance of the RF Public Healthcare Ministry, 2000 (in Russain); MUK 4.1.3589-19. Izmerenie massovoi kontsentratsii alyuminiya v biologicheskikh sredakh (krov', mocha) metodom mass-spektrometrii s induktivno svyazannoi plazmoi: utv. Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii 08.11.2019 [Measurement of aluminum mass concentration in biological media (blood and urine) by mass spectrometry with inductively coupled plasma: approved by the RF Chief Sanitary Inspector on November 08, 2019]. Moscow, The Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2020 (in Russain).

[4] PROTEAN i12 IEF System. Instruction Manual. Available at: https://www.bio-rad.com/webroot/web/pdf/lsr/literature/10022069A.pdf (January 12, 2022); PROTEAN II xi cell. PROTEAN II xi 2-D cell. Instruction Manual. Available at: https://www.bio-rad.com/webroot/web/pdf/lsr/literature/M1651801.pdf (January 12, 2022); ReadyPrep 2-D starter Kit. Instruction manual. Available at: https://www.bio-rad.com/webroot/web/pdf/lsr/literature/4110009A.pdf (January 12, 2022).

[5] The resource for approved human gene nomenclature: [web-source]. *HGNC, HUGO Gene Nomenclature Committee*. Available at: https://www.genenames.org/ (December 10, 2021).

Results and discussion. Our experiments revealed that an average fluoride-ion concentration was by 19.2 times higher in urine of rats exposed solely to this chemical in a concentration equal to 20 mg/kg of a body weight than in urine of rats from the control group ($p = 0.012$). Aluminum concentrations in urine of rats exposed to the chemical in a dose equal to 1.67 mg/kg of a body amounted to 0.057 ± ± 0.010 mg/dm^3 and was by 9.5 times higher than in the control group ($p = 0.012$) (Table 1).

Combined inhalation exposure to mixed fluoride-ion and aluminum in the same doses resulted in 5.6 times higher concentrations of fluoride-ion and 3.2 times higher concentrations of aluminum in urine of rats from Group No. 3 than in the control group ($p = 0.012$). It should be noted that bioaccumulation of fluoride-ion and aluminum in the body is more apparent under separate exposure than under combined one; this is confirmed by 3.0–3.3 times higher concentrations of aluminum and fluoride-ion in urine under separate exposure than under combined one ($p = 0.012$). This might indicate there is possible antagonism between these two chemicals when adverse effects are developing [11].

Our full-scale observations established that children from the test group who underwent long-term aerogenic exposure simultaneously to aluminum (0.0005 mg/(kg·day)) and fluoride (0.002 mg/(kg·day)) had 2.8 times higher concentrations of aluminum and 1.8 times higher concentrations of fluoride-ion in their urine than children in the reference group ($p = 0.006$–0.039).

We examined whether there were authentically different proteins in blood plasma of rats from the test groups and the control one. Overall, two-dimensional electrophoresis charts allowed identifying 10 protein fractions under separate exposure to fluoride; 13, under separate exposure to aluminum; and 13, under combined exposure to the mixture of the examined chemicals (Table 2).

We detected several proteins under combined exposure to the mixture of the examined chemicals which were identical to those detected in protein strains under separate exposure. In case of combined exposure and separate exposure to fluoride the identical proteins were plasma protease C1 inhibitor, zinc finger protein 644, nuclear receptor-coactivator 4, J chain of immunoglobulin, apolipoprotein A-I,

Table 1

Fluoride-ion and aluminum concentrations under experimental and actual exposure

Group	Indicator	Fluoride-ion, mg/dm^3	Aluminum, mg/dm^3
Experimental research			
Test group of rats under separate exposure to chemicals	Simple mean ± standard error of mean, $\bar{X} \pm SEM$	6.800 ± 1.571	0.057 ± 0.010
	Standard deviation, *SD*	3.51	0.0230
	Validity of differences between mean values in test and control groups, *p*	0.012	0.012
Test group of rats under combined exposure to chemicals	Simple mean ± standard error of mean, $\bar{X} \pm SEM$	2.07 ± 0.271	0.019 ± 0.005
	Standard deviation, *SD*	0.606	0.012
	Validity of differences between mean values in test and control groups, *p*	0.012	0.012
Control group of rats	Simple mean ± standard error of mean, $\bar{X} \pm SEM$	0.354 ± 0.062	0.006 ± 0.001
	Standard deviation, *SD*	0.138	0.010
Full-scale observation			
Test group (children)	Simple mean ± standard error of mean, $\bar{X} \pm SEM$	0.687 ± 0.076	0.011 ± 0.003
	Standard deviation, *SD*	0.378	0.019
	Validity of differences between mean values in test and control groups, *p*	0.006	0.039
Reference group (children)	Simple mean ± standard error of mean, $\bar{X} \pm SEM$	0.374 ± 0.053	0.004 ± 0.001
	Standard deviation, *SD*	0.167	0.001

Table 2

Proteins and peptides in their structure which authentically differ from the control group and are identified in proteomic blood plasma profile of rats exposed separately to fluoride and aluminum and to the mixture of these chemicals

Sequences of amino acids residues in of a peptide	Peptide identification probability, %	Protein	Authenticity of a model showing "chemical – significant protein" relationship ($p \leq 0.05$)
Separate exposure to fluoride			
DSLNMWLCPR	47.5	Nuclear receptor coactivator 4	0.009
VDCLKTFGR	18.9	Laminin Subunit Alpha 3	0.070
CYTAVVPLVYGGETK	99.1	J chain of immunoglobulin	0.043
VSFLSALEEYTK	96.4	Apolipoprotein A-I	0.025
EAMGKLYNFSTSSR	94.1	Alpha-protein kinase 1	0.011
GWVTDGFSSLK	99.4	Apolipoprotein C-III	0.030
LLVVYPWTQR	97.2	Hemoglobin subunit gamma-2	0.025
FQPTLLTLPR	39.1	Plasma protease C1 inhibitor	0.010
NSAISPQK	75.4	Zink finger protein 644	0.301
Separate exposure to aluminum			
INGKPLPGATPAK	39.8	tRNA selenocysteine 1-associated protein 1	0.0001
GLCVATPVQLR	98.7	C4-B Complement	0.0001
QRIEALSLMHPSISFSLR	61.3	DNA mismatch repair protein Mlh3	0.002
NIVQNVR	28.9	Sideroflexin-3	0.029
LMAKAEDLR	69.8	Nck-associated protein 5	0.002
DDLIIDLLNEAK	36.8	V-type proton ATPhase of E 1 subunit	0.0001
EAMGKLYNFSTSSR	86.2	Alpha-protein kinase-1	0.004
QLCGCYLTR	82.3	Thrymethyllysine dioxygenase, mitochondria	0.0001
LPLLPPQLLADLETSSMFTGD LECQKLLMEAMK	97.6	Kelch-like protein 4	0.016
GLPDDHAGPIR	35.4	Alanyl-tRNA, editing protein Aarsd1	0.001
GLEEELQFSLGSK	97.3	C4-B complement	0.001
DESSLK	42.1	Probable E3 ubiquitin-protein lygase MID2	0.0001
EILSEVER	15.2	T-complex protein 1 subunit gamma	0.0001
Combined exposure to the mixture of fluoride and aluminum			
KMGEMATSGDR	41,9	MARVEL domain containing protein 2	0,002
FQPTLLTLPR	48.7	C1protease inhibitor in plasma	0.021
YMPYNHQHK	52.8	Acyl-KoA (8-3) desaturase	0.003
APETGGAPRAPGAGR	75.3	Serine/threonine-protein kinase LMTK3	0.037
NSAISPQK	64.8	Zinc finger protein 644	0.069
DSLNMWLCPR	28.9	Nuclear receptor coactivator 4	0.008
TSESGELHGLTTEEEFVEGIYK	98.9	Transthyretin	0.006
CYTAVVPLVYGGETK	99.8	J chain of immunoglobulin	0.018
VSFLSALEEYTK	96.3	Apolipoprotein A-I	0.060
EAMGKLYNFSTSSR	93.2	Alpha-protein kinase 1	0.0001
LPLLPPQLLADLETSSMFTGD	95.1	Kelch-like protein 4	0.004
LLVVYPWTQR	98.7	Hemoglobin subunit gamma-2	0.544
EILSEVER	78.9	T-complex protein 1 subunit gamma	0.012

alpha-protein kinase 1, hemoglobin subunit gamma-2; in case of combined exposure and separate exposure to aluminum these proteins were alpha-protein kinase 1, Kelch-like protein 4, protein T-complex protein 1 subunit gamma. Growing contents of the aforementioned proteins, including apolipoprotein A-I, zinc finger protein 644 and hemoglobin subunit gamma-2, had a detected cause-effect relation with elevated concentrations of fluoride-

ion and aluminum in experimental animals' urine under exposure to their mixture (R^2 = 0.81–0.97; p = 0.0001–0.018).

We comparatively analyzed authentically different altered proteins in proteomic blood plasma profiles of children under actual aerogenic and those of against unexposed children. The analysis established 2 protein stains out of total 25 which were quantitatively and qualitatively similar to altered proteins detected under combined exposure to the mixture of fluoride and aluminum in experimental conditions. These two proteins were J chain of immunoglobulin (its expression is coded by JCHAIN gene) and Kelch-like protein 4 (expression coded by KLHL4 gene) (Table 3).

Thus, children from the test group had by 17.9–27.1 times greater volumes of proteins containing J chain of immunoglobulin and Kelch-like protein 4 than children from the reference group (p = 0.0001). This was comparable to changes in volumes of these protein stains detected in the experiment. A probability that these detected peptides would be identified varied from 98.7 % to 99.2 %. Figure shows an example two-dimensional electrophoresis chart showing one of the examined peptides.

We proved that the growth in relative volumes of Kelch-like protein 4 and J chain of immunoglobulin depended on elevated aluminum and fluoride-ion concentrations in urine under combined exposure to both chemicals in a mixture. Model parameters for Kelch-like protein 4 were as follows: R^2 = 0.07; b_0 = 1180.64; b_1 = 9141.60; b_2 = 190.10; (p = 0.046); for J chain of immunoglobulin, as follows: R^2 = 0.06; b_0 = 1804.56; b_1 = 5767.11; b_2 = 206.47; (p = 0.030).

Generalization and analysis of the existing scientific data on biological functions performed by the identified proteins in blood plasma make it possible to predict certain adverse health effects which may occur in the immune and cardiovascular system. Thus, the major function performed by J chain of

Table 3

Identical proteins detected under experimental and actual combined exposure to aluminum and fluoride ($p \leq 0.05$)

Protein	Relative protein stain volume, int Simple mean ± standard error of mean, $\bar{X} \pm SEM$			
	Experimental exposure		Actual exposure	
	Test group under combined exposure to both chemicals	Control	Test group	Reference group
Kelch-like protein 4	$4097 \pm 106^{p = 0.012}$	469 ± 224	$2548 \pm 57^{p = 0.0001}$	94 ± 36
J chain of immunoglobulin	$2635 \pm 52^{p = 0.007}$	1785 ± 86	$1807 \pm 38^{p = 0.0001}$	101 ± 34

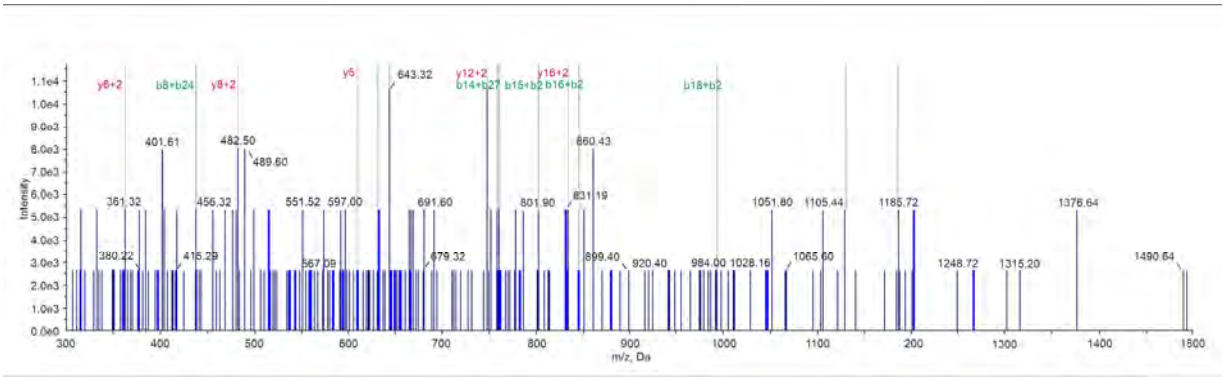

Figure. MS-identification of LPLLPPQLLADLETSSMFTGDLECQKLLMEAMK peptide (Kelch-like protein 4) in a child's blood plasma (SwissProt database)

immunoglobulin is to initiate IgM and IgA polymerization [15]. J chain inclusion into polymeric IgA and pentameric IgM gives these antibodies high valence of antigen-binding sites and zero potential of the complement activation. These alterations make for immunoglobulins to be capable to agglutinate bacteria and viruses thus preventing them from initiating a cascade of inflammatory reactions. Thereby secretory antibodies create "the first line" of protection against pathogens and adverse chemicals which penetrate the body through mucosa [16]. Relative volumes of the protein strain containing J chain of immunoglobulin grow under combined exposure to aluminum and fluoride both in experimental and actual conditions. This may indicate that the immune response is undergoing certain adaptive restructuring with further developing IgA and IgM deficiency which is typical for chronic inflammation [17].

Proteins from Kelch family play a major role in variable cellular processes including cytoskeleton organization and ion channels flickering. This process is accompanied with an ion channel transferring from its open state to a closed one [18, 19]. Ion channels (potassium- and calcium-dependent) detected in endotheliocytes are involved into electrolyte transportation. Any failure in it can make for decreasing vessel lumens and growing peripheral vascular resistance. In this regard we can assume that the excessive expression of this gene and, consequently, excessive synthesis of Kelch-like protein induces mechanisms which regulate the vascular tonus [20]. We established a direct relation between growing Kelch-like protein levels and elevated aluminum and fluoride concentrations in urine under combined exposure to the mixture of these two chemicals both in experimental and actual conditions. This can indicate that the mixture of the examined chemicals produces negative health effects such as developing sclerotic and inflammatory changes in vascular walls under combined exposure to them.

Therefore, it is vital to identify alterations in such proteins in blood plasma as Kelch-like protein 4 and J chain of immunoglobulin since it provides an opportunity to perform early diagnostics, to predict, assess, and mitigate risks of developing diseases of the cardiovascular and nervous system, blood and blood-making organs associated with long-term combined aerogenic exposure simultaneously to fluoride and aluminum compounds.

Conclusions:

1. Long-term combined aerogenic exposure simultaneously to aluminum and fluoride compounds in low average daily doses (0.0005 mg/(kg·day) and 0.002 mg/(kg·day) respectively) makes for elevated aluminum concentrations (by 2.8 times higher) and fluoride-ion concentrations (by 1.8 times higher) in urine of exposed children against non-exposed ones. This is verified by results produced in experimental studies on combined exposure to the mixture of the examined chemicals.

2. We substantiated identical omic-markers, J chain of immunoglobulin (JCHAIN gene) and Kelch-like protein 4 (KLHL4 gene) which are expressed both under experimental and actual combined aerogenic exposure simultaneously to aluminum and fluoride compounds.

3. We proved the cause-effect relation between elevated levels of the identical proteins and aluminum and fluoride-ion concentrations in urine under simultaneous exposure to both chemicals in a mixture.

4. The identified protein markers in blood plasma allow predicting certain adverse health effects under persisting combined aerogenic exposure to aluminum and fluoride compounds. These effects might be less active humoral immunity (when J chain of immunoglobulin is expressed) and disorders in the vascular wall tonus (when Kelch-like protein 4 is expressed).

5. We established cellular and molecular mechanisms determining involvement of the transformed proteomic profile into developing adverse effects. When J chain of immunoglobulin was expressed, this involvement

was characterized by growing valence of antigen-binding centers IgA and IgM and zero potential of the activated complement that determined adaptive restructuring of the immune response. When Kelch-like protein 4 was expressed, the process was characterized with sequential closing of potassium- and calcium-dependent ion channels in endotheliocytes, failure in electrolyte transportation, smaller vascular lumens and growing vascular resistance.

6. These predicted negative effects can be considered a result of simple summated (additive) toxic impacts exerted by aluminum and fluoride under combined aerogenic exposure to them in a mixture both in experimental and actual conditions.

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References

1. Assessment of combined exposures to multiple chemicals: report of a WHO/IPCS international workshop on aggregate/cumulative risk assessment. *World Health Organization*, 2009, no. 7, 83 p.

2. Considerations for Assessing the Risks of Combined Exposure to Multiple Chemicals, Series on Testing and Assessment. *OECD*, 2018, no. 296, 119 p.

3. Hadley M.B., Baumgartner J., Vedanthan R. Developing a clinical approach to mitigating risks of air pollution and protecting cardiovascular health. *Circulation*, 2018, vol. 137, no. 7, pp. 725–742. DOI: 10.1161/CIRCULATIONAHA.117.030377

4. WHO global air quality guidelines, Particulate matter ($PM_{2.5}$ and PM_{10}), ozone, nitrogen dioxide, sulfur dioxide and carbon monoxide. *World Health Organization*, 2021. Available at: https://apps.who.int/iris/bitstream/handle/10665/345329/9789240034228-eng.pdf?sequence=1&isAllowed=y (12.11.2021).

5. Zaitseva N.V., Zemlyanova M.A., Stepankov M.S., Ignatova A.M. Scientific forecasting of toxicity and evaluation of hazard potential of aluminum oxide nanoparticles for human health. *Ekologiya cheloveka*, 2018, no. 5, pp. 9–15. DOI: 10.33396/1728-0869-2018-5-9-15 (in Russian).

6. Donskikh I.V. The influence of fluorine and its compounds on people's health (literature review). *Byulleten' VSNTs SO RAMN*, 2013, vol. 91, no. 3, part 2, pp. 179–185 (in Russian).

7. Mintel M.V., Zemlyanova M.A., Zhdanova-Zaplesvichko I.G. Some aspects of synergistic action of aluminum and fluorine on human body (literature review). *Ekologiya cheloveka*, 2018, no. 9, pp. 12–18. DOI: 10.33396/1728-0869-2018-9-12-17 (in Russian).

8. Sazonova N.G., Makarenko T.A., Olovyannikova R.Ya., Kutyakov V.A., Salmina A.B. Proteomic analysis methods and their role in the diagnosis of obstetric and gynecological pathology. *Zhurnal akusherstva i zhenskikh boleznei*, 2019, vol. 68, no. 1, pp. 69–82. DOI: 10.17816/JOWD68169-82 (in Russian).

9. Zhetisheva R.A., Kovaleva M.A., Kamenihina I.A., Kovalev L.I., Naumov V.G. The protein biomarkers search in atherosclerosis using proteomic technologies – as a promising area of science. *Ateroskleroz i dislipidemii*, 2020, no. 2, pp. 12–19. DOI: 10.34687/2219–8202.JAD.2020.02.0002 (in Russian).

10. Drozdova E.V., Dudchik N.V., Sychik S.I., Shevlyakov V.V. Otsenka integral'noi toksichnosti faktorov i ob"ektov sredy obitaniya s ispol'zovaniem al'ternativnykh biologicheskikh test-modelei: metodologiya i tekhnologii [Integrated toxicity assessment of environmental factors and objects using alternative biological test models: methodology and technology]. Minsk, Belorusskii nauchno-issledovatel'skii institut transporta «Transtekhnika» Publ., 2017, 216 p. (in Russian).

11. Xiao B., Li D., Dong Q., Li Q., Li S., Zhan C. [Effects of aluminum, fluorine and their mixtures on the enzyme activities of jejunal mucus membrane in the perfusion of small intestine of rats in vivo]. *Journal of West China University of Medical Sciences*, 1992, vol. 23, no. 1, pp. 79–82 (in Chinese).

12. Strunecka A., Strunecky O., Patocka J. Fluoride plus aluminum: Useful tools in laboratory investigations, but messengers of false information. *Physiol. Res.*, 2002, vol. 51, no. 6, pp. 557–564.

13. Li L. The biochemistry and physiology of metallic fluoride: action, mechanism, and implications. *Crit. Rev. Oral Biol. Med.*, vol. 14, no. 2, pp. 100–114. DOI: 10.1177/154411130301400204

14. Suwalsky M., Norris B., Villena F., Cuevas F., Sotomayor P., Zatta P. Aluminum fluoride affects the structure and functions of cell membranes. *Food Chem. Toxicol.*, 2004, vol. 42, no. 6, pp. 925–933. DOI: 10.1016/j.fct.2004.01.016

15. Koshland M.E. The coming of age of the immunoglobulin J chain. *Annu. Rev. Immunol.*, 1985, vol. 3, pp. 425–453. DOI: 10.1146/annurev.iy.03.040185.002233

16. Johansen F.E., Braathen R., Brandtzaeg P. Role of J chain in secretory immunoglobulin formation. *Scand. J. Immunol.*, 2000, vol. 52, no. 3, pp. 240–248. DOI: 10.1046/j.1365-3083.2000.00790.x

17. Moskalets O.V. Immunoglobulin A and its selective deficiency. *Kazanskii meditsinskii zhurnal*, vol. 98, no. 5, pp. 809–813. DOI: 10.17750/KMJ2017-809 (in Russian).

18. Choi S.-H., Cho S.-Y., Song J., Hur M.-W. KLHL4, a novel p53 target gene, inhibits cell proliferation by activating p21WAF/CDKN1A. *Biochem. Biophys. Res. Commun.*, 2020, vol. 530, no. 3, pp. 588–596. DOI: 10.1016/j.bbrc.2020.07.100

19. Shi X., Xiang S., Cao J., Zhu H., Yang B., He Q., Ying M. Kelch-like proteins: Physiological functions and relationships with diseases. *Pharmacol. Res.,* 2019, vol. 148, pp. 104404. DOI: 10.1016/j.phrs.2019.104404

20. Solodkov A.P., Belyaeva L.E., Lazuko S.S. Stress i arterial'naya gipertenziya [Stress and arterial hypertension]. *Praktikuyuchii likar*, 2013, no. 3, pp. 78–80 (in Russian).

Zemlyanova M.A., Zaitseva N.V., Koldibekova Yu.V., Perezhogin A.N., Stepankov M.S., Bulatova N.I. On detecting omic-markers of negative effects associated with combined aerogenic exposure to aluminum and fluoride compounds. Health Risk Analysis, 2022, no. 1, pp. 113–122. DOI: 10.21668/health.risk/2022.1.13.eng

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Research article

PECULIARITIES DETECTED IN FORMATION OF SPECIFIC HAPTEN SENSITIZATION TO PHENOL IN CHILDREN

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Phenol contamination in ambient air is a factor which creates health risks for children living in a zone influenced by emissions from a ferrous metallurgy enterprise. Our research goal was to assess specific hapten sensitization in children living under excessive aerogenic exposure to phenol.

We performed hygienic assessment of ambient air pollution on territories of pre-school children facilities located at various distances from a zone influenced by the examined enterprise (1 km and 5 km were the test territories No. 1 and 2 accordingly) which emitted phenol thus creating elevated concentrations of the chemical in ambient air being higher than single maximum MPC. Ambient air on a selected reference territory was not polluted with any industrial emissions. The test group No. 1 was made of 99 children (the test territory No. 1); the test group No. 2, 92 children (the test territory No. 2); and the reference group, 95 children (the reference territory). We analyzed phenol contents and levels of IgG specific to phenol in blood of all the examined children. Phenol concentrations in ambient air were higher than its permissible levels on the test territory No. 1, 1.7 single maximum MPC, and the test territory No. 2, 1.1 single maximum MPC.

We comparatively assessed phenol contents in blood of children from all three groups. The assessment revealed that children from the test group No. 1 had a hydroxybenzene concentration in their blood which was statistically significantly ($p = 0.031$) by 1.9 times higher than in blood of children from the reference group. Production of specific G class antibodies was higher than the upper limit of the physiological standard in 60 % and 36 % children living and attending a preschool children facility in zones located accordingly at the minimal and maximum distance an emission source. The research results indicate that a hapten-associated increase in the level of IgG specific to phenol in preschool children is associated with excessive phenol contamination creating a substantial burden on biological media ($OR = 14.75$; 95 % CI = 6.45–33.73; $p < 0.05$).

Key words: *phenol, aerogenic pollution, haptens, immunoglobulin G specific to phenol, preschool children, contaminant burden, sensitization, risk of developing allergic pathology.*

Rapidly developing urbanization and growing industrialization make for considerable environmental pollution [1]. Anthropogenic sources make a substantial contribution to ambient air pollution with phenol and its derivatives [2, 3]. According to experts' estimates, ambient air in many megacities all over the world contains phenol in concentrations which are significantly higher than those stipulated by hygienic standards[1] [4–7]. Assessment of ambient air quality in residential areas in the RF in 2015–2020 revealed a growing share of samples which deviated from hygienic standards as per contents of hydroxybenzene (phenol) and its derivatives. This share grew by 1.45 over the period, from 0.86 to 1.25[1].

Phenol acts as a sensitizing agent in case it is inhaled and produces certain pro-allergic effects [8]. Developing IgG-specific sensitization to phenol creates a risk of bronchial asthma, allergic rhinitis, asthma-like bronchitis, pollen allergy, and hypertrophic changes in the respiratory tract mucosa. Children, as opposed to adults, are more sensitive to ef-

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

fects produced by phenol. Higher concentrations of the pollutant are identified in children's biological media under exposure to it. This is due to anatomic and physiological peculiarities of their bodies (the respiratory surface of the lungs with respect to body weight is greater in children than in adults, their airways are more narrow, the detoxification system is underdeveloped, the immune system has certain age-related peculiarities, etc.)[2] [9]. A child's age from 4 to 6 years is a crucial period in formation of the immunity when Th-2 shift occurs in the cytokine profile and IgE antibodies are produced in the highest quantities in comparison with any other period in childhood [8, 10]. Besides, children are much shorter than adults and this leads to exposure to higher phenol concentrations since its vapors are identified in greater volumes closer to the ground[2].

Obviously, ambient air pollution with hydroxybenzene creates risks of sensitization and allergic pathologies among pre-school children as the most susceptible population group. It is necessary to describe a group and an individual profile of IgG-specific sensitization to phenol if we want to detect susceptibility to technogenic chemicals as early as possible. In future this will make for implementing more effective protection activities aimed at reducing incidence associated with aerogenic exposure to phenol.

Our research goal was to assess specific hapten sensitization in children under excessive aerogenic exposure to phenol.

Materials and methods. We performed hygienic assessment of ambient air on areas around pre-school children faculties located at different distances from a ferrous metallurgy enterprise. It emitted phenol in hazardous concentrations exceeding maximum single MPC (the test territory No. 1 was located 1 km away from the enterprise; the test territory No. 2, 5 km away). Our reference territory was an area where any sources of phenol emissions were completely absent. Hygienic assessment of ambient air quality was performed in conformity with the methodical guidelines RD 52.04.186-89 "The Guide on control of ambient air pollution" [3]. We used two standard values: average daily concentration ($MPC_{av.d.}$) and maximum single concentration ($MPC_{m.s.}$). We also analyzed data on volumes and structure of emissions from stationary and mobile sources (Form No. 2–TP (air)).

All the diagnostic examinations were performed in accordance with requirements fixed by the WMA's Declaration of Helsinki (1964, last edited 2013). Our study involved assessing overall sensitization and specific sensitization to phenol. To do that, we examined 286 pre-school children who lived and attended pre-school children facilities on the examined territories. Our reference group was made up of 95 children who lived and attended pre-school children facilities on the reference territory which was considered 'conditionally" clean. The test group No. 1 included 99 children who lived and attended pre-school children facilities on the test territory No. 1; the test group No. 2, 92 children who lived and attended pre-school children facilities on the test territory No. 2. We applied several criteria to include children into our study: their age was from 4 to 6 years and their family lived on the examined territory for not less than 5 years. Participation in another study or parents not being capable or willing to give their written informed consent to participation of their children were the reasons for excluding children from our study. All parents (legal guardians) of participating children gave their informed written consent to it.

Chemical analysis of children's blood involved identifying phenol concentrations with gas chromatography in accordance with the me-

[2] Medical management guidelines for phenol. *ATSDR*, 2014. Available at: https://wwwn.cdc.gov/TSP/MMG/MMGDetails.aspx?mmgid=144&toxid=27 (March 01, 2022).

[3] RD 52.04.186-89. Rukovodstvo po kontrolyu zagryazneniya atmosfery [The Guide on control of ambient air pollution]. Moscow, USSR Goskomgidromet; USSR Public Healthcare Ministry, 1991, 695 p. Available at: https://files.stroyinf.ru/Data2/1/4293854/4293854583.pdf (March 01, 2022) (in Russian).

thodical guidelines MUK 4.1.2102-4.1.2116-06[4] on "Kristall 2000" capillary gas chromatographer (SKB "Chromatek" LLC, Russia).

We determined IgG specific to phenol using procedures for determining allergen adsorption. Total IgG was determined by ELISA tests on Sunrise analyzer (Tecan, Austria).

All the test results were statistically analyzed using Statistica 6.0 software package (StatSoft, USA). We applied Kolmogorov – Smirnov test as a criterion showing whether indicators in the children groups were distributed normally. Student's two-sample test was applied to test zero hypotheses about equality of mean values in two independent groups with normal distribution. The research data were given as simple mean (M), error of mean (m) and 95 % confidence interval for simple mean (95 % CI). We compared sampling data with physiological standards using Wilcoxon one-sample test. To assess a correlation between health outcomes and exposure to the examined factor (phenol), we calculated odds ratio (OR) and its 95 % confidence interval. Differences were considered statistically significant at $p < 0.05$ for all the accomplished tests.

Results. Ambient air pollution occurred on the test territories due to emissions of pollutants from stationary sources. Thus, the total phenol (hydroxybenzene) (code 1071) emission was equal to 97.721626 tons/years; the maximum single emission, 3.0533076 g/sec.

Phenol concentration in ambient air was lower than $MPC_{av.d.}$ (up to 0.68 MPC) on the examined territories (taken as per averaged values). We established that phenol $MPC_{av.d.}$ in ambient air was on average by 2.4 times higher on the test territories influenced by emission from the aforementioned industrial enterprise than on the reference territory where there were no industrial emissions. Having assessed maximum single concentrations of pollutants emitted by the ferrous metallurgy enterprise, we revealed that the relevant hygienic standards were violated both on the test territory No. 1 and No. 2, where phenol concentration was equal to 1.74 $MPC_{m.s.}$ and 1.09 $MPC_{m.s.}$ accordingly.

We detected that phenol contents were statistically significantly ($p = 0.031$) by 1.9 times higher in biological media (blood) of children from the test group No. 1 against the reference group (Table 1). A share of samples with phenol concentrations that deviated from hygienic standards was equal to 88.9 % in the test group No. 1 against values detected in the reference group. Average phenol contents determined in biological media of children from the test group No. 2 didn't have any statistically significant difference ($p = 0.376$) against the reference group. A share of samples with phenol concentrations which deviated significantly from hygienic standards was equal to 75 % in children living on the test territory No. 2 against concentrations detected in children living on the reference territory.

We established that concentrations of the total immunoglobulin E were statistically significantly ($p < 0.05$) higher than the physiological standard (0–49.9 IU/cm^3) in all the examined children. We comparatively analyzed indicators which described specific sensitization to the priority factor and established that children who were not exposed to phenol had IgG specific to phenol in their blood in concentrations that were within physiologically normal ranges, 0–0.13 arbitrary units. The examined children from the test group No. 1 had concentrations of IgG specific to phenol which were statistically significantly ($p = 0.003$) by 4 times higher than the same indicators in the reference group. Specific IgG sensitization to phenol was statistically significantly ($p = 0.014$) by 3.5 times higher among children from the test group No. 2

[4] MUK 4.1.2102-4.1.2116-06. Opredelenie vrednykh veshchestv v biologicheskikh sredakh: Sbornik metodicheskikh ukazanii (utv. i vved. v deistvie Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii 09.08.2006) [Identification of harmful chemicals un biological media: The collection of methodical guidelines (approved and introduced by the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, the RF Chief Sanitary Inspector on August 9, 2006)]. *KODEKS: electronic fund for legal and reference documentation.* Available at: https://docs.cntd.ru/document/1200066799 (March 01, 2022) (in Russian).

Table 1

Chemical analysis of biological media and serum immunoglobulins profile in children exposed to phenol

Indicator	Reference group $n = 95$	Test group no. 1 $n = 99$	Test group no. 2 $n = 92$	p^1	p^2
Phenol in blood, mg/dm^3					
$M\,(m)$	0.0379 (0.0083)	0.0732 (0.014)	0.0563 (0.019)	$t = 2.17$	$t = 0.89$
95 % CI	0.02–0.05	0.07–0.08	0.05–0.06	$p = 0.031$	$p = 0.376$
Serum immunoglobulins profile					
Total IgE, IU/cm^3					
$M\,(m)$	75.37 (17.00)*	144.84 (33.10)*	87.76 (25.00)*	$t = 1.87$	$t = 0.41$
95 % CI	71.84–78.90	136.42–153.26	82.52–93.00	$p = 0.634$	$p = 0.682$
IgG specific to phenol, arb. units					
$M\,(m)$	0.04 (0.005)	0.16 (0.04)*	0.14 (0.04)*	$t = 2.98$	$t = 2.48$
95 % CI	0.03–0.05	0.15–0.17	0.13–0.15	$p = 0.003$	$p = 0.014$

N o t e : p^1 means differences between the reference group and the test group No. 1 are authentic according to Student's t-test**;** p^2 means differences between the reference group and the test group No. 2 are authentic according to Student's t-test**; *** means that differences form physiological standard are authentic as per Wilcoxon one-sample test, differences are considered statistically significant at $p < 0.05$.

Table 2

Frequency of allergy indicators deviating from physiological standards in children with different levels of phenol contamination in biological media

Indicator	Physiological standard	Reference group $n = 95$		Test group no. 1 $n = 99$		Test group no. 2 $n = 92$	
		A share of samples deviating from physiological standard, %					
		higher	lower	higher	lower	higher	lower
Total IgE	0–49.9	38.3	0	58	0	43.3	0
IgG specific to phenol	0–0.13	8.7	0	58	0	36.2	0

against those from the reference group. We also established that production of IgG specific to phenol was on average statistically significantly ($p < 0.05$) by 1.2 times higher than the upper limit of the physiological standard in children who lived and attended preschool children facilities on the test territories (located at different distances from the source of industrial emissions).

A share of samples with total IgG concentration being significantly higher than the physiological standard amounted to 38.3, 58 and 43.3 % among children from the reference group, test group No. 1 and test group No. 2 accordingly (Table 2). Hyperproduction of IgG specific to phenol was detected in 58 % of analyzed samples taken in the test group No. 1 and this result was by 6.7 times higher than in the reference group. A share of samples with concentrations of IgG specific to phenol being higher than the physiological standards equaled to 36.2 % in the test group No. 2 against 8.7 % in the reference group and this was by 4.2 times higher.

Odds ratio analysis indicated there was a correlation between phenol contamination and elevated specific sensitization to phenol in children from the test group No. 2 ($OR = 6.08$; 95 % CI = 2.62–14.09; $p < 0.05$). It was established that as hapten (phenol) loads grew, there was also a growth in risks of excessive production of total IgE and IgE specific to phenol in the examined children living on the test territory No. 1 ($OR = 2.22$; 95 % CI = 1.25–3.95; $p < 0.05$ and $OR = 14.75$; 95 % CI = 6.45–33.73; $p < 0.05$ accordingly).

Discussion. Negative effects produced by phenol on the immune system and associated with development of allergic reactions have been discussed over the last decades in many

research papers [9–11]. Immune-modulating effects produced by phenol are assumed to be mediated by the chemical being tropic to estrogen receptors (ER), peroxisome proliferator-activated receptors (PPAR), aryl hydrocarbon receptors (AhR), and its ability to induce Th2-shift in the cytokine profile [8, 12–15].

Estrogen receptors which are exhibited in significant quantities on many immune-competent cells play a most important role in regulating proliferative and functional activity of immunocytes. They also maintain the balance between Th1 and Th2-cytokines. Activation of estrogen receptors induces mast cells degranulation by altering intracellular calcium homeostasis. Additionally, estrogen-like chemicals stimulate rapid dose-dependent release of β-hexosaminidase from mast cells thus enhancing IgG-mediated release of histamine from them [15]. PPAR belongs to major regulators of the energy balance in a cell and activity performed by NF-κB transcription factor. It is also a significant participant in regulation of inflammation and fibrosis [16]. Several experimental and clinical studies established that phenol and its metabolites (hydroquinone) were able to induce hyperproduction of interleukin 4 and elevated levels of IgE [10, 12, 13]. Th2-dependent deviation in the immune response was studied using experimental models of asthma and turned out to make for generation of reactive oxygen species in considerable quantities thus making the inflammatory process more severe [16]. The role played by AhR in producing a protective response by the body to exposure to xenobiotics has been proven. Aryl hydrocarbon receptor acts as a protector in case an autoimmune pathology, an oncologic process or an allergy develops in the body. Indoleamine-pyrrole-2,3-dioxygenase enzyme (IDO) catalyzes degradation of the essential amino acid tryptophan (TRP) into N-formyl-kynurenine and produces protective effects when bronchial asthma develops. It was shown in *in vivo* systems (in animal models) that AhR and NF-κB participated in regulation of IDO expression [17]. It was established that aryl hydrocarbon receptor also made a substantial contribution to production of immunoglobulins (IgA, IgG, IgM, IgE) and processes of their switching between different types (IgG – IgE) as well as production of IgG isotypes in a plasmatic cell[5].

Intensive ambient air pollution with industrial emissions (hydroxybenzene (phenol) and its derivatives) results in poorer human health [18–20]. Children who live in zones influenced by emissions from industrial enterprises are the most sensitive risk group under exposure to substantial adverse environmental loads. It was established that excessive ambient air pollution with phenol resulted in apparent sensitization of the body. Meanwhile, we should remember about an existing danger associated with sensitization with low doses of an immune-tropic chemical. Phenol is also a chemical with high allergenic potential[2] [8]. Several allergenic diseases develop as per an IgE-dependent and IgG4-dependent scenario thus causing an elevated level of specific antibodies in blood serum. However, identification of total IgE and specific IgG within a physiological range doesn't mean there is no developing sensitization and / or an allergic reaction since we can't exclude that immunoglobulin G can be bound by tissues or that IgG is produced locally. Our research results are well in line with those produced by previous research works focusing on negative impacts exerted by aerogenic exposure to phenol on the immune system which involve developing sensitization associated with a level of exposure to an immune-tropic chemical[2] [10].

Therefore, children who live on territories where phenol is the priority anthropogenic pollutant are exposed to risks of developing specific sensitization. This induces occurrence and manifestation of allergic diseases associated with inhalation exposure to an immune-tropic chemical during a crucial period in childhood. Phenol was detected in excessive concentrations up to 1.7 $MPC_{m.s.}$ on the test territory No. 1 which was only 1 km away

[5] Kashgari B.F. Determining the role of the AhR in immunoglobulin expression and class switch recombination: diss. thesis for MS. *Wright State University*, 2015, 85 p. Available at: https://corescholar.libraries.wright.edu/etd_all/1591 (March 01, 2022).

from the industrial enterprise and this was higher than permissible levels. It was detected in concentrations up to 1.1 $MPC_{m.s.}$ on the test territory No. 2 which was located 5 km away from the source of industrial emissions. Average group phenol concentration was statistically significantly ($p = 0.031$) by 1.9 times higher in blood of children who lived close to the emission source (the test group No. 1) against children from the reference group who were not exposed to phenol. There were no statistically significant differences in phenol concentrations in blood of children from the test group No. 2 (who lived 5 km away from the emission source) and children from the reference group. We established a statistically significantly ($p = 0.003–0.014$) higher level of IgG specific to phenol in blood of children living at the minimum and maximum distance from the industrial enterprise which emitted phenol into ambient air (1 km and 5 km), by 4 and 3.5 times accordingly. Hyperproduction of IgG specific to phenol was detected in 60 % children from the test group No. 1 and 36 % children from the test group No. 2. The results produced by mathematical modeling confirm the immunologically mediated increase in the body sensitivity to chronic exposure to phenol ($OR = 6.08–14.75$; $p < 0.05$). The research results indicate that levels of aerogenic exposure to phenol influence contamination of biological media with this chemical thus determining frequency and severity of developing sensitization and autoimmune disorders.

Inhalation hapten chemical loads (phenol) on bodies of children aged 4–6 years make for developing specific sensitization to an anthropogenic immune-tropic chemical and create risks of developing allergic diseases. Comparative characteristics of group and individual profiles of IgG specific to phenol outlined in this paper confirms that a degree of sensitization under chronic aerogenic exposure to phenol is associated with a level to exposure to hapten (phenol) in doses lower than maximum permissible concentrations. We have shown that a hapten-associated level of IgG specific to phenol in pre-school children living under aerogenic exposure to the chemical in low doses is a criterion indicating early manifestations of sensitization and developing allergic pathology ($OR = 14.75$; 95 % CI = 6.45–33.73; $p < 0.05$).

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References

1. Masnavieva L.B., Efimova N.V., Kudaeva I.V. Risk of sensitization to ecopollutants in teenagers with inherited chemical burden. *Health Risk Analysis*, 2021, no. 2, pp. 123–131. DOI: 10.21668/health.risk/2021.2.12.eng

2. Rubio M.A., Bustamante P., Vásquez Y.P. Atmospheric phenolic derivatives as tracers in an urban area. *J. Chil. Chem. Soc.*, 2019, vol. 64, no. 2, pp. 4407–4411. DOI: 10.4067/S0717-97072019000204407

3. Lee H., Jun Z., Zahra Z. Phytoremediation: the sustainable strategy for improving indoor and outdoor air quality. *Environments,* 2021, vol. 8, no. 11, pp. 118. DOI: 10.3390/environments8110118

4. Delhomme O., Morville S., Millet M. Seasonal and diurnal variations of atmospheric concentrations of phenols and nitrophenols measured in the Strasbourg area, France. *Atmos. Pollut. Res.,* 2010, vol. 1, no. 1, pp. 16–22. DOI: 10.5094/APR.2010.003

5. Kynadi A.S., Suchithra T.V. Bacterial degradation of phenol to control environmental pollution. In: J. Patra, C. Vishnuprasad, G. Das eds. *Microbial biotechnology. Volume 1. Applications in Agriculture and Environment*. Singapore, Springer, 2017. Chapter 11, pp. 245–263. DOI: 10.1007/978-981-10-6847-8_11

6. Molina L.T. Introductory lecture: air quality in megacities. *Faraday Discuss.,* 2021, vol. 226, pp. 9–52. DOI: 10.1039/D0FD00123F

7. Vasiljevic T., Harner T. Bisphenol A and its analogues in outdoor and indoor air: Properties, sources and global levels. *Sci. Total Environ.*, 2021, no. 789, pp. 148013. DOI: 10.1016/j.scitotenv.2021.148013

8. Vernet C., Pin I., Giorgis-Allemand L., Philippat C., Benmerad M., Quentin J., Calafat A.M., Ye X. [et al.]. *In utero* exposure to select phenols and phthalates and respiratory health in five-year-old boys: a prospective study. *Environ. Health Perspect.*, 2017, vol. 125, no. 9, pp. 097006. DOI: 10.1289/EHP1015

9. Zaitseva N.V., Dianova D.G., Dolgikh O.V. Adaptatsionnye vozmozhnosti immunnoi sistemy v usloviyakh khronicheskogo vozdeistviya fenola [Adaptive capabilities of the immune system under chronic exposure to phenol]. *Izvestiya Samarskogo nauchnogo tsentra Rossiiskoi akademii nauk*, 2013, vol. 15, no. 3 (6), pp. 1779–1782 (in Russian).

10. Dolgikh O.V. Dianova D.G. Features of hapten specific sensitization and immune status in different student age groups. *Rossiiskii immunologicheskii zhurnal*, 2020, vol. 23, no. 2, pp. 209–216. DOI: 10.46235/1028-7221-266-FOH (in Russian).

11. Nowak K., Jabłońska E., Ratajczak-Wrona W. Immunomodulatory effects of synthetic endocrine disrupting chemicals on the development and functions of human immune cells. *Environ. Int.*, 2019, vol. 125, pp. 350–364. DOI: 10.1016/j.envint.2019.01.078

12. Kim H.J., Kang B.N., Cho S.W., Son H.Y., Jeong K.S., Park S.J., Kim S.H., Kim S.R. [et al.]. Effects of benzo[a]pyrene, 2-bromopropane, phenol and 2,3,7,8-tetrachlorodibenzo-p-dioxin on proinflammatory cytokines gene expression by mice spleen cells. *J. Vet. Sci.,* 2002, vol. 3, no. 4, pp. 247–254. DOI: 10.4142/jvs.2002.3.4.247

13. Enguita F.J., Leitão A.L. Hydroquinone: environmental pollution, toxicity, and microbial answers. *Biomed Res. Int*., 2013, vol. 2013, pp. 542168. DOI: 10.1155/2013/542168

14. Webster F., Gagné M., Patlewicz G., Pradeep P., Trefiak N., Judson R.S., Barton-Maclaren T.S. Predicting estrogen receptor activation by a group of substituted phenols: An integrated approach to testing and assessment case study. *Regul. Toxicol. Pharmacol*., 2019, vol. 106, pp. 278–291. DOI: 10.1016/j.yrtph.2019.05.017

15. Fan Z., Che H., Yang S., Chen C. Estrogen and estrogen receptor signaling promotes allergic immune responses: Effects on immune cells, cytokines, and inflammatory factors involved in allergy. *Allergol. Immunopathol.,* 2019, vol. 47, no. 5, pp. 506–512. DOI: 10.1016/j.aller.2019.03.001

16. Rodriguez-Coira J., Villaseñor A., Izquierdo E., Huang M., Barker-Tejeda T.C., Radzikowska U., Sokolowska M., Barber D. The importance of metabolism for immune homeostasis in allergic diseases. *Front. Immunol*., 2021, no. 12, pp. 692004. DOI: 10.3389/fimmu.2021.692004

17. Salazar F., Hall L., Negm O.H., Awuah D., Tighe P.J., Shakib F., Ghaemmaghami A.M. The mannose receptor negatively modulates the Toll-like receptor 4–aryl hydrocarbon receptor–indoleamine 2,3-dioxygenase axis in dendritic cells affecting T helper cell polarization. *J. Allergy Clin. Immunol*., 2016, vol. 137, no. 6, pp. 1841–1851.e2. DOI: 10.1016/j.jaci.2015.10.033

18. Emoto Y., Yoshizawa K., Shikata N., Tsubura A., Nagasaki Y. Autopsy report for chemical burns cresol solution. *Exp. Toxicol. Pathol.*, 2016, vol. 68, no. 1, pp. 99–102. DOI: 10.1016/j.etp.2015.09.005

19. EPA/635/R-02/006. Toxicological review of phenol (Cas No. 108-95-2). *U.S. EPA*. Washington D.C., 2002, 213 p.

20. Michalowicz J., Duda W. Phenols – Sources and Toxicity. *Polish J. Of Environ. Stud.*, 2007, vol. 16, no. 3, pp. 347–362.

Dolgikh O.V., Dianova D.G. Peculiarities detected in formation of specific hapten sensitization to phe-nol in children. Health Risk Analysis, 2022, no. 1, pp. 123–129. DOI: 10.21668/health.risk/2022.1.14.eng

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Research article

IMBALANCE IN LYMPHOCYTE COMPOSITION AND CYTOKINE PROFILE AS A RISK FACTOR OF VIBRATION DISEASE

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To provide consistent functioning of the immune and nervous systems, both in normal conditions and in case of any pathology, is among the most significant functions performed by the cytokine system. It seems important to examine mechanisms underlying the well-coordinated working of the immune system since such studies can give grounds for developing certain criteria applied to assess risks of developing vibration disease (VD) and making prognosis for it. Our research goal was to identify peculiarities related to the balance in the phenotypic composition of lymphocytes and cytokines as risk factors of developing vibration disease.

We estimated the phenotypic structure of lymphocytes by indirect immunofluorescence using monoclonal antibodies to $CD3^+$, $CD4^+$, $CD8^+$, $CD16^+$, $CD20^+$, $CD25^+$, and $CD95^+$ molecules. IL-2, IL-4, IL-8, and INF-γ cytokines were determined in blood serum with the solid-phase ELISA method.

We analyzed cytokine contents in patients with VD and established a statistically significant growth in levels of IL-8 and INF-γ and a decrease in IL-2 contents against the reference group. We also found certain differences in the correlations between lymphocytes and cytokines in patients with VD and healthy people. Thus, in patients with VD, there was a positive correlation between the absolute number of $CD3^+$-lymphocytes and the level of the immune-stimulating IL-2 and a positive correlation between the quantity of $CD4^+$-lymphocytes and IL-4 concentration. At the same time, having examined healthy people from the reference group, we detected a negative correlation between IFNγ and the absolute quantity of $CD3^+$ and $CD95^+$-lymphocytes. Therefore, the risk of developing and progressing vibration disease is to a certain extent associated with its pathogenetic peculiarities based, among other things, on complex functional relationships between lymphocytic phenotypes and pro-anti-inflammatory cytokines. In future this will allow substantiating new biomarkers in the additional VD diagnostics.

Key words: *vibration disease, workers, lymphocytes, cytokines, immune response, risk of developing pathology, inflammation.*

Vibration disease (VD) is a widely-spread occupational pathology which occurs in working population and is medically and socially significant owing to the risk of social and economic losses caused by it. Working people are exposed to a set of harmful occupational factors; therefore, it is vital to perform monitoring over their health and implement timely activities aimed at preventing development of occupational and work-related diseases. All this is extremely important for achieving longer employment periods and life expectancy [1–3].

Neural and vascular disorders are the key elements in the VD clinical picture and peripheral circulatory disorders play a special role among them [4, 5]. Hypoxia and microcirculatory disorders activate cells which then start to release active substances, notably cytokines. Cytokines are molecules responsible for a type and duration of an immune response. They are synthesized immediately as a response to tissue lesions. Cytokines facilitate interactions between the immune system and organs and tissues in the body at the molecular

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level. The same mechanism mediates regulation of an immune response[1]. In case there are no pathological processes, cytokines are not detected in blood under the primary immune response. Their occurrence in blood indicates there are local functional disorders in the cytokine system which are the most frequent in case there are intense inflammatory reactions and create risks of a disease becoming more severe [6, 7]. Interleukins and interferons accumulated in an inflammation focus and produce their effects on most cells participating in this reaction. Such affected cells include granulocytes, macrophages, T- and B-lymphocytes as well as fibroblasts, endotheliocytes, and epithelial cells [8–10].

Examining mechanisms which underlie the well-coordinated working of the immune and nervous system can give grounds for developing criteria applied to assess risks of developing VD.

Our research goal was to estimate changes in the balance and ratio between the phenotypic structure of lymphocytes and cytokines as risk factors causing developing vibration disease.

Materials and methods. 54 men with diagnosed VD took part in our study. The disease was induced by local vibration or combined exposure to local and overall vibration. VD was diagnosed by occupational pathologists at the clinic of the East-Siberian Institute of Medical and Ecological Research according to the International Classification of Diseases, version ICD-10. Patients' average age was 51.45 ± 0.87 years; average working experience, 25.5 ± 2.13 years. The most common occupations in this (test) group were riveters, mechanic assemblers, dozer drivers, timber lorry drivers, crane operators, loader drivers, and tractor drivers. The reference group was comparable as per age and sex (51.06 ± 0.95 years, males) and included 27 practically healthy people who were not occupationally exposed to vibration. We used the following criteria to include patients with VD into our research: VD diagnosis was verified, they gave their written informed consent to take part in the research, and their working experience under exposure to vibration exceeded 10 years.

We examined peripheral blood taken in the morning on an empty stomach from the ulnar vein. The blood was taken into a vial with heparin (to extract leukocyte suspension) and a vial with a coagulation activator (to obtain serum). Lymphocytes and their populations were quantified in vitro by indirect immunofluorescence using monoclonal antibodies specific to differentiation antigens ($CD3^+$, $CD4^+$, $CD8^+$, $CD9^+$, $CD16^+$, $CD20^+$, $CD21^+$, $CD23^+$, $CD25^+$, $CD95^+$) ("Klonospektr", Moscow). We calculated a relative quantity of CD-positive cells in the total lymphocytes numbers using "Olimpus CX-41" microscope (Japan). IL-2, IL-4, IL-8, INFγ cytokines were determined in blood serum with the solid-phase ELISA method using relevant test-systems ("Vector-Best", Novosibirsk). All the data were statistically analyzed with Statistica 6.0 applied software package (StatSoft, USA). We applied non-parametric Mann-Whitney U test to compare different samplings. The samplings were described with median and interquartile range (*Me* (Q25–Q75)). We applied Spearmen's correlation analysis to establish correlations between indicators. The critical level of significance (p) was taken at 0.05 when statistical hypotheses were tested. Our research is in full conformity with the ethical standards stipulated by the Helsinki Declaration (2000)[2] and the Order No. 200n issued by the RF Public Healthcare Ministry on April 01, 2016[3].

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[1] Paltsev M.A., Kvetnoi M.I. Rukovodstvo po neiroimmunoendokrinologii [The guide on neural and immune endocrinology]. Moscow, Meditsina, 2008, 512 p. (in Russian).

[2] Declaration of Helsinki. Ethical principles for medical research involving human subjects. *The WMA, Inc*. Available at: https://www.wma.net/wp-content/uploads/2016/11/DoH-Oct2008.pdf (July 18, 2021).

[3] Ob utverzhdenii pravil nadlezhashchei klinicheskoi praktiki: Prikaz Ministerstva zdravookhraneniya RF ot 1 aprelya 2016 g. № 200n [On Approval of the rules for good clinical practice: The Order by the RF Public Healthcare Ministry issued on April 01, 2016 No. 200n]. *GARANT: the information and legal support*. Available at: https://base.garant.ru/71473446/ (July 18, 2021) (in Russian).

Results and discussion. In our previous study we analyzed the sub-population structure of lymphocytes in the same patients with VD. The study established changes in the immune response, notably growing quantities of $CD3^+$-, $CD4^+$-, $CD8^+$-lymphocytes and declining levels of $CD20^+$, $CD25^+$-lymphocytes in the patients with VD; the changes were caused by exposure to local vibration. We also revealed growing quantities of $CD3^+$-, $CD4^+$-, $CD8^+$-, $CD16^+$-, $CD20^+$-, $CD25^+$-, $CD95^+$-lymphocytes in the patients with VD caused by combined exposure to local and overall vibration, All this indicated that the immune system was apparently activated owing to this occupational pathology [11]. Bearing in mind that lymphocytes subpopulations produced cytokines [6, 12], we analyzed levels of those cytokines which reflected how active lymphocytic cells were.

Our analysis of cytokine contents in patients with VD (Table 1) established a statistically significant increase in contents of proinflammatory cytokines IL-8 and INFγ in the test group against the reference one ($p = 0.007$ and $p = 0.016$ respectively). As for the contents of regulatory IL-2, we detected a decline in it in the test group in contrast to the reference group ($p = 0.0003$).

Interleukins and interferons in Table 1 create a whole network of interactions where they have crossing functions and can act in synergy with other cytokines and lymphocytes [13]. Therefore the next stage in our research involved analyzing possible correlations between the phenotypic structure of lymphocytes and cytokines levels in the examined people. We established that those correlations in patients with VD were different from those detected for healthy people. This can be due to risks of more severe vibration disease. Significantly, all those correlations were positive.

Thus, the patients with VD had a positive correlation between the absolute quantity of the overall $CD3^+$ lymphocytes population ($r = 0.46$, $p = 0.029$) and the level of immune-stimulating IL-2 (Table 2). Also there was a positive correlation between the quantity of T-helpers $CD4^+$ and IL-4 contents in the examined patients with VD ($r = 0.39$, $p = 0.027$).

On the contrary, our examination of correlations between cellular immunity parameters and cytokines concentrations in the healthy people from the reference group established negative correlations between IFNγ and absolute quantities of $CD3^+$ ($r = –0.68$, $p = 0.029$)

Table 1

Cytokine contents in blood serum in patients with vibration disease, *Me* (Q25–Q75)

Indicators, pg/ml	Patients with VD, $n = 54$	Reference group, $n = 27$	p
IL-2	4.16 (1.97–7.55)	6.01 (5.68–8.32)	0.0003
IL-4	0.01 (0.01–2.71)	0.01 (0.01–0.32)	
IL-8	15.84 (0.94–37.38)	10.3 (0.01–14.6)	0.007
INFγ	1.63 (0.01–38.96)	0.23 (0.01–9.49)	0.016

Note: p shows the level of statistically significance for differences between the groups.

Table 2

Results produced by analyzing correlations between the quantity of lymphocytes and cytokines in the patients with VD and the reference group

Correlation pairs lymphocytes – cytokines	Patients with VD	Reference group
$CD3^+$ – IL-2	0.459	–
$CD4^+$ – IL-4	0.389	–
$CD3^+$ – INFγ	–	-0.681
$CD95^+$ – INFγ	–	-0.633

Note: the given values of r (Spearman's rank correlation coefficient) correspond to $p < 0.05$; dashes mean there are no statistically significant correlations, $p > 0.05$.

and $CD95^+$-lymphocytes ($r = –0.68$, $p = 0.047$) (Table 2). Given that there were no correlations between IFNγ and lymphocytes in the patients with VD, we can conclude that this interferon was completely excluded from the immune regulation in their bodies.

The basic function performed by the cytokines system is to provide well-coordinated working of the immune and nervous systems as a response to stress [14]. Our analysis of cytokines contents in the patients with VD allowed establishing hyperactivity of pro-inflammatory cytokines IL-8 and INFγ. It should be noted that IL-8 has a specific property which is its ability to regulate fast secretion of IL-8 protein product due to its release from neutrophilic granulocytes (they contain preformed IL-8) migrating after cells activation. In its turn, following the positive feedback principle, a drastic IL-8 ejection can induce its synthesis by the same cells and activate its functional properties and block up apoptosis of granulocytes [15–17]. We can assume that this mechanism for self-regulating the production of the aforementioned interleukin can underlie chronic inflammation supporting its acute phase in tissues in patients with VD. Undoubtedly, this creates a risk that the disease will last longer and be more severe. A significant growth in INFγ level is also related to the process becoming chronic when its production by type I T-helpers is enhanced [18]. This can explain a situation when IL-4 was determined within its reference values in patients with VD. Elevated concentrations of pro-inflammatory cytokines which we detected in such patients indicate that the inflammation process is highly active in them and has already become systemic. However, the examined patients had reduced IL-2 levels. We should note that they had lower contents of $CD25^+$ lymphocytes which expressed the receptor to IL-2 (IL-2R). Reduced IL-2 contents in blood don't properly support IL-2 binding to IL-2R thus disrupting T-helpers proliferation[1]. Obviously, prolonged VD caused by exposure to vibration results in depleting secretion of the aforementioned cytokine and the latter in its turn leads to apparent disorders in immune responses.

We performed the correlation analysis with its focus on correlations between lymphocytes sub-population and cytokines in the examined people. The analysis established a positive correlation between the absolute quantity of $CD3^+$-lymphocytes and the level of immune-stimulating IL-2. We can assume that lower IL-2 concentration in blood of the patients with VD occurred against an imbalance between the structure of lymphocytes population and subpopulation which developed due to immune cells differentiating and ripening improperly as well as their migration into an inflammation focus. The number of $CD4^+$-lymphocytes in the examined patients with VD was associated with the level of IL-4 which was mainly produced by Th2-lymphocytes. Besides, mast cells, basophils and D-lymphocytes also participate in synthesizing this interleukin. IL-4 induces T-lymphocytes differentiating into Th-2 cells thus inhibiting Th-1 lymphocytes development, activates macrophages, and evokes proliferation of activated mature T-cells [6, 19]. All this becomes obvious due to detecting positive correlations between concentrations of this cytokine and the quantity of T-helpers ($CD4^+$). Later this can be used in developing informative criteria showing severity of the pathological process. People in the reference group had negative correlations between the absolute quantity of $CD3^+$ and $CD95^+$-lymphocytes and IFNγ. This is easily explained since $CD3^+$-cells produce IFNγ which simultaneously activates $CD3^+$-lymphocytes whereas $CD95^+$-cells promote its apoptosis [20, 21].

A change in the nature of interrelations between lymphocytes sub-populations and cytokines contents can be due to a change in cytokine producers as well as a lea sensitive cellular response to cytokines [20, 22]. This creates elevated risks of developing immune pathologic reactions playing an important role in VD pathogenesis.

Conclusions. Therefore, risks of developing and progressing vibration disease are to a certain extent associated with its pathogenetic peculiarities. These peculiarities are related to, among other things, an imbalance of lympho-

cytic phenotypes and pro-anti-inflammatory cytokines characterized with the direct correlation between $CD3^+$ and IL-2, $CD4^+$and IL-4 against activated pro-inflammatory cytokines IL-8 and INFγ and reduced levels of IL-2. Our research data provide evidence that there are complex functional interrelations in the immune system. These data can be used in future research for substantiating new biomarkers in the additional VD diagnostics. To preserve workers' health, it seems advisable to draw on experience in examining the immune status during periodical medical examinations aimed at minimizing risks of developing occupational diseases.

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References

1. Popova A.Yu. Working conditions and occupational morbidity in the Russian Federation. *Meditsina truda i ekologiya cheloveka*, 2015, no. 3, pp. 7–13 (in Russian).

2. Onishchenko G.G. Actual problems of hygiene science and practice in the preservation of public health. *Gigiena i sanitariya*, 2015, vol. 94, no. 3, pp. 5–9 (in Russian).

3. Dolgikh O.V., Starkova K.G., Krivtsov A.V., Bubnova O.A. Variability of immunoregulatory and genetic markers in conditions of the combined effects of industrial environmental factors. *Gigiena i sanitariya*, 2016, vol. 95, no. 1, pp. 45–48. DOI: 10.18821/0016-9900-2016-95-1-45-48 (in Russian).

4. Zheglova A.V., Fedina I.N. Modern approaches to carrying out preventive examinations of workers of vibration-dangerous occupations. *Gigiena i sanitariya*, 2016, vol. 95, no. 11, pp. 1048–1064. DOI: 10.1882/0016-9900-2016-95-11-1048-1051 (in Russian).

5. Saarkoppel' L.M., Kir'yakov V.A., Oshkoderov O.A. Role of contemporary biomarkers in vibration disease diagnosis. *Meditsina truda i promyshlennaya ekologiya*, 2017, no. 2, pp. 6–10 (in Russian).

6. Simbirtsev A.S. Tsitokiny v patogeneze i lechenii zabolevaniy cheloveka [Cytokines in the pathogenesis and treatment of human diseases]. St. Petersburg, Foliant, 2018, 512 p. (in Russian).

7. Maslyanskiy A.L., Penin I.N., Cheshuina M.D., Trichina I.N., Novikova A.N., Kolesova E.P., Lazareva N.M., Mazing A.V. [et al.]. Common consistent patterns of the cytokine and chemokine production in patients with diffuse connective tissue diseases, inflammatory arthropathies and atherosclerosis]. *Tsitokiny i vospalenie*, 2014, vol. 13, no. 3, pp. 9–21 (in Russian).

8. Aksu I., Topcu A., Camsari U.M., Acikgoz O. Effect of acute and chronic exercise on oxidant-antioxidant equilibrium in rat hippocampus, prefrontal cortex and striatum. *Neurosci. Lett.*, 2009, vol. 452, no. 3, pp. 281–285. DOI: 10.1016/j.neulet.2008.09.029

9. Savchenko A.A., Zdzitovetsky D.E., Borisov A.G., Luzan N.A. Peculiarities of the cellular and humoral immunity status and the levels of concentrations of cytokines in patients with extensive purulent peritonitis. *Sibirskoe meditsinskoe obozrenie*, 2013, no. 1, pp. 24–28. DOI: 10.20333/25000136-2013-1-24-28 (in Russian).

10. Petrov R.V., Khaitov R.M., Chereshnev V.A. Physiology of the immune system: cellular and molecular-biological mechanisms. *Vestnik Rossiiskogo fonda fundamental'nyh issledovanii*, 2017, no. S1, pp. 96–119. DOI: 10.22204/2410-4639-2017-094-02S-96-119 (in Russian).

11. Kurchevenko S.I., Bodienkova G.M., Lakhman O.L. Comparative characteristics of the subpopulation composition of lymphocytes and heat shock protein in patients with vibration disease. *Rossiiskii immunologicheskii zhurnal*, 2019, vol. 13, no. 2–2, pp. 846–848. DOI: 10.31857/S102872210006677-9 (in Russian).

12. Zakharenkov V.V., Kazitskaya A.S., Mikhailova N.N., Romanenko D.V., Zhdanova N.N., Zhukova A.G. Influence of occupational hazards on human immune state. *Meditsina truda i promyshlennaya ekologiya*, 2017, no. 12, pp. 19–23 (in Russian).

13. Koval'chuk L.V., Gankovskaya L.V., Khoreva M.V., Sokolova E.V. Sistema tsitokinov, komplementa i sovremennye metody immunnogo analiza [The system of cytokines, complement and modern methods of immune analysis]. Moscow, RGMU Publ., 2001, 158 p. (in Russian).

14. Chernii V.I., Nesterenko A.N. Narusheniya immuniteta pri kriticheskikh sostoyaniyakh: osobennosti diagnostiki [Immune disorders in critical states: diagnostic features]. *Vnutrennyaya meditsina*, 2007, vol. 3, no. 3, pp. 11–14 (in Russian).

15. Serebrennikova S.N., Seminsky I.Zh. The role of cytokines in the inflammatory process (Part 1). *Sibirskii meditsinskii zhurnal (Irkutsk)*, 2008, vol. 81, no. 6, pp. 5–8 (in Russian).

16. Voronina M.S., Shilkina N.P., Vinogradov A.A., Butusova S.V. Interleukins 4, 6, 8 in the pathogenesis of rheumatoid arthritis and its complications. *Tsitokiny i vospalenie*, 2014, vol. 13, no. 1, pp. 5–10 (in Russian).

17. Ketlinskii S.A., Simbirtsev A.S. Tsitokiny [Cytokines]. St. Petersburg, Foliant, 2008, 552 p. (in Russian).

18. Eivazi S., Bagheri S., Hashemzadeh M.S., Ghalavand M., Qamsari E.S., Dorostkar R., Yasemi M. Development of T follicular helper cells and their role in disease and immune system. *Biomed. Pharmacother*., 2016, vol. 84, pp. 1668–1678. DOI: 10.1016/j.biopha.2016.10.083

19. Jiménez E., Sacedón R., Vicente A., Hernández-López C., Zapata A.G., Varas A. Rat peripheral CD4+CD8+ T-lymphocytes are partially immunocompetent thymus-derived cells that undergo post-thymic maturation to become functionally mature CD4+ T lymphocytes. *J. Immunol.*, 2002, vol. 168, no. 10, pp. 5005–5013. DOI: 10.4049/jimmunol.168.10.500

20. Singh R., Kumar A., Creery W.D., Ruben M., Giulivi A., Diaz-Mitoma F. Dysregulated expression of IFNγ and IL-10 and impaired IFNγ mediated responses at different disease stages in patients with genital herpes simplex virus-2 infection. *Clin. Exp. Immunol.*, 2003, vol. 133, no. 1, pp. 97–107. DOI: 10.1046/j.1365-2249.2003.02183.x

21. Drannik G.N. Klinicheskaya immunologiya i allergologiya [Clinical immunology and allegrology]. Moscow, MIA, 2003, 604 p. (in Russian).

22. Cousins W.S., Espinosa-Heidmann D.G., Miller D.M., Pereira-Simon S., Hernandez E.P., Chien H., Meier-Jewett C., Dix R.D. Macrophage activation associated with chronic murine cytomegalovirus infection results in more severe experimental choroidal neovascularisation. *PLoS Pathog.*, 2012, vol. 8, no. 4, pp. e1002671. DOI: 10.1371/journal.ppat.1002671

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Research article

NEOPTERIN AS A BIOMARKER SHOWING RISKS OF DEVELOPING PATHOLOGY IN BRONCHI AND LUNGS AMONG WORKERS WHO HAVE OCCUPATIONAL CONTACTS WITH INDUSTRIAL AEROSOLS

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Our research goal was to estimate neopterin level in blood serum of workers occupationally exposed to industrial aerosols with predominantly fibrogenic effects; to establish a relationship between this level and workers' age, working experience in hazardous working conditions, spirometric parameters and the level of C-reactive protein. We also aimed to assess neopterin as a possible biomarker showing risks of the developing inflammatory process in the bronchi and lungs at its early stage.

Our observation covered the following groups: workers employed at a metallurgic plant who had occupational contacts with industrial aerosols (exposure factors included welding and silicon-containing aerosols with predominantly fibrogenic effects in concentrations exceeding maximum permissible ones in workplace air); people suffering from chronic obstructive pulmonary disease of occupational etiology (COPD OE) in their post-exposure period; workers who didn't have any occupational contacts with industrial aerosols. We determined neopterin contents in blood serum with ELISA test using "Neopterin ELISA" reagent kit (IBL, Hamburg). Elevated neopterin levels were detected in blood serum of 56.1 % workers who were occupationally exposed to industrial aerosols and 53.3 % of patients with COPD OE; we also found a direct correlation between levels of neopterin and interferon gamma. Only 18.7 % workers without any occupational contacts with industrial aerosols had elevated neopterin levels in their blood serum and there were no authentic correlations between these levels and interferon gamma contents in this group. Workers who were occupationally exposed to industrial aerosols had a more apparent increase in the average level of neopterin at an age younger than 40 years and working experience shorter than 20 years in comparison with workers without any such exposure.

Neopterin can be used as a potential sensitive biomarker showing risks of an early inflammatory reaction in the lungs occurring in workers who are occupationally exposed to industrial aerosols. People with elevated neopterin levels in blood, especially those who are occupationally exposed to industrial aerosols, can be recommended to have their bronchi and lungs monitored in dynamics.

Key words: *neopterin, macrophages, industrial aerosols, pathology in the bronchi and lungs, risk factor.*

Diseases of the bronchi and lungs are among the most widely spread occupational pathologies. Pneumoconiosis, occupational bronchitis, and chronic obstructive pulmonary disease (COPD) often result from occupational exposure to industrial aerosols.

Industrial aerosols occur in workplace air when metal items are processed mechanically (when moldings are purified, polished, and ground), or due to thermal processes or sublimation of solid substances (melting, welding, etc.). Depending on their chemical structure,

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industrial aerosols can produce fibrogenic, irritating, toxic, allergenic, carcinogenic, and ionizing effects on the body[1]. Workers employed at metallurgic production or civil engineering enterprises are primarily exposed to aerosols with fibrogenic effects. Exposure to chemicals in contents not exceeding maximum permissible concentrations (MPC) doesn't exclude probable health disorders in excessively sensitive people[2]. Industrial aerosols can cause acute and, in case of long-term exposure, even chronic damage to the lungs that usually develops into fibrosis.

Health outcomes that may result from occupational exposure to industrial aerosols are given a lot of attention by experts in the field and studies usually concentrate on examining pathogenetic mechanisms of interaction between aerosol particles in workplace air and lung tissue cells [1]. Silicon-containing welding aerosols have significant capacity to activate the monocytic-macrophage system of the body.

Macrophages that circulate in blood and occur in lung tissues are the first barrier protecting the body from foreign substances. Alveolar macrophages (AMs) play a leading role in activating mucosal immunity mechanisms when various pathogenic substances penetrate airways mucosa. AMs generate reactive oxygen species (ROS) and reactive nitrogen species (RNS), phagocytize actively and neutralize infectious agents; they are the key component that regulates inflammation [2, 3].

Macrophages are highly plastic and able to polarize. M1 phenotype macrophages produce apparent cytotoxic and antimicrobial effects. When activated classically, they maintain inflammation in the lung tissue by producing pro-inflammatory cytokines (interleukins-1β, -6, -12, -23, tumor necrosis factor alpha) and destructing an inflammation focus [4]. M2 phenotype macrophages, which are activated as per an alternative way, make for fibrogenesis, proliferative processes, and tissue regeneration [5, 6].

Chronic clinical course of lung diseases occurs obviously due to macrophages "reprogramming" themselves towards M2 profile [7]. We should note that lung macrophages phagocytize actively and neutralize infectious agents but they are unable to remove aerosol particles completely. Inert particles are not destroyed by macrophage lysosomal apparatus. Besides, aerosols activate the bactericide oxygen system of macrophages and thereby stimulate production of reactive oxygen species and make for oxidation stress development. Free radicals that occur in abundance destroy phospholipid membranes of phagosomes and, as a result, a macrophage dies, aerosol particles are released into the surrounding medium, are then captured by another macrophage, and the process repeats itself again and again [8]. When macrophages are activated and then destroyed, this results in release of proteases and chemokines that enhance inflammation and subsequently cause tissue lesions [9]. Besides, other factors are activated including those responsible for macrophage flow to a place where aerosols are deposited, for example, colony-stimulating factors, factors of granulocyte proliferation in the bone marrow, etc. Inflammation mediators are synthesized in greater quantities and neopterin is among them [10].

According to the latest concepts, neopterin is a non-specific highly sensitive marker showing activation of the monocytic section in the cellular immunity. Neopterin is a pteridine released by specific immune cells, primarily macrophages and monocytes, when a specific immune response involving T-cells is activated due to their stimulation by interferon gamma (IFNγ). Production of neopterin is usually directly linked to synthesis of IFNγ which can be released by inborn or adaptive immunity cells, in particular, so called "natural

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

[2] R 2.2.2006-05. 2.2. Occupational hygiene. Guide on Hygienic Assessment of Factors of Working Environment and Work Load. Criteria and Classification of Working Conditions: approved by G.G. Onishchenko, the RF Chief Sanitary Inspector on July 29, 2005. *KODEKS: an electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200040973 (November 18, 2021) (in Russian).

killers". Quantity of synthesized neopterin is directly proportionate to quantity of IFNγ [11]. A lot of research works focus on a role that belongs to neopterin in cardiovascular pathology developing and progressing as well as prognosis for it. Neopterin has been shown to be a predictor of clinical outcomes for chronic and acute ischemic heart disease (IHD). Coronary angiography has established that neopterin levels in blood serum depend on how IHD progresses in patients with stable angina pectoris. Research works by many authors confirm that neopterin is a significant component in estimating stability of atheromas in patients with IHD and in monitoring over health of patients after coronary stent implantation [12, 13]. Not so many works dwell on examining a role neopterin plays in lung diseases. Results produced by few studies indicate that monitoring over neopterin levels can have some diagnostic and prognostic value in case of diseases caused by exposure to silicon dioxide, for example, silicosis [14]. Some authors have considered neopterin to be an immunological biomarker eligible for assessing clinical course of pneumoconiosis in workers employed in coal mining [15]. Neopterin in blood serum has also been proved to be a significant indicator of inflammation and exacerbations in patients with COPD [16–18].

Our research goal was to estimate the neopterin level in blood serum of workers occupationally exposed to industrial aerosols with predominantly fibrogenic effects; to establish a relationship between this level and workers' age, working experience in hazardous working conditions, spirometric parameters and the level of C-reactive protein. We also aimed to assess neopterin as a possible biomarker showing risks of a developing inflammatory process in the bronchi and lungs at its early stage.

Materials and methods. Overall, 194 people took part in our research; they were divided into three groups:

– the 1st group (or the test group) included workers employed at a metallurgic plant located in Nizhniy Novgorod region (57 men aged 39.1 ± 9.5 years with their working experience being 13.8 ± 7.7 years) who were occupationally exposed to welding and silicon-containing aerosols with predominantly fibrogenic effects (electrogas welders, workers dealing with strops, metal cutters, rollers, and millers);

– the 2nd group (or the control group) was made up of patients with COPD OE with stable clinical course caused by long-term exposure to welding and silicon-containing aerosols with predominantly fibrogenic effects. They were all treated in the clinic of the Rospotrebnadzor's Nizhny Novgorod Scientific Research Institute for Hygiene and Occupational Pathology (30 patients overall (8 women and 22 men) aged 56.8 ± 7.8 years and with their working experience being 26.0 ± 8.0 years). The modified Tiffeneau-Pinelli index amounted to less than 70 % of its physiological standard in all of them. COPD was diagnosed based on criteria outlined in the Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease – GOLD, 2021, and clinical recommendations developed by the Russian respiratory society[3]. The disease was proven to have occupational etiology in the course of medical examinations according to the rules stipulated in the National guide on occupational respiratory diseases (sanitary-hygienic conditions at workplaces were analyzed, working experience under harmful and hazardous conditions was taken into account, and medical records were thoroughly examined)[4];

– the 3rd group (or the reference one) included people employed at various productions who were not exposed to industrial aerosols at their workplaces (107 people overall (49 men and 58 women) aged 40.8 ± 9.9 years and working experience being 13.9 ± 8.5 years).

[3] Khronicheskaya obstruktivnaya bolezn' legkikh: klinicheskie rekomendatsii [Chronic obstructive pulmonary disease: clinical recommendations]. *The RF Public Healthcare Ministry*. Moscow, the Russian Respiratory Society Publ., 2018. Available at: https://cr.minzdrav.gov.ru/schema/603_1 (May 27, 2021) (in Russian).

[4] Professional'nye zabolevaniya organov dykhaniya: natsional'noe rukovodstvo [Occupational respiratory diseases: the national guide]. In: N.F. Izmerov, A.G. Chuchalin eds. Moscow, GEOTAR-Media Publ., 2015, 806 p. (in Russian).

People from the 1st and the 3rd group had periodical medical examinations at the consultative polyclinic of the Rospotrebnadzor's Nizhny Novgorod Scientific Research Institute for Hygiene and Occupational Pathology.

We excluded people with acute communicable diseases, malignant neoplasms, diabetes mellitus, and exacerbated chronic diseases from our research.

Working conditions were estimated according to the Federal Law No. 426 issued on December 28, 2013 "On special assessment of working conditions"[5]. According to these estimates contents of particulate matter (dusts) were sometimes higher than maximum permissible concentrations in workplace air where people from the 1st group worked and working conditions there belonged to hazard category 3.1 (harmful, the 1st degree). Average shift concentrations of diiron trioxide in dusts varied from 0.65 to 7.2 mg/m^3 at different spots (MPC is 6.0 mg/m^3); silicon dioxide (accounting for 10 to 70 % in dusts), from 0.44 to 2.4 mg/m^3 (MPC is 2.0 mg/m^3); iron, from 1.65 to 2.6 mg/m^3 (MPC is 10.0 mg/m^3); electro-corundum (aluminum oxide), from 1.8 to 6.6 mg/m^3 (MPC is 6.0 mg/m^3); manganese (with its share in dusts being up to 20 %), from 0.25 to 0.72 mg/m^3 (MPC is 0.6 mg/m^3). Maximal concentrations of manganese, silicon dioxide, electro-corundum, and diiron trioxide in workplace air were by 1.1–1.2 times higher than MPC (working conditions belong to hazard category 3.1) at workplaces of metal cutters, millers and electrogas welders. When welding was performed, ozone contents in an area where a welder breathed were by 1.1 times higher than MPC. Occupational noise was higher than its maximum permissible level (more than 80 dBA) at the examined workplaces and reached 90–95 dBA at some of them (working conditions belonging to hazard category 3.2, ("harmful", the 2nd degree)). Overall assessment of working conditions assigned them into hazard categories 3.1–3.2 ("harmful conditions", the 1st and 2nd degree).

All participants gave their informed consent to take part in our research; the research work was approved by the local ethical committee at the Rospotrebnadzor's Nizhny Novgorod Scientific Research Institute for Hygiene and Occupational Pathology.

We examined external respiration in all patients using "SpirolabIII OXY" spirometer (Italy) and estimating the following spirometric parameters: forced vital capacity (FVC, $\%_{standard}$), forced expiratory volume over the 1st second (FEV_1, $\%_{standard}$), calculated ratio of these two indicators (FEV_1/FVC, %) or the modified Tiffeneau-Pinelli index (MTPI), and peak expiratory flow at 75 % FVC (PEF 75 %).

We determined neopterin and IFNγ contents in blood serum with ELISA tests using "Neopterin ELISA" reagent kit (IBL, Hamburg) and "gamma-Interferon-ELISA-BEST" ("Vector-Best" JSC, Russia). C-reactive protein (CRP) in blood serum was also detected with ELISA tests using highly sensitive "CRP-ELISA-BEST" reagent kit ("Vector-Best" JSC, Russia) with its detection limit being 0.05 IU/l.

To estimate age-specific neopterin contents in blood serum, we divided people in the 1st and 3rd groups into four age sub-groups: aged 25–30 years, 31–40 years, 41–50 years, 51–60 years and older.

To estimate neopterin contents in blood serum depending on working experience, people in the 1st and 3rd group were divided into three sub-groups: with working experience not exceeding 10 years, from 11 to 20 years, and longer than 20 years.

The results were statistically analyzed with variation statistic procedures using "Statistica 6.1" software package (StatSoft Inc., USA). We applied Shapiro – Wilk test to check if indicators were distributed normally and to analyze dispersion equality. In case indicators were distributed normally, we ana-

[5] O spetsial'noi otsenke uslovii truda: federal'nyi zakon FZ № 426 ot 28.12.2013 g. (prinyat Gos. Dumoi 23.12.2013, odobren Sovetom Federatsii 25.12.2013) [On special assessment of working conditions: The Federal Law No. 426 issued on December 28, 2013 (approved by the State Duma on December 23, 2013, approved by the Federation Council on December 25, 2013)]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_156555/ (November 27, 2021) (in Russian).

lyzed them using parametric statistic procedures. Distributions were estimated by calculating simple mean (*M*) and root-men-square deviation (δ). We estimated authenticity of differences between mean values obtained for different groups using parametric Student's t-test. We applied Pearson's correlation coefficient to determine whether there was a linear correlation between two quantitative indicators. In case indicators were not distributed normally, we applied non-parametric statistic procedures, for example, Mann – Whitney U test. The data were given as *Med* ± *IQR* (25–75 %). We applied non-parametric goodness-of-fit test χ^2 (Pearson's test) to estimate statistical significance of differences between several relative indicators (frequencies).

Critical level of significance was taken at $p < 0.05$. Values of p from 0.05 and up to 0.1 inclusively were considered to be trends.

Results and discussion. We didn't detect any sex-related differences in neopterin contents in blood serum and frequencies of its elevated levels (more than 10.0 nmol/l) in the exposed and non-exposed workers as well as patients with COPD OE ($p > 0.05$). Table 1 provides the data on neopterin contents in blood serum and frequencies of its elevated levels in the examined people from all three groups.

Neopterin concentrations in blood serum of the examined people varied from 2.8 to 21.9 nmol/l as we established by analyzing the obtained data. Its average concentration was the highest in blood serum of the workers exposed to industrial aerosols (Group 1) and patients with COPD (Group 2). Neopterin levels in blood serum of the patients with COPD OE were authentically higher that the same indicator in blood serum of the workers exposed to industrial aerosols ($p_{1–2} = 0.009$). The non-exposed workers had neopterin levels in their blood serum within reference values and these levels were authentically different from those detected in the first two groups ($p_{1–3} = 0.0001$; $p_{2–3} = 0.0001$). Elevated neopterin levels (more than 10.0 nmol/l) were detected in a half of the workers who were occupationally exposed to industrial aerosols and patients with COPD OE, 56.1 % and 53.3 % respectively. Such elevated levels were detected only in 18.7 % of the non-exposed workers, hence by 2.8–3 times less frequently against the first two groups.

Table 2 provides data on neopterin levels indifferent age sub-groups of the workers in the test group (Group 1) and reference group (Group 3). We detected the lowest neopterin levels among the workers exposed to industrial aerosols and non-exposed ones in the age sub-group from 25 to 30 years (9.1 ± 2.7 nmol/l and 6.3 ± 2.1 nmol/l respectively). Neopterin levels detected in this age sub-group were authentically different from those detected in people aged from 31 to 60 years ($p = 0.002$ for Group 1 and $p = 0.039$ for Group 3 (Student's t-test)). We should note that neopterin concentration in blood serum was authentically higher

Table 1

Neopterin concentration in blood serum and frequency of its elevated levels in workers and patients with COPD OE

Indicator	Examined groups		
	Group 1 (test) ($n = 57$)	Group 2 (control) ($n = 30$)	Group 3 (reference) ($n = 107$)
Neopterin concentration (nmol/l), $M \pm \delta$	10.4 ± 1.7	11.9 ± 2.3	7.5 ± 1.8
p (Student's t-test)	$p_{1–2} = 0.009$; $p_{1–3} = 0.0001$; $p_{2–3} = 0.0001$		
Frequency of elevated neopterin level (more than 10.0 nmol/l), abs. (%)	32 (56.1)	16 (53.3)	20 (18.7)
p^* (χ^2 test)	$\chi^2 = 0.528$, $p_{1–2} = 0.468$; $\chi^2 = 24.086$, $p_{1–3} < 0.001$; $\chi^2 = 14.514$, $p_{2–3} < 0.001$		

Note: p (Student's t-test) is authenticity of differences in neopterin contents between the groups; p^* (χ^2 test) is authenticity of differences in frequencies of elevated neopterin levels between the groups.

Table 2

Neopterin concentration in blood serum and frequency of its elevated levels in different age sub-groups

Age sub-groups							
Sub-group 1 (from 25 to 30 years)		Sub-group 2 (from 31 to 40 years)		Sub-group 3 (from 41 to 50 years)		Sub-group 4 (from 51 to 60 years)	
Group 1 test (n = 23)	Group 3 reference (n = 12)	Group 1 test (n = 11)	Group 3 reference (n = 35)	Group 1 test (n = 13)	Group 3 reference (n = 39)	Group 1 test (n = 10)	Group 3 reference (n = 21)
Age (years), $M \pm \delta$							
28.4 ± 1.6	27.5 ± 2.1	38.1 ± 1.19	37.8 ± 1.15	43.0 ± 2.44	43.3 ± 3.43	54.0 ± 2.8	55.0 ± 3.2
p_{1-3} = 0.19		p_{1-3} = 0.41		p_{1-3} = 0.91		p_{1-3} = 0.92	
Neopterin concentration (nmol/l), $M \pm \delta$							
9.1 ± 2.7	6.3 ± 2.1	12.0 ± 2.9	7.6 ± 2.5	11.7 ± 2.7	8.2 ± 2.6	10.7 ± 1.6	7.7 ± 2.5
p_{1-3}* = 0.007		p_{1-3}* = 0.0001		p_{1-3}* = 0.001		p_{1-3}* = 0.008	
Frequency of elevated neopterin levels (more than 10.0 nmol/l), abs. (%)							
9 (39.1)	0 (0)	6 (54.5)	4 (11.4)	9 (69.2)	10 (25.6)	8 (80.0)	6 (28.5)
χ^2 = 8.37 p_{1-3}** = 0.004		χ^2 = 12.538 p_{1-3}** < 0.001		χ^2 = 10.517 p_{1-3}** = 0.002		χ^2 = 10.608 p_{1-3}** = 0.002	

Note:

p (Student's t-test) is authenticity of differences in age in each age sub-group between Group 1 and Group 3;

p* (Student's t-test) is authenticity of differences in neopterin concentration each age sub-group between Group 1 and Group 3;

p** (χ^2 test) is authenticity of differences in frequencies of elevated neopterin levels in each age sub-group between Group 1 and Group 3.

in all age sub-groups of exposed workers (Group 1) against non-exposed ones (Group 3) (p_{1-3}* = 0.007 for the age sub-group from 25 to 30 years; p_{1-3}* = 0.0001, from 31 to 40 years; p_{1-3}* = 0.001, from 41 to 50 years; p_{1-3}* = 0.008, from 51 to 60 years).

Frequency of elevated neopterin levels (more than 10.0 nmol/l) grew with age in both groups (from 39.1 to 80.0 % in Group 1 and from 0 to 28.5 % in Group 3). This indicator was authentically higher in all age sub-groups of the workers who were occupationally exposed to industrial aerosols than in all age sub-groups of their non-exposed counterparts (p_{1-3}* = 0.004 for the age sub-group from 25 to 30 years; p_{1-3}* < 0.001, from 31 to 40 years; p_{1-3}* = 0.002, from 41 to 50 years; p_{1-3}* = 0.002, from 51 to 60 years).

Most patients with COPD OE were older than 50 years. Neopterin concentration in their blood serum didn't differ from those detected in age-sub-groups 2, 3 and 4 in Group 1 (p_{1-2} = = 0.42 from 31 to 40 years; p_{1-2} = 0.42 from 41 to 50 years; p_{1-2} = 0.41 from 51 to 60 years, Student's t-test). Frequency of elevated neopterin levels (more than 10.0 nmol/l) didn't differ from this indicator in Group 1 either in the age sub-groups 2, 3 and 4 (χ^2 = 0.005, p_{1-2} = 0.9 from 31 to 40 years; χ^2 = 0.94, p_{1-2} = 0.33 from 41 to 50 years; χ^2 = 2.222, p_{1-2} = 0.137 from 51 to 60 years).

Table 3 provides the data on neopterin concentration in the examined workers' blood serum and frequency of its elevated levels depending on working experience.

Having analyzed all the obtained data, we established that neopterin concentration in blood serum grew as working experience got longer in the sub-groups 1 and 2 in both test and reference group (p = 0.004 for Group 1; p = 0.01 for Group 3). Neopterin concentration in blood serum of the workers with their working experience being longer than 20 years (sub-group 3) didn't differ from levels detected in workers with their working experience being from 11 to 20 years and not longer than 10 years. Frequency of elevated neopterin levels grew as working experience got longer in both groups (from 33.3 % to 90.0 % in Group 1 and from 12.1 % to 27.3 %

in Group 3). This indicator was authentically higher in all sub-groups of the exposed workers with different working experience than in their non-exposed counterparts ($p_{1–3}$** = 0.024 for the workers with their experience not exceeding 10 years; $p_{1–3}$** = 0.014, from 11 to 20 years; $p_{1–3}$** < 0.001, longer than 20 years).

We analyzed correlations between neopterin concentration in the workers' blood serum and spirometric parameters. Table 4 provides the results.

Our research established that FEV_1 and PEF 75 % were authentically lower in the workers who were occupationally exposed to industrial aerosols than in their non-exposed counterparts ($p_{1–3}$ = 0.042 for FEV_1; $p_{1–3}$ = 0.015 for PEF 75 %). A trend for an inverse correlation was detected only between neopterin concentration and PEF 75 % (R = –0.26, p = 0.06).

Table 5 provides the results produced by analyzing CRP and IFNγ levels in blood serum of the examined people.

We analyzed CRP concentrations in blood serum of the examined people and established that they varied from 0.5 to 15.0 mg/l. Its average value was the highest in blood serum of patients with COPD OE and was authentically different from the values detected among

Table 3

Neopterin concentration in blood serum frequency of its elevated levels depending on working experience

Sub-groups as per working experience					
Sub-group 1 (not longer than 10 years)		Sub-group 2 (from 11 to 20 years)		Sub-group 3 (longer than 20 years)	
Group 1 test (n = 24)	Group 3 reference (n = 58)	Group 1 test (n = 23)	Group 3 reference (n = 16)	Group 1 test (n = 10)	Group 3 reference (n = 33)
Neopterin concentration (nmol/l), $M \pm \delta$					
9.2 ± 2.8	7.7 ± 2.1	11.5 ± 2.5	8.5 ± 2.6	10.9 ± 1.4	7.8 ± 2.9
$p_{1–3}$* = 0.009		$p_{1–3}$* = 0.001		$p_{1–3}$* = 0.002	
Frequency of elevated neopterin levels (more than 10.0 nmol/l), abs. (%)					
8 (33.3)	7 (12.1)	15 (65.2)	4 (25.0)	9 (90.0)	9 (27.3)
χ^2 = 5.136 $p_{1–3}$** = 0.024		χ^2 = 6.109 $p_{1–3}$** = 0.014		χ^2 = 12.4 $p_{1–3}$** < 0.001	

Note:

p* (Student's t-test) is authenticity of differences in neopterin concentration in each sub-group as per working experience between Group 1 and Group 3;

p** (χ^2 test) is authenticity of differences in frequencies of elevated neopterin levels in each sub-group as per working experience between Group 1 and Group 3.

Table 4

Spirometric parameters and correlations between them and neopterin concentrations in workers' blood serum

Parameter, $M \pm \delta$	Examined group			
	Group 1 (test) (n = 57)	Group 3 (reference) (n = 107)	$p_{1–3}$	R
FVC, $\%_{standard}$	105.0 ± 15.6	109 ± 14.7	0.12	–0.07, p = 0.57
FEV_1, $\%_{standard}$	97.4 ± 13.6	102 ± 13.1	0.042	–0.11, p = 0.38
MTPI, %	92.8 ± 7.7	94.3 ± 9.0	0.23	–0.03, p = 0.81
PEF 75 %	70.3 ± 20.8	80.4 ± 26.3	0.015	–0.26, p = 0.06

Note:

$p_{1–3}$ (Student's t-test) is authenticity of differences in spirometric parameters between Groups 1 and 3;

R is Pearson's correlation coefficient showing correlations between neopterin concentration in workers' blood serum (Groups 1 and 3) and spirometric parameters.

Table 5

CRP and IFNγ concentrations in blood serum and frequencies of their elevated levels in the workers and patients with COPD OE

Indicator	Examined groups		
	Group 1 (test) (n = 57)	Group 2 (control) (n = 30)	Group 3 (reference) (n = 107)
CRP concentration (mg/l), *Med* ± *IQR* (25–75 %)	4.9 (1.94–7.29)	9.25 (4.4–16.2)	3.57 (1.49–6.99)
p	$p_{1-2} = 0.001$; $p_{1-3} = 0.32$; $p_{2-3} = 0.0001$		
Frequency of elevated CRP level (more than 8.0 mg/l), abs. (%)	9 (15.7)	15 (50.0)	21 (19.7)
p*	$\chi^2 = 8.124$, $p_{1-2} = 0.005$; $\chi^2 = 3.547$, $p_{1-3} = 0.06$; $\chi^2 = 12.4$, $p_{2-3} < 0.001$		
IFNγ concentration (pg/l), $M \pm \delta$	1.24 ± 0.85	1.25 ± 0.91	0.88 ± 0.59
p**	$p_{1-2} = 0.82$; $p_{1-3} = 0.004$; $p_{2-3} = 0.005$		
Frequency of elevated IFNγ level (higher than 20.0 pg/ml), abs. (%)	0 (0)	0 (0)	0 (0)

Note:
p (Mann – Whitney test) is authenticity of differences in CRP concentration between Groups 1, 2 and 3;
p* (χ^2 test) is authenticity of differences in frequencies of elevated CRP concentrations between Groups 1, 2 and 3;
p** (Student's t-test) is authenticity of differences in IFNγ concentrations between Groups 1, 2 and 3.

workers from Group 1 and 3 (p_{1-2} = 0.001; p_{2-3} = 0,0001). We didn't detect any differences in CRP concentrations between the workers from Groups 1 and 3 (p_{1-3} = 0.32). Elevated CRP level (more than 8.0 mg/l) was detected in 15.7 % of the workers who were occupationally exposed to industrial aerosols; in 19.7 % of non-exposed workers; and in 50.0 % of the patients with COPD OE. We didn't detect any correlation between neopterin and CRP.

Our analysis of IFNγ concentrations in blood serum of the examined people established that they were within reference levels both in the workers and patients with COPD OE (Table 5). However, IFNγ concentration was authentically higher in the workers who were occupationally exposed to industrial aerosols and in the patients with COPD OE than in the non-exposed workers (p_{1-2} = 0.82; p_{1-3} = 0.004; p_{2-3} = 0.005).

The correlation analysis showed a direct correlation between IFNγ and neopterin concentrations in the exposed workers and patients with COPD OE (Groups 1 and 2), R = 0.35, p = 0.04 and R = 0.48, p = 0.01 respectively. We revealed only a trend for a correlation between neopterin and IFNγ concentrations for the non-exposed workers (Group 3) (R = 0.18, p = 0.08). However, we found an authentic direct correlation between neopterin and IFNγ levels (R = 0.51, p = 0.01) in the workers from this group who had high neopterin levels in their blood serum.

Therefore, the research results indicated that 56.1 % the workers who were occupationally exposed to industrial aerosols had elevated neopterin level in their blood serum which was also detected in the patients with COPD OE (53.3 %). This implies that industrial aerosols produced negative effects on the bronchi and lungs of the exposed workers. Elevated neopterin levels were by 3 times less frequently detected in the workers who didn't have any contacts with industrial aerosols at their workplaces. Neopterin synthesis is linked to IFNγ as it is confirmed by the detected direct correlations between neopterin and IFNγ concentrations. These correlations were more apparent in the workers who were occupationally exposed to industrial aerosols and in the patients with COPD OE in the post-exposure period. This fact shows that stimulated cellular immunity can possibly participate in developing and progressing bronchopulmonary diseases.

We established common regularities and differences in how neopterin levels changed and how frequently they were elevated in the workers who were occupationally exposed to industrial aerosols and in non-exposed ones. Average neopterin concentration grew in all workers who were younger than 40 years and was higher than the reference value (up to 10.0 nmol/l) in the workers exposed to industrial aerosols whereas it was within reference values in all age sub-groups of the non-exposed workers. Frequency of elevated neopterin levels also grew in all workers depending both on age and working experience; however, this growth was more apparent in the workers who were occupationally exposed to industrial aerosols. This growing neopterin level depending on working experience is probably due to only young workers (aged from 25 to 30) being included into the sub-group with working experience not exceeding 10 years. However, we can't exclude probable influence exerted on neopterin concentration in blood serum by longer contacts with industrial aerosols.

Research works performed by some authors indicate there is a correlation between neopterin and age. But their conclusions don't clarify whether higher neopterin levels occur due to normal immune ageing in a healthy body or they can be related to more patients with diseases which haven't been diagnosed so far but are accompanied with elevated neopterin levels. Some authors detected a weak linear growth in neopterin levels in older patients that started somewhere between the 3rd and 4th decades of their age. This allowed assuming that an increase in neopterin level could be considered a part of physiological immune ageing; however, we still can't exclude an alternative explanation, notably, occurrence of age-related diseases [19, 20].

Currently most authors consider neopterin to be a highly sensitive marker of inflammation [21]. Our comparative analysis of neopterin and CRP levels suggests that neopterin is a more specific factor reflecting inflammation in the bronchi and lungs. Elevated neopterin levels were detected in the workers who were occupationally exposed to industrial aerosols and in the patients with COPD OE in more than 50.0 % cases whereas CRP levels were detected with the same frequency among both exposed and non-exposed workers (15.7 % and 19.7 % respectively). We didn't detect any differences in CRP concentrations in blood serum between the workers from both groups (1 and 3) and there were authentic differences only between the workers and patients with COPD OE.

Since neopterin is closely connected with early stages in inflammatory processes in the lungs, it can provide an insight into early changes in the bronchial tubes and bronchioles of workers who are occupationally exposed to industrial aerosols. This is proven by a trend for an inverse correlation between neopterin level and PEF 75 % ($p = 0.06$).

Therefore, neopterin can be used as a diagnostic marker of developing inflammation in the bronchi and lungs at its early stage caused, among other things, by occupational exposure to industrial aerosols. On one hand, neopterin can be considered a biomarker of effect which is expressed by activated macrophages in the lungs as a result of exposure to a foreign substance, industrial aerosols being a good example here. On the other hand, neopterin reflects activation of macrophage section in the immunity that results from exposure to industrial aerosols. The latter seems to be an important pathogenetic mechanism of developing pathologies in the lungs caused by exposure to industrial aerosols.

Our research data indicate it is necessary not only to further investigate neopterin as a biomarker of effect and a risk of early developing pathologies in the bronchi and lungs but also to determine its clinical significance as a prognostic immunologic criterion regarding occupational lung pathologies. Our results can stimulate further clinical and experimental research aimed at examining immune pathogenesis of bronchopulmonary diseases and searching for new immunologic biomarkers which can be used in early diagnostics and prognosis. They can also be eligible for developing new therapeutic strategies for treatment of occupational lung diseases involving immunomodulatory drugs.

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References

1. Radnoff D., Todor M.S., Beach J. Occupational exposure to crystalline silica at Alberta work sites. *J. Occup. Environ. Hyg.*, 2014. vol. 11, no. 9, pp. 557–570. DOI: 10.1080/15459624.2014.887205

2. Taylor P.R., Martinez-Pomares L., Stacey M., Lin H.H., Brown G.D., Gordon S. Macrophage receptors and immune recognition. *Annu. Rev. Immunol.*, 2005, vol. 23, pp. 901–944. DOI: 10.1146/annurev.immunol.23.021704.115816

3. Knapp S., Leemans J.C., Florquin S., Branger J., Maris N.A., Pater J., van Rooijen N., van der Poll T. Alveolar macrophages have a protective antiinflammatory role during murine pneumococcal pneumonia. *Am. J. Respir. Crit. Care Med.*, 2003, vol. 167, no. 2, pp. 171–179. DOI: 10.1164/rccm.200207-698OC

4. Mantovani A., Biswas S.K., Galdiero M.R., Sica A., Locati M. Macrophage plasticity and polarization in tissue repair and re-modeling. *J. Pathol.*, 2013, vol. 229, no. 2, pp. 176–185. DOI: 10.1002/path.4133

5. Swirski F.K., Nahrendorf M. Leukocyte behavior in atherosclerosis, myocardial infarction, and heart failure. *Science*, 2013, vol. 339, no. 6116, pp. 161–166. DOI: 10.1126/science. 1230719

6. Possamai L.A., Thursz M.R., Wendon J.A., Antoniades C.G. Modulation of monocyte / macrophage function: a therapeutic strategy in the treatment of acute liver failure. *J. Hepatol.*, 2014, vol. 61, no. 2, pp. 439–445. DOI: 10.1016/j.jhep.2014.03.031

7. Joshi A.D., Raymond T., Coelho A.L., Kunkel S.L., Hogaboam C.M. A systemic granulomatous response to Schistosoma mansoni eggs alters responsiveness of bone-marrow-derived macrophages to Toll-like receptor agonists. *J. Leukoc. Biol.*, 2008, vol. 83, no. 2, pp. 314–324. DOI: 10.1189/jlb.1007689

8. Arora S., Dev K., Agarwal B., Das P., Syed M.A. Macrophages: Their role, activation and polarization in pulmonary diseases. *Immunobiology*, 2018, vol. 223, no. 4–5, pp. 383–396. DOI: 10.1016/j.imbio.2017.11.001

9. Svedberg F.R., Brown S.L., Krauss M.Z., Campbell L., Sharpe C., Clausen M., Howell G.J., Clark H. [et al.]. The lung environment controls alveolar macrophage metabolism and responsiveness in type 2 inflammation. *Nat. Immunol.*, 2019, vol. 20, no. 5, pp. 571–580. DOI: 10.1038/s41590-019-0352-y

10. Mosser D.M., Edwards J.P. Exploring the full spectrum of macrophage activation. *Nat. Rev. Immunol.*, 2008, vol. 8, no. 12, pp. 958–969. DOI: 10.1038/nri2448

11. Michalak Ł., Bulska M., Strząbała K., Szcześniak P. Neopterin as a marker of cellular immunological response. *Postepy Hig. Med. Dosw. (Online)*, 2017, vol. 71, no. 1, pp. 727–736. DOI: 10.5604/01.3001.0010.3851

12. Yoshiyama T., Sugioka K., Naruko T., Nakagawa M., Shirai N., Ohsawa M., Yoshiyama M., Ueda M. Neopterin and cardiovascular events following coronary stent implantation in patients with stable angina pectoris. *J. Atheroscler. Thromb.*, 2018, vol. 25, no. 11, pp. 1105–1117. DOI: 10.5551/jat.43166

13. Kaski J.C. Neopterin for prediction of in-hospital atrial fibrillation – the "forgotten biomarker" strikes again. *J. Intern. Med.*, 2018, vol. 283, no. 6, pp. 591–593. DOI: 10.1111/joim.12761

14. Altindag Z.Z., Baydar T., Isimer A., Sahin G. Neopterin as a new biomarker for the evaluation of occupational exposure to silica. *Int. Arch. Occup. Environ. Health.*, 2003, vol. 76, no. 4, pp. 318–322. DOI: 10.1007/s00420-003-0434-9

15. Ulker O.C., Yucesoy B., Durucu M., Karakaya A. Neopterin as a marker for immune system activation in coal workers' pneumoconiosis. *Toxicol. Ind. Health*, 2007, vol. 23, no. 3, pp. 155–160. DOI: 10.1177/0748233707083527

16. Pizzini A., Lunger F., Sahanic A., Nemati N., Fuchs D., Weiss G., Kurz K., Bellmann-Weiler R. Diagnostic and Prognostic Value of Inflammatory Parameters Including Neopterin in the Setting of Pneumonia, COPD, and Acute Exacerbations. *COPD*, 2017, vol. 14, no. 3, pp. 298–303. DOI: 10.1080/15412555.2016.1266317

17. Rybka J., Korte S.M., Czajkowska-Malinowska M., Wiese M., Kędziora-Kornatowska K., Kędziora J. The links between chronic obstructive pulmonary disease and comorbid depressive symptoms: role of IL-2 and IFN-γ. *Clin. Exp. Med.*, 2016, vol. 16, no. 4, pp. 493–502. DOI: 10.1007/s10238-015-0391-0

18. Naumov A.V., Prokofieva T.V., Saroyanc L.V., Polunina O.S. Clinical-diagnostic value of the study of neopterin in myocardial infarction on the background of chronic obstructive pulmonary disease.

Kubanskii nauchnyi meditsinskii vestnik, 2018, vol. 25, no. 2, pp. 121–126. DOI: 10.25207/1608-6228-2018-25-2-121-126 (in Russian).

19. Spencer M.E., Jain A., Matteini A., Beamer B.A., Wang N.-Y., Leng S.X., Punjabi N.M., Walston J.D., Fedarko N.S. Serum levels of the immune activation marker neopterin change with age and gender and are modified by race, BMI, and percentage of body fat. *J. Gerontol. A Biol. Sci. Med. Sci.*, 2010, vol. 65, no. 8, pp. 858–865. DOI: 10.1093/gerona/glq066

20. Dibakou S.E., Souza A., Boundenga L., Givalois L., Mercier-Delarue S., Simon F., Prugnolle F., Huchard E., Je Charpentier M. Ecological, parasitological and individual determinants of plasma neopterin levels in a natural mandrill population. *Int. J. Parasitol. Parasites Wildl.*, 2020, vol. 11, pp. 198–206. DOI: 10.1016/j.ijppaw.2020.02.009

21. Gladkikh R.A., Molochniy V.P., Polesko I.V. Neopterin as a Modern Marker of Inflammation. *Detskie infektsii*, 2016, vol. 15, no. 2, pp. 19–23. DOI: 10.22627/2072-8107-2016-15-2-19-23 (in Russian).

Blinova T.V., Umnyagina I.A., Troshin V.V., Strakhova L.A., Kolesov S.A. Neopterin as a biomarker showing risks of developing pathology in bronchi and lungs among workers who have occupational contacts with industrial aerosols. Health Risk Analysis, 2022, no. 1, pp. 136–146. DOI: 10.21668/health.risk/2022.1.16.eng

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Review

URBAN PLANNING AND PUBLIC HEALTH: ANALYTICAL REVIEW

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This review focuses on certain challenges related to hygienic assessment of urban planning. Studies by Soviet (and later Russian) hygienists that have been accomplished since 1970ties have brought about optimal solutions for planning urban districts, climatic peculiarities taken into account. Specific hygienic standards have been developed with respect to insolation, building density, minimum safe distances from housing to parking areas, recommendations on creating green spaces along the busiest motorways as well as some other parameters that are now a part of regulatory documents on construction. A comfortable urban environment can hardly be created in Russian cities without adherence to hygienic standards regarding ambient air quality, noise levels, insolation, creating easily available open green spaces. All this should be implemented without any limitations on building density, especially in downtowns areas. Hygienic standards stipulate transition from fossil fuels to more environmentally friendly ones in cities located in Siberia and the Far East. There are also other multiple indicators of urban environment quality that shouldn't be neglected. The review also considers how important insolation is for health of urban citizens, especially bearing in mind the latest data on significance of vitamin D for prevention of osteoporosis. A great attention is paid to positive effects produced by open green spaces on population health including mental health, higher levels of physical activity, better social interactions and mutual trust, and reduced social isolation. All these aspects are becoming truly vital after the COVID-19 pandemic. Green spaces are also important since they help mitigate certain negative consequences of living in an aggressive urban environment.

Key words: *public health, COVID-19, urban planning, building density, ambient air, noise, insolation, green spaces, vitamin D.*

Urbanization has been growing over the last 20 years as has a share of urban population in Russia and it has already reached 74.3 %. It means that a lot of attention should be given to living conditions in cities. In 2020 the share of urban population in Russia was by almost 20 % higher than on average in the world where it amounted to 55 %.

Historical background. In Russia studies on peculiar features of different territories, climate included, started as far back as in the 18th century. They enabled determining population groups with high mortality and morbidity rates. Over a period from 1797 to 1861 provincial boards of health created more than 150 topographies describing wind directions, smells, and other territorial features[1]. F.F. Erismann, a pioneer and founder of scientific hygiene in Russia, stated it was necessary to study health as profoundly as possible bearing in mind associations with sanitary factors. Later the idea was implemented by many doctors working in urban and rural areas. The 20th century brought about rapid industrialization resulting in occurrence of a lot of new cities. Some of them were properly located on the windward side with respect to metallurgic productions (Magnitogorsk as an example) but there were also poor choices on layouts of industrial and residential areas. Some cities were located in hollows between

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[1] Ivanov B.D. Mediko-topograficheskie opisaniya Rossii (do 1861 g.) [Medical and topographical descriptions of Russia (prior to 1861)]. *Sovetskoe zdravookhranenie*, 1960, pp. 46–52 (in Russian).

mountain ranges and their development led to higher ambient air pollution, the city of Chita being a good example here. As scientific hygiene advanced, new data were accumulated and applied to develop relevant standards for territorial layouts. It is very interesting to note that in 1943, during the Great Patriotic War, V.A. Ryazanov, the chief sanitary inspector and deputy public healthcare minister in Perm region, in future an academician and the director of the A.N. Sysin's Chief Hygienic Institute of the Russian Academy of Medical Sciences, defended his doctoral thesis. Its subject was "Urban development with respect to smoke as a major issue"[2]. In his work, he substantiated the necessity to establish maximum permissible concentrations of pollutants in ambient air and to assess ambient air pollution in urban planning. And it was 9 years prior to the infamous London smog that became a worldwide phenomenon and stimulated overall refusal from firewood and coal as fuels. The study by V.A. Ryazanov paved the way for the Soviet hygienic standardization school that established standards for concentrations of pollutants in ambient air. Up to 80ties last century this school occupied the leading place in the world developing this direction together with studies and research in the sphere of urban planning hygiene. Some hygienic recommendations on urban planning became a part of the construction regulations SN 41-58, supplemented in 1967.

After the WWII, hygienists took active part in teams dealing with master plan creation when cities were being developed and reconstructed in the country. Data on various components of an urban environment as well as use of sanitary rules and standards gave grounds for developing science-based requirements to residential areas layouts and their improvement. These tasks were tackled by institutes for hygiene located in Moscow, Leningrad, Saratov, Ufa, Sverdlovsk, Novosibirsk and other cities as well as by experts of hygiene departments at medical institutes. A new trend appeared in practical hygiene, so called preventive sanitary surveillance. It covered a lot of issues starting from hygienic assessment of land allocation for construction and up to commissioning.

When making his report on the meeting devoted to sanitary-hygienic issues of urban development and construction, K.I. Akulov[3, 4] mentioned a growth in designed building density, failure to meet standards for insolation of houses and territories, placing large industrial objects too close to cities, and deteriorating sanitary conditions. Also, it was noted that urban development didn't conform to valid sanitary and construction rules and standards[5]. An issue regarding "smart regulation of city growth" was also very topical at the end of the 60ties last century.

The sanitary service was an influential authority and had a power to veto a project to build an enterprise within city boundaries as it was the case in Krasnoyarsk with the project to build a large lavsan production facility there[4]. Unfortunately, other productions were developed in that city and a dam was built on Yenisei. All this resulted in "black sky" effect, elevated levels of ambient air pollution, and increased population mortality due to respiratory diseases[6] [1]. Reports that were made at the above-mentioned meeting gave examples on

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[2] Ryazanov V.A. Planirovka gorodov v svyazi s problemoi dyma [Urban planning with respect to smoke as a major issue]: thesis for a degree of a Doctor of Medical Sciences. Molotov, 1943 (in Russian).

[3] RSFSR Chief Sanitary Inspector, deputy RSFSR Public Healthcare Minister (1965–1990).

[4] Akulov K.I. Sostoyanie i zadachi sanitarnoi sluzhby po gigiene planirovki naselennykh mest [The existing situation and tasks to be solved by the sanitary service regarding hygiene of urban planning]. *The proceedings of the organizational and methodical meeting on sanitary-hygienic issues of urban development and construction*. Moscow, RSFSR Public Healthcare Ministry, Erismann's Moscow Scientific Research Institute for Hygiene, 1970, pp. 3–10 (in Russian).

[5] Kovshilo V.E., Zaichenko A.I., Nedogibchenko M.K. Gosudarstvennyi sanitarnyi nadzor za proektirovaniem i stroitel'stvom naselennykh mest v SSSR [The state sanitary surveillance over planning and construction of settlements in the USSR]. *Gigiena planirovki i blagoustroistvo gorodov [Urban development hygiene and improvement in cities]: The proceedings of the first all-Soviet scientific conference*. Moscow, the USSR Public Healthcare Ministry, 1974, pp. 11–14 (in Russian).

[6] O sostoyanii i okhrane okruzhayushchei sredy v Krasnoyarskom krae v 2017 godu: Gosudarstvennyi doklad [On the ecological situation and environmental protection in Krasnoyarsk region in 2017: The State Report]. Krasnoyarsk, The Krasnoyarsk Ministry of Ecology and Regional Use of Natural Resources, 2018. Available at: http://mpr.krskstate.ru/dat/File/3/doklad%202017..pdf (June 08, 2021) (in Russian).

how to develop recommendations for northern territories using uninterrupted ribbon development with high ground floors. Results produced by hygienic expertise of development and construction projects were taken into account when a new edition of construction standards and rules was being prepared in 1967 (SN and P-P-K.2-62). For example, an item 2.7.D was added; according to this item, "when functional division of a territory is taking place, it is necessary to design recreational zones within a settlement". There was also a requirement to provide the least possible building density in residential areas in regions with hot climate (the 4th climatic zone); moderate building density, for regions with moderate climate (the 2nd and 3rd climatic zones); and elevated building density, for cold regions. The document stipulated some other useful provisions, but still, it didn't contain any hygiene-based standards for a minimum green area per 1 person though such standards are truly vital for Moscow and other Russian cities with their population exceeding 1 million people.

It is quite interesting to note that in 1967 the RSFSR Public Healthcare Ministry was made responsible for control over implementation of city master plans by the Order of the RSFSR Council of Ministers and the authority performed it ever since. The sanitary-epidemiological service took active part in developing these master plans working in close cooperation with such project institutes as the Central Scientific and Research Institute for Town Planning, the Ukraine State Institute for Town Planning (Giprograd), institutes responsible for developing master plans of Moscow city and Moscow region, design and town planning institutes in regional centers. Accumulated and generalized experience in town planning hygiene[7] provided an opportunity to develop a scheme how to perform a complex hygienic assessment of residential planning and construction. The assessment involved estimating the environmental conditions and recreation zones, social and demographic characteristics of a given territory, and social surveys among population about living conditions. The latter aimed to determine whether daily rest was efficient enough for people and to analyze children morbidity as well as some other parameters.

We can give a specific example of a hygienic assessment with respect to residential areas planning and development. There was a study performed in Omsk that involved using a wind tunnel and a device reproducing natural lighting. The study revealed that insolation in residential areas wasn't sufficient and there were defects in line building due to free space being too limited. Results produced by aerodynamic filming were especially indicative since they proved hyperventilation to be quite possible due to formation of whirlwinds in small yards not exceeding 0.5 hectare. Drastic fluctuations in wind mode were also possible in areas with line building that wasn't planned properly. An area can cool down more significantly in case of line building (49 % whereas closed-type building results in only 27–31 %). The study also allowed developing a well-grounded recommendation not to use a building system with a complicated configuration when its open angle was northward since it could create unfavorable temperature and humidity conditions in winter that made for drastic cooling of the body and deteriorated insolation[8]. There was also a suggestion to exclude closed building along motorways and to promote more open location of residential buildings with protective green areas between them aiming to prevent polluted air masses from spreading onto residential areas[9]. All the aforementioned are examples of hygi-

[7] Metodicheskie rekomendatsii po gigienicheskomu obosnovaniyu razmeshcheniya i razvitiya proizvoditel'nykh sil na territoriyakh novogo osvoeniya i v promyshlenno razvitykh regionakh [Methodical guidelines on hygienic substantiation of locating and developing production facilities on new territories being developed and in industrially developed regions]. Moscow, USSR Public Healthcare Ministry, A.N. Sysin's Institute for Common and Communal Hygiene, 1983, 69 p. (in Russian).

[8] Sokhoshko I.A. Gigienicheskaya otsenka planirovki i blagoustroistva zhilykh mikroraionov v klimaticheskikh usloviyakh Omska [Hygienic assessment of residential planning and improvement of residential microdistricts in climatic conditions in Omsk]: the abstract of the thesis for a Candidate of Medical Sciences degree. Omsk, 1974, 13 p. (in Russian).

[9] Feldman Yu.G. Gigienicheskaya otsenka avtotransporta kak istochnika zagryazneniya atmosfernogo vozdukha [Hygienic assessment of motor transport as an air pollution source]. Moscow, Meditsina, 1975, 160 p. (in Russian).

enic recommendations on creating the most comfortable living conditions for population. Unfortunately, at present these recommendations are not always followed.

Almost 20 years after the Omsk project another study was accomplished in Nizhniy Novgorod with its focus on assessing the city master plan and several projects on detailed planning and construction, building density, and some other parameters. Many-stories building in the city was accompanied with higher building density, smaller green areas, improper insolation, and elevated noise levels. Microdistricts were planned in such a way that it produced negative effects on incidence among children; incidence rates were by 1.5–2.0 times higher in blocks with closed perimeters and high population density than in semi-open blocks and population density being by 3–4 times lower[10].

The situation in 2021. In 21st century new economic relations stimulated, on one hand, a demand for apartments that could be rented, but on the other hand, a demand for construction of social housing within renovation programs. All this resulted in further sustainable growth of cities with their population exceeding 100 thousand people, and megacities accounted for 33 % in this growth. The highest growth rates (17–20 %) are typical for the southern regions in the country (Bataisk, Krasnodar, or Novorossiysk), in the "oil city" of Surgut, and some others. There have been drastic changes in the situation with town building and reconstruction; developers now determine architectural layouts in a city, infill development has grown in volumes, and microdistricts are developed as unified complexes. The Federal Project "Creating a favorable urban environment" which is a part of the National Project "Housing and urban environment" stipulates a goal to improve quality of the urban environment by 1.5 times by 2030. Efficiency is to be monitored using an index of urban environment quality. Some other indicators are also important and should be monitored to preserve health of urban population. They include a share of population living in dilapidated housing; a share of population with free access to public green spaces; a share of population provided with qualitative drinking water from public water systems; a number of services available in a city that can make life of immobile people more comfortable. However, some important parameters mentioned in the new sanitary-Epidemiologic Rules SanPiN 2.1.3684-21[11] and parameters of sustainable development are neglected, for example, ambient air quality and insolation level.

An index of urban environment quality[12] includes such a parameter as "a share of public green spaces (parks, gardens, etc.) in the total square of all green spaces in a city". This share should be not less than 25 % in a microdistrict (or a block) with apartment buildings; but if we take Moscow, we can see that the requirement is met only in 15 districts of 111 located within the Moscow Automobile Ring Road, the average share in the city amounts to 7 % and it is even lower than 5 % in 37 districts.

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[10] Baranova T.F. Gigienicheskoe obosnovanie planirovki i zastroiki zhilykh kvartalov krupnogo goroda [Hygienic substantiation of residential planning and construction in a big city]: the abstract of the thesis for a Candidate of Medical Sciences degree. Nizhniy Novgorod, 1992, 29 p. (in Russian).

[11] SanPin 2.1.3684-21. Sanitarno-epidemiologicheskie trebovaniya k soderzhaniyu territorii gorodskikh i sel'skikh poselenii, k vodnym ob"ektam, pit'evoi vode i pit'evomu vodosnabzheniyu, atmosfernomu vozdukhu, pochvam, zhilym pomeshcheniyam, ekspluatatsii proizvodstvennykh, obshchestvennykh pomeshchenii, organizatsii i provedeniyu sanitarno-protivoepidemicheskikh (profilakticheskikh) meropriyatii: utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha RF ot 28 yanvarya 2021 goda № 3 [SanPiN 2.1.3684-21. Sanitary-epidemiological requirements to maintenance of territories in urban and rural settlements, to water objects, to drinking water and drinking water supply, ambient air, soils, housing, exploitation of production and public facilities, organization and accomplishments of sanitary and anti-epidemic (prevention) activities: approved by the Order of the RF Chief Sanitary Inspector on January 28, 2021 No. 3]. *KODEKS*. Available at: https://docs.cntd.ru/document/573536177 (August 02, 2021) (in Russian).

[12] Ob utverzhdenii Metodiki opredeleniya indeksa kachestva gorodskoi sredy munitsipal'nykh obrazovanii Rossiiskoi Federatsii: Prikaz Minstroya Rossii ot 31 oktyabrya 2017 g. № 1494/pr [On approval of the procedure for determining the index of the urban environment quality in municipal settlements in the Russian Federation: the Order by the RF Ministry of Construction issued on October 31, 2017 No. 1494/pr]. *The RF Ministry of Construction*. Available at: https://minstroyrf.gov.ru/upload/iblock/ddc/prikaz-1494pr.pdf (August 02, 2021) (in Russian).

Another important requirement is that cities with their population exceeding 100 thousand people should have green spaces with their total area being 10 km^2 for public territories and 4 km^2 for residential areas; the figures are 7 and 6 km^2 accordingly for average-sized cities with their population from 50 to 100 thousand. However, this approach doesn't conform to up-to-date recommendations issued by the WHO on green spaces being available to reach on foot. Guided by expert evidence, "Environment and Health" center of the WHO Regional Office for Europe recommends estimating a residential area as per certain quantitative parameters describing availability and square of green spaces. These are the quantitative characteristics of the indicator: a share of people who leave no farther than 300 meters from a green space with its area being not less than 0.5 hectare and therefore can reach this space on foot: a share of people living no farther than 900 meters form a green space with its area being not less than 5 hectares; and a share of people living no farther than 1.5 km from a green space with its area being not less than 10 hectares. These data can be acquired from databases on land-use, satellite photos, OpenStreetMap and some other sources. Therefore, if we want to improve quality of the environment in the close proximity to residential areas, we should include data on green spaces being available to reach on foot in detailed town planning projects. Besides, the WHO Regional office for Europe recommends using some other indicators of urban population health associated with green spaces availability in residential areas. These indicators are mortality rates, mental health, and prevalence of allergic diseases, tuberculosis, and pneumonia. Certainly, these indicators are too general and it is necessary to establish more precise ones for cities in Russia allowing for the available medical statistics and experience in the field. These generalized indicators of urban environment quality established in Russia seem rather insufficient for estimating green spaces in residential areas based only on their availability to reach on foot. Therefore, any decisions on town planning should include recommendations developed by the WHO. Besides availability of green spaces, it is necessary to have data on their condition and morphology. That is why it is important to use a new tool developed by the "Environment and Health" Center of WHO Regional Office for Europe which is called GreenUr. The tool is applied to quantitatively estimate benefits of green spaces in cities for public health. It is a plagin for QGIS which is a free and open-source desktop GIS. GreenUr gives an opportunity to measure presence and availability of green spaces in cities, includes algorithms for calculating potential direct effects produced by green spaces on physical activity, mental health, and some other parameters. This program can be used as educational, communicational and scientific support by various experts and managers dealing with urban economy. The review by the WHO on urban green space interventions and health [2] dwells on how to develop green spaces in cities and estimates their effectiveness for preserving urban population health as per such parameters as physical activity, mental health, and others. Living in a city close to a spatial open green area (especially located near the apartment blocks) makes for reducing levels of stress, anxiety, and depression. Size of green spaces, their availability as well as presence of different kinds of green spaces and ratios between them in a residential area are all statistically significant predictive parameters of stress occurrence [3]. Results produced by an epidemiological study in Denmark are especially interesting since they provide data on more than 940 thousand people born from 1985 to 2003 and estimation of their mental health depending on how close to green spaces they lived in their childhood. Adults who grew up in places with the smallest available green spaces faced elevated risks of mental disorders such as depression, anxiety, and psychoactive drugs abuse in an older age. These risks were by 55 % higher than among people who spent their childhood in areas with large available green spaces [4].

Another wide-scale study in England established that green spaces in cities located near places where people of pre-retirement age live reduce mortality due to all causes [5]. In Canada green spaces in cities made for reduction in

mortality due to respiratory diseases [6], lower risks of mortality due to cardiovascular diseases and greater probability of survival after ischemic stroke [7]. Available green spaces support growing physical activity, make for reduced risks of cardiovascular diseases, type II diabetes, and obesity. Regular walks in a park relieve tachycardia and diastolic blood pressure and can be considered a rehabilitation procedure in case of coronary insufficiency. When residential blocks are located close to green spaces, especially forests, it produces a lot of positive effects including better immune system functioning [8–10], reduced risks of ischemic heart disease [11–14], making for weight loss [15], relieving stress and cognitive fatigue, improving attention and emotional recovery [16], making a society more united [17] though the latter can vary depending on an area covered by a park. Green spaces close to places where pregnant women live make for greater body weight of their newborns which is an important indicator of infant's health [18]. They make a significant contribution to solving vital health issues directly associated with specific features of any megacity: they reduce level of noise and improve sleeping.

According to the WHO estimates, losses caused by anthropogenic noises amount to 1.0–1.6 million of DALY (Disability Adjusted Life Years) in the EU [19]. Properly designed green spaces can considerably mitigate negative effects produced by anthropogenic noises on people living in megacities. The most effective way to get protected from motor transport noises is to take into account landscape peculiarities and to design a motorway bearing in mind how close a residential area is to it and to plan green "shields" between a motorway and residential housing. The necessary width of such shields should be from 1.5 to 10 meters. Positive impacts exerted by green barriers to a great extent occur due to psychological effects since practically all respondents were sure that a green barrier had positive influence but they also tended to overestimate its actual potential of protecting from noise by more than half [20].

Green spaces in a city are not only a necessary recreational resource for health protection but also a way to protect residential areas from polluted ambient air and noise created by motorways. Specific model research performed in 70ties last century showed that trees and bushes planted in several rows (3 or 4 usually) were quite efficient in isolating residential and other buildings from polluted ambient air coming from traffic areas. When trees are planted in one row, they provide protection from gases that amounts to only 3 % in winter growing to 7–10 % in summer. Trees planted in two rows together with bushes reduce introduction of polluted air by 30–40 %[9, 13]. A contribution made by green spaces into reducing motorway noises was also estimated. Trees and bushes planted between a traffic area and a pedestrian area allow a two-fold reduction in noise levels[14]. Earlier these data were actively used by the Moscow Sanitary Service in its practical activities and experts highlighted certain drawbacks when estimating development projects for some microdistricts, in particular, green spaces being distributed unevenly, absence of a compact green area, and others[15].

Results produced by another present-day study that focused on examining five parks in Moscow (Severnoe Medvedkovo, Lefortovo, Golyanovo, Maryino and a park in babushkinskiy district) showed that the greatest noise reduction was achieved when there was horizontal canopy density together with bushes covering spaces below tree crones; elevated noise levels were detected at a 300-meter dis-

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[13] Sidorenko V.F., Kirillov G.P., Feldman Yu.G. Issledovanie gazozashchitnoi effektivnosti zelenykh nasazhdenii na avtomagistralyakh [A study on efficiency of green spaces in protecting from gases along motorways]. *Gigiena i sanitariya*, 1974, no. 10, pp. 6 (in Russian).

[14] Karagodina I.L., Osipov G.L., Shishkin I.A. Bor'ba s shumom v gorodakh [Fighting against noise in cities]. Moscow, Meditsina, 1972, 160 p. (in Russian).

[15] Zaretskaya G.P., Kushchinskaya L.G., Sinitsyn V.I., Gerashchenko V.V., Faifer F.I. Gigienicheskaya otsenka zastroiki nekotorykh mikroraionov g. Moskvy [Hygienic assessment of development plans for some microdistricts in Moscow]. *Gigiena planirovki i blagoustroistvo gorodov [Hygiene of town planning and improvement]: the proceedings of the I All-Soviet scientific conference*. Moscow, USSR Public Healthcare Ministry, 1974, pp. 119–123 (in Russian).

tance from motorways[16]. Results produced by all these studies stress out the necessity to make changes into the structure of green spaces near motorways with intense traffic, to plant trees and bushes together bearing in mind their capability to protect from gases.

At present it is more obvious that green spaces are greatly required near large office centers as a recreational resource for a lot of office workers. As it was stated by S. Polonskiy, a notorious developer of the Moscow International Business Center (Moscow-City), this office space didn't meet contemporary demands for necessary comfort since "there is no creativity without proper offline".[17] This statement is further proved by foreign researchers who focus on influence exerted by green spaces on urban population health in their works. Apart from effects on health, green spaces in megacities are making a more and more substantial contribution to their socioeconomic development and bring them new competitive advantages on the global "market" of megacities. Ideas related to sustainable development and greater focus on environmental issues, both with respect to economy and society, are becoming more and more popular among people. Therefore, available green spaces that are effectively integrated into the urban environment are becoming a key factor of a megacity investment potential, its prospects in attracting advanced personnel and high-tech productions [21].

In a wider context, green spaces act as a powerful stabilizing factor given the more intensive climatic change and we should remember that people living in megacities are more susceptible to risks associated with it. Experts of the Organization for Economic Cooperation and Development (OECD) spot out three types of the most significant climatic threats to cities, megacities included. These threats have direct influence on living conditions and include heat waves, floods, and increased vulnerability of poor urban population who are the least protected from such phenomena. Heat waves in megacities occur both due to growing weather instability and peculiarities of the urban environment, such as great amounts of concrete and asphalt and elevated heat emissions from variable equipment. As a result, average temperature in cities is by 3.5–4.5 ^{o}C degrees higher than in rural areas and this discrepancy is predicted to grow by 1 ^{o}C over each following decade [22].

Given great deficiency of green spaces in many largest world megacities, all the aforementioned factors lead to occurring "heat islands", or considerable areas in a megacity (up to several km^2) where heat waves produce the greatest effects. Therefore, a role played by parks in a city is becoming more vital since they can cool off air temperature by 1 °C on average and it can be felt on a distance up to 1 km around park boundaries; water reservoirs enhance the effect [23].

Building density and / or population density is another significant parameter applied in assessing how comfortable a residential area is. Average population density in 14 Russian cities with their population exceeding 1 million people amounts to 2.4 thousand people/ square km; it is also close to this value in 24 cities located in the European part of the country with their population being 260–500 thousand people and amounts to 2.3 thousand people per square km. This density corresponds to levels detected in European cities, large capitals excluded. Lower density which is equal to 2.06 thousand people/square km is typical only for 11 cities (Nizhnekamsk, Engels, Stariy Oskol, and some other cities in the central European part of the country) with their population varying from 100 to 250 thousand people. We should note that Nizhnekamsk was developed according to one of the

[16] Luk'yanets A.G. Vliyanie razmeshcheniya tipov parkovykh nasazhdenii na komfortnost' sredy v gorodskikh parkakh [Influence exerted by location of different types of trees and bushes in parks on creating a comfortable environment in them]: the abstracts of the thesis for a degree of Candidate of Agricultural Sciences. Moscow, 2011, 20 p. (in Russian).

[17] "Konvoiry aplodirovali, kogda menya otpuskali na svobodu" ["Escort applauded when I was being released"]: an interview with S. Polonskiy. *Novaya gazeta*, 2021, no. 37, pp. 12–13. Available at: https://novayagazeta.ru/articles/2021/04/05/konvoiry-aplodirovali-kogda-menia-otpuskali-na-svobodu (June 15, 2021) (in Russian).

most successful master plans created by Giprogor Institute and was granted several awards. An industrial zone in the city is located several kilometers away from residential areas with remaining forests, parks, and public gardens. The city has been repeatedly awarded as a winner of "Comfortable urban environment" contest.

The situation in Moscow is quite the opposite. Population density varies from 7 to 21 thousand people/square km in 112 Moscow districts located within the Moscow Automobile Ring Road with its average value being 11.1 thousand people per square km. It is close to New York (10.8 thousand people/square km) and higher than in such large European cities as London, Berlin, or Madrid. Building density is high in Moscow and other million cities, predominantly in their centers with only small green spaces. This creates "heat islands" where air temperature is by 2–3 °C higher than on average in a city, insolation is poorer, ambient air pollution, noise and electromagnetic fields are elevated in some locuses.

Population density in other 56 "conditional" megacities in Russia which are regional capitals (without 13 capitals of autonomous republics, regions, and areas with population density being lower than 1 thousand people / square km) can be divided into 4 quartiles. The list also includes 9 cities with population exceeding 200 thousand people (Table).

High building density creates certain health risks for urban population. They occur due to hindered dispersion of pollutants in ambient air when residential areas are located too close to industrial zones and motorways with intense traffic, smaller green spaces and greater "closed" territories, and formation of heating microclimate. Some municipal authorities make a lot of effort to increase population in their cities but it is not arithmetical values of human resources that should measure management efficiency in the post-industrial era. If we look at a rating showing life quality in megacities, then we can see that, according to estimates by Economist Intelligence Unit, leading places are occupied by relatively small Canadian (Calgary, Vancouver, and Toronto) and European cities (Vienna, Hamburg, and Helsinki).

Growing climatic changes, temperature rise in Russia included, have brought about the necessity to work out such town planning decisions that could allow achieving optimal microclimate in residential blocks located on territories with the most severe climate in Arctic regions and in the southern regions in the country where air temperatures are extremely high. This necessity is dictated by excessive mortality during heat and cold temperature waves since their number will only grow given further global warming. Therefore, it is vital to build up variable town planning models that provide an opportunity to create optimal microclimate in residential areas [24].

Direct inclusion of hygienic recommendations into construction standards and rules became a considerable, though temporary, success in town planning. Thus, T.E. Bobkova, a leading expert on the environmental hygiene, Doctor of Medical Sciences, Professor, took

RF regional capitals and large cities distributed as per population density

A quartile as per average city square, km^2	Average square, km^2	Average population, thousand people	Average population density, thousand people/km^2
1st	276.6	359.9	1.3
2nd	228.4	438.4	1.9
3rd	185.8	427.1	2.3
4th	129.9	395.8	3.2
Large industrial cities (Angarsk, Bratsk, Volzhskiy, Komsomolsk-na-Amure, Magnitogorsk, Novokuznetsk, N. Tagil, Sterlitamak, Cherepovets)	314.1	264	1.6

N o t e : all calculations are based on data provided by Rosstat.

part in development of Construction standards and rules 07.01.89. "Town planning. Building planning and development of urban and rural settlements". She acted as a co-author in preparing important sections in this document including environmental protection, residential areas, and standards for calculating and designing parking lots for various objects. This document establishes standards for building density in residential areas but they have been neglected for a long time [25]. Shorter sanitary gaps between residential areas and children facilities and parking lots also make the urban environment less comfortable. This reduction has become possible since requirements stipulated by Construction rules SP 42.13330.2016 "Town planning. Building planning and development of urban and rural settlements. The updated edition" are no longer valid. And it should be noted that according to those rules parking lots were to be located not less than 10–30 meters away from residential buildings.

Unfortunately, there is no such a juridical concept in Russia as infill development and it is not regulated by any standards or norms. In the RF the Town Planning Code, Moscow Town Planning Code or regional documents in the sphere do not determine this concept and do not contain any up-to-date hygienic recommendations on how to assess population density bearing preservation of people's health in mind. Moreover, any issues related to infill development are considered in town planning only with a focus on effective development of a city, although certain social risks caused by such development are recognized [26] since it involves reduction in sanitary gaps between residential buildings, schools and pre-schools and parking lots and sometimes there are even demands to open pre-school playgrounds for public access [26]. These issues are vital in foreign countries as well, even in such ecologically-oriented states as Sweden where massive development can cause damage to green infrastructure [27].

There are certain limitations imposed on construction in foreign megacities, for example, in a situation when sanitary conditions can deteriorate. For example, Moscow with its new sky-scrapers would use experience of New York City administration. New York authorities introduced provisions according to which when a new building was constructed with its height exceeding heights of neighboring buildings by 15 meters, it was necessary to calculate trajectories of its shade for a whole year. Variable limitations imposed on construction of such buildings are also valid in Canada, Great Britain, and some other countries [28].

Infill development in Russian cities has resulted in multiple complaints of people living in low-rise buildings when high buildings were constructed in close proximity. People complain of poor insolation and lack of natural light and courts have been asking for an inspection in such cases [29]; there are court decisions on insufficient insolation due to a new multi-storey building. We can't fail to mention an opinion held by S. Kuznetsov, the Chief Architect in Moscow, who believes that standards on insolation are archaic documents developed at the time when prevalence of tuberculosis was high among population and now they only create difficulties for "qualitative development of city architecture".

An insolation issue in Russia cities is truly vital at the moment. Insolation standards exist in Germany, Italy, the Netherlands, Sweden, France, and some other countries [30]; proper insolation produces bactericide effects thus improving quality of living spaces as per their microbiological parameters since it prevents pathogenic microflora from developing. Ultraviolet insolation is known to produce a lot of health-improving effects including better immune and psychophysiological state, better metabolism, increased hemoglobin, better wound healing and some others. But apart from that, some recent research works have shown that insufficient insolation can be a risk factor of a stroke [31].

Sanitary standards for insolation were first established by the USSR Public Healthcare Ministry in 1963 and amounted to 3 hours a day. They were based on the results produced by examining bactericide effects of insolation, that is, its capacity for providing bacteriological wellbeing in living and public spaces. 40 years later, in 2002 required insola-

tion period was reduced to 2 hours and we have every reason to believe that it was primarily done in the interests of developers. There was no such concept as land value in the USSR but transition to the market economy resulted in drastic increase in land value in cities, especially in their downtowns and places with developed infrastructure. Construction businesses and developers are extremely interested in maximum compact building on city territories and, obviously, lobby for the revision of existing regulatory documents including standards on insolation. There was another change in these standards in 2017 when insolation period was reduced further by 0.5 hours. We can hardly say that this change is favorable for public health. These new standards permit to considerably increase height of new buildings to be constructed and to reduce a number of hours during which sunlight can enter apartments in neighboring houses in areas with compact building, especially those located on lower stories. Previously sanitary standards stipulated a period of insolation for living spaces from March 22 to September 22. Now this period is one month shorter in spring and one month shorter in autumn, that is, we have lost insolation by low spring and autumn sun. Now it is allowed in Moscow to build higher buildings that cast a shade over windows of neighboring lower ones [32]. If this new standard is followed, a number of sun hours in living spaces will fall down in a situation when a new building is being constructed in cities located in the center of the European part of the country and this building is by 5–6 stories higher than neighboring ones. It is especially true for apartments with their windows facing north-west and north-east. We can also state that people living in Moscow will have less sunlight in their apartments than people living in Moscow region [33]. Insolation issues can also occur in rooms with windows facing south in case they have deep recessed balconies [31]. A study focusing on bactericide effects produced by insolation revealed its low effectiveness in living spaces with northward windows [34]. Experts from RosBuzinessConsulting (RBC) believe that an actual coefficient of building density in towns reaches 2.18 in locuses with high-rise buildings and imposes a real threat to a comfortable urban environment [35]. Some foreign standards on insolation stipulate certain periods of insolation in winter that amount to 4 hours a day from September 21 to March 21 in Germany and more than 5 hours a day in northern Sweden. Unfortunately, there are no such regulations in Russian standards in spite of insolation being especially necessary exactly in this time of the year [30]. Changes in insolation standards, buildings with a greater number of stories, and an increase in building density in residential areas can lead to shading of living spaces, fewer hours during which direct sunlight can reach them, and greater energy consumption, whereas in Russia the energy saving strategy has already been implemented for 9 years.

It seems inadequate to estimate positive influence by solar radiation based only on bactericide effects in megacities with compact and extremely compact building without taking into account its psychophysiological effects on urban population. We should also bear in mind that insolation in cities to a great extent depends on relief peculiarities, especially given growing building density, since the European part of Russia is located on territories where vertical wall structures are typically used in construction [36]. The author suggests estimating influence exerted by a certain relief on insolation conditions with an indicator showing a deviation in its maximum permissible density on this relief from its maximum density on a plane surface.

The second issue of insufficient insolation is associated with poor availability of green spaces in dense town building. There are huge green areas in Moscow, “Losinyi ostrov” for example, and they are very important for the overall ecological situation in the city; still, they are not enough for improving mobility and health of people living in Moscow. The WHO Regional Office for Europe recommends placing open green spaces not farther from a residential area than a 20-minute walk on foot. Even these small spaces can provide people with certain amount of ultraviolet which is in great deficiency in a northern country and sup-

ply them with vitamin D (protohormone D, to be more exact). Over the last years a much better insight into significance of this substance for health has been achieved and it is obvious that this vitamin helps prevent various chronic non-communicable diseases. And here we mean not only metabolic disorders where its contribution has long been examined profoundly but also oncologic, cardiovascular, and other diseases. However, as opposed to any other vitamin, vitamin D is not a vitamin in a classical meaning of this term due to not being biologically active whereas other vitamins are. In the body, vitamin D transforms into a biologically active hormonal form through a 2-stage metabolization using genomic and non-genomic mechanisms. It produces variable biological effects due to interactions with specific receptors localized in cell nuclei in many tissues and organs as well as on plasmatic cellular membranes. In this respect an active metabolite of vitamin D acts as a true steroid hormone; that's why this vitamin is called "D-hormone" [37]. Low D-hormone concentration creates elevated risks of ischemic heart disease, type II diabetes mellitus, and some other diseases. Vitamin D deficiency is typical in people who live on territories located to the north from 35°, that is, practically on the whole territory of Russia. Vitamin D deficiency leads to osteoporosis and osteopathy. This has been proved by studies on its contents in blood of people living in the northwestern region where vitamin D deficiency is detected in 50 % of pregnant women and this condition results in statistically significant growth in anxiety and depression ($r = –0.11$, $p = 0.03$) [38]. When this hormone deficiency is detected in men, it is a risk factor of chronic prostatitis, prostate hyperplasia and other andrologic disorders [39]. Another issue is D-hormone deficiency detected in 13 % of European children. This results in improper bone mineralization, developing rachitis, bronchial asthma, diabetes mellitus, and many other diseases [40].

Conclusion. So far creating a comfortable urban environment hasn't become the main objective of urbanists, architects, and other experts on town planning in Russia. The rules are dictated by developers, especially in downtowns; there is infill development involving high-rise buildings shading neighboring lower ones; less strict limitations are now imposed regarding insolation; a number of state standards and other regulatory documents in the sphere of construction has gone down by 1/3. Russian regulatory documents on town planning don't incorporate recommendations developed by the WHO on open green spaces that should be available to reach on foot. Population density is growing persistently in large cities. Russian indicators in ratings for sustainable urban development [41] don't include a very significant one, namely, average annual concentrations of fine particulate matter in ambient air. This indicator is included in the Sustainable Development Goal No. 11 "Make cities and human settlements inclusive, safe, resilient, and sustainable". Instead of this indicator that gives the most precise idea of ambient air quality in a city, our regulations rely on archaic ones developed as far back as in 70ties last century. An example can be "specific emissions of pollutants from stationary sources and motor transport per 1 square km". To assess health risks caused by motor transport, we should apply calculated concentrations of pollutants caused by traffic flows instead of this indicator that can hardly be considered informative. Starting from 2019, the ecological situation in cities has been assessed by the Analytical Credit Rating Agency (ACRA) that has developed a new complex indicator showing environmental conditions in a given region. This indicator incorporates emissions of hazardous chemicals, discharges of polluted sewage, industrial wastes, communal wastes, etc., calculated per a unit of gross regional products (GDP) as well as environmental expenses per a unit of budget expenditure. Still, these indicators do not give a clear picture of urban environment quality. Foreign estimates indicate that urban environment quality is rather poor in Russian cities. As per estimates given by The Economist, only Moscow was included into the rating of cities with the comfortable urban environment occupying the 68th place (New York holds the 58th place; London, 48th; Berlin, 21st; and Vienna is the

leader). Experts from IESE business school have made up a rating that includes 174 cities all over the world and estimates their stability. Moscow is on the 87th place in this rating; Saint Petersburg, 124th; and Novosibirsk, 159th place. The leaders with the most comfortable urban environment are London, New York, Paris, Tokyo, and Reykjavik [42].

If we turn to such fashionable concepts as "smart city" or "healthy city", we can see that most publications about them don't contain any hygienic assessment and this fact makes their image "not so ideal". A good example is Volgograd as a "smart city" [43]. Architects consider any issues with respect to public health only bearing in mind medical aid provision and building new medical centers; the only things important about green spaces are their volume and a number of planted trees. There is a postulate that "a density of a city is directly proportionate to its development rate and inversely proportionate to comfortable living conditions which influence its appeal" [44]. But Russian cities haven't yet reached enormous scales of Asian megacities and we still have a possibility to make our urban environment truly comfortable. There is certain progress even in cities with the highest ambient air pollution and population mortality and new activities are being developed aiming to reduce health risks due to decreasing emissions of priority pollutants [45].

This paper was accomplished in summer 2021 when experts from a lot of spheres including epidemiologists, geographers, economists, physicians and others were trying to determine risk factors in the urban environment that could make for COVID-19 spread. There was a review of foreign research works focusing on relationships between ambient air pollution and COVID-19 mortality among population [46]. Relationships between the disease and another indicator of urban environment quality, namely population density, are not so obvious [47]. But it is important to note that these research works also gave some attention to such risk factors as a degree of urbanization, socioeconomic status, public transport availability, ambient air quality, strictness of quarantine measures, etc. Two basic processes occur in cities during an epidemic due to various factors. One of them results in an improving epidemiological situation due to better access to high-quality medical aid; the other makes this situation worse due to higher population density and more frequent trips on public transport. As new data on COVID-19 incidence and mortality among urban population are being accumulated, relationships with other risk factors in the urban environment will be studied more profoundly. This will allow developing new prevention activities aimed at protecting health of urban population. Hopefully, this will also help estimate infill compact development in Russian downtowns differently and better understand the significance of ambient air quality and open green spaces in cities.

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Reference

1. Revich B.A., Kharkova T.L., Kvasha E.A. Selected health parameters of people living in cities included into «Clean air» federal project. *Health Risk Analysis*, 2020, no. 2, pp. 16–27. DOI: 10.21668/health.risk/2020.2.02.eng

2. Urban green space interventions and health: A review of impacts and effectiveness. Full report (2017). *WHO, Regional Office for Europe*, 2017, 57 p.

3. Tompson W.C., Aspinali P., Roe J., Robertson L., Miller D. Mitigating stress and supporting health in deprived urban communities: The importance of green space and the social environment. *Int. J. Environ. Res. Public Health*, 2016, vol. 13, no. 4, pp. 440. DOI: 10.3390/ijerph13040440

4. Engemann K., Pedersen K.B., Arge L., Tsirogiannis C., Mortensen P.B., Svenning J.-C. Residential green space in childhood is associated with lower risk of psychiatric disorders from adolescence into adulthood. *PNAS*, 2019, vol. 116, no. 11, pp. 5188–5193. DOI: 10.1073/pnas.1807504116

5. Mitchell R., Popham F. Effect of exposure to natural environment on health inequalities: an observational population study. *Lancet*, 2008, vol. 372, no. 9650, pp. 1655–1660. DOI: 10.1016/S0140-6736(08)61689-X

6. Villeneuve P.J., Jerrett M., Su J., Burnett R.T., Chen H., Wheeler A.J., Goldberg M.S. A cohort study relating urban green space with mortality in Ontario, Canada. *Environ. Res.*, 2012, vol. 115, pp. 51–58. DOI: 10.1016/j.envres.2012.03.003

7. Wilker E.H., Wu C.D., Mcneely E., Mostofsky E., Spengler J., Wellenius G.A., Mittleman M.A. Green space and mortality following ischemic stroke. *Environ. Res.*, 2014, vol. 133, pp. 42–48. DOI: 10.1016/j.envres.2014.05.005

8. Park B.J., Tsunetsugu Y., Kasetani T., Kagawa T., Miyazaki Y. The physiological effects of Shinrin-yoku (taking in the forest atmosphere or forest bathing): evidence from field experiments in 24 forests across Japan. *Environ. Health Prev. Med.*, 2010, vol. 15, no. 1, pp. 18–26. DOI: 10.1007/s12199-009-0086-9

9. Lee J., Park B.J., Tsunetsugu Y., Ohira T., Kagawa T., Miyazaki Y. Effect of forest bathing on physiological and psychological responses in young Japanese male subjects. *Public Health*, 2011, vol. 125, no. 2, pp. 93–100. DOI: 10.1016/j.puhe.2010.09.005

10. Song C., Ikei H., Miyazaki Y. Physiological effects of nature therapy: A review of the research in Japan. *Int. J. Environ. Res. Public Health*, 2016, vol. 13, no. 8, pp. 781. DOI: 10.3390/ijerph13080781

11. Cohen D., Sehgal A., Williamson S., Golinelli D., Lurie N., McKenzie T.L. Contribution of public parks to physical activity. *Am. J. Public Health*, 2007, vol. 97, no. 3, pp. 509–514. DOI: 10.2105/AJPH.2005.072447

12. Cohen D.A., Marsh T., Williamson S., Derose K.P., Martinez H., Setodji C., McKenzie T.L. Parks and physical activity: why are some parks used more than others? *Prev. Med.*, 2010, vol. 50, suppl. 1, pp. S9–12. DOI: 10.1016/j.ypmed.2009.08.020

13. Maas J., Verheij R.A., de Vries S., Spreeuwenberg P., Schellevis F.G., Groenewegen P.P. Morbidity is related to a green living environment. *J. Epidemiol. Community Health*, 2009, vol. 63, no. 12, pp. 967–973. DOI: 10.1136/jech.2008.079038

14. Schipperijn J., Bentsen P., Troelsen J., Toftager M., Stigsdotter U.K. Associations between physical activity and characteristics of urban green space. *Urban For. Urban Green.*, 2013, vol. 12, no. 1, pp. 109–116. DOI: 10.1016/j.ufug.2012.12.002

15. Ellaway A., Macintyre S., Bonnefoy X. Graffiti, greenery, and obesity in adults: secondary analysis of European cross sectional survey. *BMJ*, 2005, vol. 331, no. 7517, pp. 611–612. DOI: 10.1136/bmj.38575.664549.F7

16. Cattella V., Dines N., Gesler W., Curtis S. Mingling, observing, and lingering: Everyday public spaces and their implications for well-being and social relations. *Health Place*, 2008, vol. 14, no. 3, pp. 544–561. DOI: 10.1016/j.healthplace.2007.10.007

17. Astell-Burt T., Mitchell R., Hartig T. The association between green space and mental health varies across the life course. A longitudinal study. *J. Epidemiol. Community Health*, 2014, vol. 68, no. 6, pp. 578–583. DOI: 10.1136/jech-2013-203767

18. Dzhambov A.M., Dimitrova D.D., Dimitrakova E.D. Association between residential greenness and birth weight: Systematic review and meta-analysis. *Urban For. Urban Green.*, 2014, vol. 13, no. 4, pp. 621–629. DOI: 10.1016/j.ufug.2014.09.004

19. Burden of disease from environmental noise: quantification of healthy life years lost in Europe. Copenhagen, WHO, Regional Office for Europe, 2011, 106 p.

20. Yang C.Y., Bao Z.Y., Zhu Z.J. An assessment of psychological noise reduction by landscape plants. *Int. J. Environ. Res. Public Health*, 2011, vol. 8, no. 4, pp. 1032–1048. DOI: 10.3390/ijerph804103

21. Terentiev N.E., Revich B.A. Green environment in megacities as health saving factor. *Problemy teorii i praktiki upravleniya*, 2018, no. 9, pp. 43–53 (in Russian).

22. Cities and Climate Change. OECD Publ., 2010, 278 p.

23. Bowler D.E., Buyung-Ali L., Knight T.M., Pullin A.S. Urban greening to cool towns and cities: A systematic review of the empirical evidence. *Landscape and Urban Planning*, 2010, vol. 97, no. 3, pp. 147–155. DOI: 10.1016/j.landurbplan.2010.05.006

24. Drobotov V.I., Shagieva E.V. Formation of town-planning entities in adverse climatic conditions. *Vestnik Volgogradskogo gosudarstvennogo arkhitekturno-stroitel'nogo universiteta. Seriya: Stroitel'stvo i arkhitektura*, 2018, vol. 71, no. 52, pp. 166–173 (in Russian).

25. Chepchugov M.A. Sealing development as a form of effective (qualitative) city development. *Noema (Arkhitektura, Urbanistika, Iskusstvo)*, 2019, vol. 3, no. S3, pp. 44–50 (in Russian).

26. Dubynin N., Bobkova T., Dubynin V., Panova A. Architecture in the context of contemporary ecology. *Proekt Baikal*, 2019, vol. 16, no. 60, pp. 123–127. DOI: 10.7480/projectbaikal.60.1484 (in Russian).

27. Berg P.G., Eriksson F., Eriksson T. Paradoks uplotnitel'noi zastroiki: umen'shenie zelenykh prostranstv s rostom ikh vostrebovannosti [The paradox of compact building: a decrease in green spaces with an increasing demand for them]. *Formirovanie komfortnoi gorodskoi sredy. Vodnye landshafty v epokhu urbanizatsii: sbornik trudov mezhdunarodnoi konferentsii*. In: M.E. Ignat'eva, I.A. Mel'nichuk, A.B. Bubnova eds. St. Petersburg, Saint Petersburg State Forest Technical University Publ., 2019, pp. 49–50 (in Russian).

28. Akimova M.I., Chechulina A.S. Infill development of large cities: internal and external. *Izvestiya vuzov. Stroitel'stvo*, 2015, vol. 678, no. 6, pp. 55–62 (in Russian).

29. Timofeeva S.S., Kustov O.M. Insolation as a factor of litigation. *Vestnik IrGTU*, 2015, vol. 99, no. 4, pp. 105–110 (in Russian).

30. Shmarov I.A, Zemtsov V.A., Korkina E.V. Insolyatsiya: praktika normirovaniya i rascheta [Insolation: practice of regulation and calculation]. *Zhilishchnoe stroitel'stvo*, 2016, no. 7, pp. 48–53 (in Russian).

31. Kent S.T., McClure L.A., Judd S.E., Howard V.J., Crosson W.L., Al-Hamdan M.Z., Wadley V.G., Peace F., Kabagambe E.K. Short and Long-Term Sunlight Radiation and Smoke Incidence. *Ann. Neurol.*, 2013, vol. 73, no. 1, pp. 32–37. DOI: 10.1002/ana.23737

32. Danilov P.B., Benuzh A.A. Evolution of insolation requirements for residential real estate in Moscow. *Nedvizhimost': ekonomika, upravlenie*, 2019, no. 2, pp. 42–44 (in Russian).

33.Grabovyy P.G., Manukhina L.A. National strategy of introduction of energy resources and ecologically safe (green) technologies and productions in construction and housing and communal services. *Nedvizhimost': ekonomika, upravlenie*, 2014, no. 1–2, pp. 6–8 (in Russian).

34. Fokin S.G., Bobkova T.E., Shishova M.S. Assessment of hygienic principles in the standardization of insolation under the conditions of a city in case of Moscow. *Gigiena i sanitariya*, 2003, no. 2, pp. 9–11 (in Russian).

35. Andreeva P.N. The insolation rights and renovation programme in Moscow. *Pravovaya politika i pravovaya zhizn'*, 2018, no. 1, pp. 42–48 (in Russian).

36. Kharchenko S.V. Relief as a factor of solar exposure in urban areas. *Vestnik Moskovskogo universiteta. Seriya 5: Geografiya*, 2013, no. 4, pp. 30–35 (in Russian).

37. Schwarz G.Ya. Renaissance of Vitamin D: molecular biological, physiological and pharmacological aspects. *Meditsinskiy sovet*, 2015, no. 18, pp. 102–103. DOI: 10.21518/2079-701X-2015-18-102-103 (in Russian).

38. Karonova T.L., Mikheeva E.P., Nikitina I.L., Belyaeva O., Todieva A.M., Popova P.V., Andreeva A.T., Globa P.Yu., Beletskaya I.S. [et al.]. Uroven' obespechennosti vitaminom D u zhitelei Severo-Zapadnogo regiona RF i znachenie defitsita vitamina D dlya zdorov'ya [The level of vitamin D supply in residents of the North-Western region in the Russian Federation and the importance of vitamin D deficiency for health]. *Osteoporoz i osteopatiya*, 2016, vol. 19, no. 2, pp. 45–46 (in Russian).

39. Kalinichenko S.Yu., Tyuzikov I.A., Gusakova D.A., Vorslov L.O., Tishova Yu.A., Grekov E.A., Fomin A.M. Vitamin D as a novel steroid hormone and its role for men's health. *Effektivnaya farmakoterapiya*, 2015, no. 27, pp. 38–47 (in Russian).

40. Zakharova I.N., Dolbnya S.V., Kuryaninova V.A., Klimov L.Y., Kipkeev S.O., Tsutsaeva A.N., Yagupova A.V., Enina E.A. [et al.]. Role of vitamin D in pre-school children's health. *Meditsinskii sovet*, 2021, no. 1, pp. 37–49. DOI: 10.21518/2079-701X-2021-1-37-48 (in Russian).

41. Reiting ustoichivogo razvitiya gorodov Rossii 2020 [Rating of sustainable development of cities in Russia 2020]. *SGM*, 2020, no. 8. Available at: https://www.agencysgm.com/projects/%D0%91%D1%80%D0%BE%D1%88%D1%8E%D1%80%D0%B02019.pdf (20.04.2021) (in Russian).

42. IESE Cities in Motion Index 2020. IESE Business School University of Navarra, 2020. Available at: https://media.iese.edu/research/pdfs/ST-0542-E.pdf (20.04.2021).

43. Maksimchuk O.V., Baulina O.A., Klyushin V.V. "Smart" living as one of the aspects of the formation of a "smart" city. *Sotsiologiya goroda*, 2017, no. 1, pp. 61–77 (in Russian).

44. Bashkaev T. Vektor razvitiya – effektivnost' [The vector of development is efficiency]. Moskovskii tsentr urbanistiki, 2020. Available at: https://urbanru.ru/almanahs/vektor-razvitiya-effektivnost-timur-bashkaev/ (09.04.2021) (in Russian).

45. Zaitseva N.V., May I.V. Main results, prospects of application and improvement of the health risk assessment of the population of Siberian cities – participants of the "Clean air" project (Bratsk, Norilsk, Krasnoyarsk, Chita). *Gigiena i sanitariya*, 2021, vol. 100, no. 5, pp. 519–527. DOI: 10.47470/0016-9900-2021-100-5-519-527 (in Russian).

46. Revich B.A., Shaposnikov D.A. The COVID-19 pandemic: New knowledge on the impact of air quality of the spread of coronavirus infection in cities. *Stud. Russ. Econ. Dev.*, 2021, vol. 32, no. 4, pp. 357–363. DOI: 10.1134/S1075700721040134

47. Teller J. Urban density and COVID-19: towards an adaptive approach. *Buildings and Cities*, 2021, vol. 2, no. 1, pp. 150–165. DOI: 10.5334/ bc.89

Revich B.A. Urban planning and public health: analytical review. Health Risk Analysis, 2022, no. 1, pp. 147–161. DOI: 10.21668/health.risk/2022.1.17.eng

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Review

ON HARMONIZATION OF HEALTH RISK INDICATORS CAUSED BY IONIZING RADIATION EXPOSURE AND OTHER HARMFUL FACTORS BASED ON DALY ESTIMATES

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Radiation detriment is a basic measure which is currently applied to assess health risks caused by exposure to ionizing radiation. This concept was developed by the International Commission on Radiological Protection (ICRP) more than 30 years ago; it has both certain advantages and drawbacks that limit the scope of its possible application. A certain drawback is that this value is used exclusively to assess effects produced on health by radiation thus making it ineligible for correct comparative analysis of different risks. This review focuses on contemporary scientific papers devoted to various approaches to calculating radiation detriment. There is also an attempt to analyze whether it is possible to apply the WHO methodology for assessing burden of disease as a basis for calculating universal risk rates taking into account effects produced by exposure to harmful environmental factors on population health. A possibility to use DALY (disability-adjusted life years) estimate is considered as one of possible approaches to harmonizing health risk assessment methodologies. DALY is among estimates that are frequently used to assess population health when solving various tasks in public healthcare. The review dwells on discussing whether it is advisable and feasible to gradually change a methodology for calculating radiation detriment in order to use the effective dose as a measure of health risk more correctly.

Key words: *radiation risk, radiation detriment, DALY, public health, health risk, global burden of disease, disease severity, mortality, morbidity.*

There are three applied directions of the scientific research in health risk analysis and they all are tightly connected. The 1st one is population health analysis (including development of summary population health measures); the 2nd one is developing and calculating health risks associated with exposure to various harmful environmental factors; and the 3rd one is comparative analysis of various risks. Historically it has turned out in health risk assessment that ionizing radiation has been studied a bit apart from other various environmental factors producing negative effects on human health. Given that, issues related to harmonizing approaches to assessment of radiation risks and other health risks arise quite frequently and discussed independently [1, 2]. In addition, recently it has often been noted that it is necessary to revise the assessment methodology and measures of radiation health risks that are currently applied [3–6]. When tackling multiple issues related to public healthcare organization and population health assessment, the expert society more and more often suggest a gradual transition from mortality-based health measures to more informative summary health measures based on calculating how many years of healthy life have been lost due to disease, disability or injury, that is, number of lost healthy life years without any

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limitations on activity, functionality, and working capacities [7, 8].

This paper is a short review focusing on the latest scientific works on the aforementioned applied research directions; there is also an attempt to analyze probable ways to improve the existing methodology for radiation risk assessment and to harmonize radiation health risks with health risks caused by other harmful factors.

Radiation detriment as a health risk. The "detriment" concept[1] was first introduced in radiation protection in 1977 by the International Commission on Radiological Protection (ICRP) in its Publication 26 "to identify, and where possible, to quantify, all these deleterious effects" [9]. In general, this concept was determined in a "population" as "the mathematical expectation of the harm incurred from an exposure to radiation taking into account not only the probability of each type of deleterious effect but also the severity of the effect". "Detriment" included not only negative effects on health but also "other effects" that were not directly related to health. For example, it could be a necessity to limit consumption of specific products or use of some territories. The same document introduced a concept of "detriment to health" to estimate negative influence on human health.

At that time, data on negative health outcomes of exposure to ionizing radiation were primarily provided by observing the cohort of people who had been exposed to radiation due to atomic bombing of Hiroshima and Nagasaki in August 1945 (Life Span Study (LSS cohort)). At present, it is well-known that elevated probability of oncologic diseases in exposed people is among the most significant long-term radiological effects produced by radiation on health. A growth in this probability depends, among other factors, on a radiation dose and these outcomes can be delayed for years and even decades. In this relation as a period of observation over the LLS cohort grew longer, the character of the aforementioned dependence was constantly adjusted [11, 12].

It is important to note that the term "exposure dose" is rather specific when applied to radiation. "Dose"[2] is not measurable but rather calculated value and there is a complicated association between this value and a radiation situation in case of external exposure and introduction of radionuclides into the body in case of internal one. "Exposure dose" is used as a universal integral measure since there are multiple types of ionizing radiation ("alpha", "beta", "gamma", "neutron"). This concept allows brining all forms and types of radiation exposure to just one value, "an effective dose" which can be used to determine risks of long-term negative effects produced by exposure on health.

By 1990 when the ICRP Publication 60 was issued [13], the accumulated scientific knowledge made for formulating basic concepts applied in estimating health outcomes of exposure. Four types of such outcomes were spotted out and described: "change, damage, harm, and detriment" (more details here [14, 15]).

As a result, the ICRP developed a multidimensional measure of detriment to health and recommended it to be used for solving certain tasks related to radiological protection. This measure is a sum of lethal radiation-induced cancer cases F and a number of non-lethal cancers weighted as per lethality fraction k for specific malignant neoplasms (MNs) [14]. For a specific nosology of a MN, detriment can be given as:

$$D = F + k \cdot (1-k) \cdot \frac{F}{k} = F \cdot (2-k), \quad (1)$$

[1] The Russian translation of the ICRP Publication 26 [9] gives both terms, "detriment" and "harm", in the same item in the text; however, the glossary made up for this Publication and the later translated ICRP Publication 60 [10] fix the distinction between them in Russian terminology.

[2] In this review, unless stated otherwise, "exposure dose" is used in the widest sense as a certain quantitative characteristics of various types of ionizing radiation. The more detailed information on various dose units can be found, for example, in this document: https://www-pub.iaea.org/MTCD/publications/PDF/IAEASafetyGlossary2007/Glossary/SafetyGlossary_2007r.pdf) and SanPiN 2.6.2523-09 "The radiation safety standards (RSS-031 99/2009)" (https://docs.cntd.ru/document/902170553) (in Russian).

where D is radiation detriment to health; F is a number of lethal radiation-induced cancers; k is lethality fraction for a MN; $\frac{F}{k}$ is the overall number of radiation-induced MNs; $(1-k)$ is a fraction of non-lethal MNs; $(1-k)\cdot\frac{F}{k}$ is the overall number of non-lethal MNs.

In the course of observation over the LLS cohort, it became obvious that assessments of radiation health risks based on data regarding detected oncologic incidence in this group were more precise than assessments based on registration of lethal cases due to cancer. Given that, without any changes in the overall concept of detriment estimation, the formula used to calculate radiation detriment was slightly changed in the ICRP Publication 103[3]:

$$R_D = R\cdot q + R\cdot(1-q)\cdot\left(q_{\min}+(1-q_{\min})\cdot q\right), \quad (2)$$

where R_D is a detriment-adjusted risk of a radiation-induced cancer[4]; R is a risk of radiation-induced cancer; q is lethality fraction for a MN; $R\cdot q$ is a risk of a lethal cancer; $R\cdot(1-q)$ is a risk of non-lethal cancers; $\left(q_{\min}+(1-q_{\min})\cdot q\right)$ is a weight attributed to non-lethal cancers when calculating detriment; $q_{\min}$ is a minimum weight for non-lethal cancers.

The weight attributed to non-lethal MNs in this formula deserves special attention and is among central elements in the methodology for assessing radiation detriment to health which is currently applied by the ICRP.

The items (A 144)–(A 145) in the ICRP Publication 103 give a clear picture of the ICRP position regarding this weighting factor and a change in it in comparison with that applied in the ICRP Publication 60 [16]:

"(A 144) *Quality of life detriment.* Cancer survivors generally experience adverse effects on their quality of life. … cancers should be weighted not only by lethality but also for pain, suffering, and any adverse effects of cancer treatment. To achieve this, a factor termed $q_{\min}$, is applied … the minimum weight for non-lethal cancer.

(A 145) The value of $q_{\min}$ was set equal to 0.1 (in most instances the result is not highly sensitive to the value chosen). …However, the $q_{\min}$ adjustment was not used for skin cancer because radiogenic skin cancer is almost exclusively of the basal cell type which is usually associated with very little pain…".

Although the ICRP was quite clear about the necessity to take into account deteriorated life quality, pain, and suffering associated with radiation-induced cancer, we can see from the structure of the weighting coefficient for non-lethal cancer that the current methodology for assessing radiation detriment neglects these factors completely. The reason is that when the ICRP recommendations were issued in 1990 there was no universal and commonly accepted methodology for assessing severity of diseases which could be considered eligible for use within the risk assessment methodology. In 2007 the ICRP Publication 103 were issued but still any revision of the implemented methodology didn't seem imminent at that moment. Besides, the ICRP didn't see development of a unified methodology for radiation risk assessment as a task to be solved. The existing methodology for detriment assessment was mostly used to develop and substantiate standardized dose values as well as to allow for differences in radiation sensitivity of specific organs, tissues, and systems in the body.

Radiation detriment as a measure was created to solve various tasks related to radiological protection (in particular, to calculate weighting factors for organs, tissues, and systems in the body taking their radiation sensitivity into account, that is, factors used to cal-

[3] As opposed to a detriment value described in the ICRP Publication 60, the authors of the Publication 103 determined the measure given below not in absolute numbers but in probabilistic values, that is in terms of risk. However, it is not important for the goals stated in this review since the transition from one values to others doesn't seem at all complicated.

[4] The term "detriment-adjusted risk" is used in the ICRP Publication 103 for this value; however, at present the authors of the methodology have abandoned it and apply the term "radiation detriment" [4].

culate a so called "effective dose"). In ICRP experts' opinion, this measure would be applied in a rather limited area. However, a value of an effective dose calculated as per this methodology turned out to be so eligible that it could spread far beyond its original application area outlined by its developers. Therefore, the ICRP managed to develop a quite successful quantitative health risk indicator and dose values that were established based on it became widely used in radiological protection. However, this indicator turned out to be ineligible for comparative assessment of different risks as it will be illustrated in detail later.

It is important to note that authoritative foreign and international scientific organizations developed mathematical models that provided an opportunity to calculate various measures of mortality and morbidity due to radiation-induced cancer [17, 18] depending on several factors such as sex and age of exposed people, exposure dose, etc. However, these rates are hardly eligible for solving tasks related to comparative risk analysis. It is to a great extent due to medical radiological outcomes of exposure being delayed and it means that the radiation factor can actually be compared only with those factors which produce comparably delayed effects. And there is still no solution to the task how to comparatively analyze diseases which have different severity and are caused by exposure to different risk factors. All these aforementioned reasons call for developing such risk measures that are eligible for comparative analysis and take into account severity of diseases and different distribution of risk realization over time.

Summary measure of population health and assessment of disease severity. Summary measures of population health give a clear picture of complex epidemiological data; they can be used to create effective development strategies for public healthcare systems with respect to prevention of the most socially significant diseases [19]. These measures are primarily applied to:

– assess population health "in different social groups in dynamics";

– provide the best possible insight into what diseases, injuries and risk factors make the greatest contribution to deteriorating health of a specific population including identification of the most significant health issues and their dynamic, that is, whether they get better or worse over time (this is probably the most widely spread application of summary health measures);

– assess whether there are sufficient amounts of precise and qualitative data on population health [19].

Summary measures of population health have been developed for more than 50 years[5] [20]. Over many years population health has been assessed using only mortality-based indicators. In other words, population health was determined by how and why people died or reasons for mortality and its rates [19, 21].

Life expectancy, mortality due to all reasons, infant (children) mortality and mortality due a specific disease were compared between regions, countries, and on the international level [22].

Currently, a methodology applied to calculate most summary measures of population health[6] is based on analyzing age-sex-specific mortality rates due to various reasons and epidemiology of nonfatal diseases. For example, the profile of the "Public healthcare" national project contains certain targets fixed for the period 2019–2024 and some of them directly concern population health assessment (the first 4 targets) but all these targets are mortality-based ones [23]. Targets stated by the RF Public Healthcare Ministry within the National Security Strategy of the Russian Federation

[5] Hereinafter Summary Measures of Population Health (SMPH) mean such integral values characterizing expected health as health index or unified mortality and morbidity index.

[6] An important reservation here is most postulates stated in this section concern exclusively summary measures of population health and not analysis of medical and demographic data as a whole. A great number of variable partial indicators can be used in the latter case to give a picture of specific aspects in population health.

have some additions such as “life expectancy at birth” and “average life expectancy of patients with a chronic pathology after it has been diagnosed”[7]. Meanwhile, such measures as well as any measures based on data on morbidity, birth rate or disability among population, do not provide us with comprehensive but still effectively brief information which is eligible for assessing population health as a whole or for analyzing whether public healthcare systems are being developed efficiently enough[8]. In particular, some important aspects are neglected including severity of chronic diseases, long-term or permanent disability, and injuries [21].

Obviously, it is quite convenient to use mortality-based measures when solving multiple tasks related to health risk analysis [24, 25]. Primarily, a death case due to exposure to a harmful factor is clear enough as a measure of risk. Incidence is no less clear measure of risk though it is not so informative with relation to population detriment [26]. Since these measures are truly clear and simple to be estimated, they have become widely used in population health assessment [27]. Thus, for example, the state report issued by Rospotrebnadzor and entitled “On sanitary-epidemiological welfare of the population in the Russian Federation in 2020”[9] mentions several groups of primary population health measures. They can be influenced by various sanitary-hygienic factors; when it comes down to physical and/or chemical risk factors, the report covers the following measures:

1) Overall morbidity among population;

2) Overall mortality among population;

3) Sex-specific incidence with temporary disability;

4) Injuries and poisonings;

5) Congenital malformations in children;

6) Infant mortality, birth rate, natural population decrease;

7) Prevalence of:

– respiratory diseases;

– digestive diseases;

– circulatory diseases;

– malignant neoplasms;

– congenital malformations in children.

Such population health measures based on mortality and morbidity are simple, graphic and widely used; their use resulted in health risks rates due to exposure to harmful environmental factors also being frequently determined based on mortality and morbidity.

Meanwhile, these measures have at least two serious drawbacks which are significant for describing health risks [28] [10]:

1) when assessing health risks caused by weak exposure to an environmental factor or exposure to a factor that has not been studied profoundly[11], the assessment results given as “expected number of death cases” or “expected number of diseases” can create a false idea of actual outcomes of such an exposure and they often do just that;

2) these measures produce rather scarce data on detriment to population health when effects are long-term and delayed over time since they don’t provide an opportunity to directly estimate both economic outcomes of adverse exposure on the state level (for example, those related to temporary or permanent disability) and average individual risks (for

[7] O Strategii natsional'noi bezopasnosti Rossiiskoi Federatsii: Ukaz Prezidenta Rossiiskoi Federatsii ot 02.07.2021 № 400 [On the National Security Strategy of the Russian Federation: The Order by the RF President issued on July 02, 2021 No. 400]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_389271/ (December 14, 2021) (in Russian).

[8] To be fair, we should note that targeting should be considered exclusively with respect to its relation to formulating specific goals achievement of which should be analyzed using these established targets.

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

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

[11] It concerns exposure to small radiation doses, low concentrations of chemicals and other adverse exposures they create a lot of uncertainties in risk assessment.

example, when average life expectancy decreases in a given risk group) [29].

Indeed, occupational injuries tend to have almost instant outcomes (death, temporary or permanent disability) whereas occupational exposures (that is, when workers employed at radiation-hazardous objects face exposures which are fractioned over time) can have outcomes that become obvious after many years. Besides, occupational injuries are personalized whereas risks related to exposure to harmful factors are often estimated as probabilistic for one person or as a frequency for a group of people (attributable risks).

Health as a concept, apart from meaning "absence of a disease", also means there are no disorders or functional limitations due to previous diseases and injuries. The WHO determines health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity"[12] [30]. Summary health measures have been developed to take this factor into account in population health analysis together with developing systems for collecting medical and demographic data. The measures were being developed the most actively in 90ties last century. It was exactly at that time when age-sex-specific mortality and morbidity rates grouped as per their causes were added with new developing measures that were more informative and allowed for functional limitations and decreased working abilities as well as factors that reduced "quality of life" due to disease or disability[13]. This activity was to a great extent due to the WHO creating and developing a new project entitled "Global Burden of Disease" (hereinafter GBD) [31].

One of its targets was to quantify population burden due to premature deaths and disability for the most common diseases and groups of diseases as well as to quantify years of life lost due to the aforementioned reasons and years of life with complete or partial disability weighted as per a degree of their severity [31].

According to GBD terminology and ICF classification (International Classification of Functioning, Disability and Health) by the World Health Organization (WHO) [32]), the term "disability" is widely used in analyzing disease severity (Burden of Diseases) to determine deviations from good or ideal health. These deviations include limitations in the following spheres: mobility, self-care, participation in usual activities, pain and discomfort, anxiety and depression, and cognitive impairment [33].

Such an approach to health assessment suing a standard description of health was, for example, applied in the WHO GBD 2000 project [34].

A list of summary health measures developed by various organizations is quite wide and can be conditionally divided into two main groups:

1) Health Expectancies;

2) Health Gaps.

The first group includes the following measures [35]:

1) HALE or Health-Adjusted Life Expectancy;

2) DFLE or Disability Free Life Expectancy;

3) DALE or Disability-Adjusted Life Expectancy;

4) ALE or Active Life Expectancy; etc.

The second group includes such measures as:

1) DALY or Disability-Adjusted Life Years;

2) QALY or Quality-Adjusted Life Years.

When measures from the first group are calculated, the process, as a rule, involves taking into account not only mortality but also disability induced by various reasons. Differences in calculations of these measures occur due to use of various weights and approaches to allowing for significance of diseases and

[12] Constitution of the WHO. Available at: https://www.who.int/governance/eb/who_constitution_en.pdf (December 15, 2021).

[13] Taking into account poorer quality of life due to disease or acquired disability usually involves using specific values with the common name HRQL (Health-Related Quality of Life) [19].

other reasons for health deterioration [36, 37]. Besides, some measures, such as DFLE, for example, don't allow for any differences in severity of health disorders since they all have the same zero weight when the measure is calculated. That is, DFLE takes into account only "perfect health". And if calculating a measure involves taking into account various severity of "not perfect health", different weights are recommended to be used for the several "categories of health disorders".

The second group that includes so called HALY measures[14] describes influences exerted by reasons that cause health deterioration on a reduction in healthy life, that is, changes in population health due to a specific health disorder in comparison with a situation when this disorder is absent.

To calculate HALY measures associated with a specific disease, we should complete three basic tasks:

1. To describe a health state associated with this disease;
2. To develop a numeric measure or a weight for this health state;
3. To combine numeric measures of each health state with estimated life expectancies [19].

If we consider using summary measures of health as a probable measure of risk associated with impacts exerted on health by various environmental factors, then, obviously, measures from the second group are more eligible for the purpose since they can reflect exactly changes in health. In other words, they allow quantifying a difference between health of a given population group without any exposure to a harmful factor and health influenced by this exposure, that is, spotting out a component associated directly with this exposure to this harmful factor.

At present it is QALY and DALY that are the most widely used measures combining life expectancy estimates and health estimates. But still there are certain differences in how DALY and QALY are used in practice [35].

QALY measures were developed in early 1970ties as "a health index" that combined life expectancy and quality. First, they were applied in tuberculosis screening. At present QALY are primarily used to make economic estimates by multiple regulating authorities that consider cost-effectiveness analysis to be an integral part of decision-making. QALY measures make it possible to compare interventions into health that can make life longer but have severe side effects (for example, permanent disability due to radiotherapy or chemotherapy in cancer treatment) with interventions that raise quality of life without making it longer (for example, palliative aid or pain relief) [19].

DALY is a summary measure of population health that combines mortality and nonfatal health outcomes. Initially this measure was developed to quantify severity of diseases within the GBD project aiming to measure a relative loss of healthy life associated with different reasons for disease or disability [30]. Procedures for calculating DALY are based on the assumption that time is the most eligible indicator of disease severity and it includes a period of time with disability and a period of time lost due to dying early [19].

The basic principle in calculating DALY is that each disease or any other reason for reduced working abilities is weighted taking its severity into account (starting from 0 which means "good health" and up to 1 which means death). On the population level, this weight is multiplied by exposure duration as well as by a number of people exposed to a specific disease or any other reason for losing their full working abilities. Therefore, DALY is calculated as a sum of years lost due to dying early and lost years of healthy life resulted from not being completely healthy due to harmful exposure. "A major advantage this measure has is an opportunity to summarize outcomes caused by various exposures (for example, environmental ones) as well as to combine quantitative and qualitative characteristics of life" [15].

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[14] Health-Adjusted Life Years is the common term to describe a group of measures including DALY, QALY etc.

[15] Bychkova S.G. Sotsial'naya statistika: uchebnik dlya akademicheskogo bakalavriata [Social statistics: the manual for academic bachelor students]. Moscow, Izd-vo Yurait, 2019, 864 p. (in Russian).

QALY and DALY measures can be and are actually applied when estimating returns on investments into public healthcare, though only QALY was initially designed for this purpose [35]. The most significant difference between DALY and QALY measures is that QALY is more eligible for assessing medical intervention with the focus on consequences this intervention might have on quality of life whereas DALY measure allows quantifying negative effects produced by a disease itself on average individual or population levels bearing in mind "disease severity" or population burden ("disease burden"[16]). Therefore, it is DALY measure which is much better as a basis for calculating losses associated with exposures to variable harmful factors.

Most generally, formula applied to calculate DALY can be given as follows:

$$DALY = YLL + YLD, \quad (3)$$

where YLL is years of life lost due to premature death, that is, a number of years a person failed to live up to an average life expectancy due to dying early caused by a disease; YLD is a number of years lived with disability caused by disease or any other reason.

In its turn,

$$YLL = M \times LE, \quad (4)$$

where M is a number of deaths due to condition; LE is standard life expectancy at age of death.

YLD is calculated as per the following formula which includes a weighting factor showing a decrease in quality of life due to disease:

$$YLD = DW \times I \times DD, \quad (5)$$

where I is a number of nonfatal incident cases; DD is average duration of disability due to specific disease until remission (or death); DW is weighting factor of specific condition that reflects decreasing quality of life due to this condition.

The methodology for calculating DALY has been constantly developed [22, 38]. At present DALY calculation allows a possibility to assign different weights to years lived with health disorders at different age. When experts use weights for different ages (in some procedures for calculating DALY), they usually prefer young adults to infants and elderly people since this population cohort is considered to be a "more productive" part of the society and makes the greatest contribution into economic development. However, this approach is not accepted in some countries. Weighting age-related factors are probably the most controversial social parameters applied in DALY calculations.

Age- and disability-related weights are not the only social values applied in calculating DALY measures. The GBD project implementation outlined some other issues (in addition to those discussed above: standard number of years lost due to premature death and disability weights) influencing how and why DALY are calculated:

1) How long "should" people live?

2) Is a year of life saved today more valuable for the society than a year of healthy life preserved in the future, say, 20 years from now?

3) Should years of healthy life be estimated differently at different age? For example, the GBD project gives more value to a year of a young adult than those of an elderly person or an infant.

4) Are all people equally important?

5) Do all people of specific age lose the same number of healthy years due to death even if their life expectancy is different in different social groups? [39].

However, not all experts agreed with this approach regarding both differences and

[16] In the Russian text of the paper, this term, "burden of disease", is translated word by word here since it is used in this way in official Russian translations of the WHO publications. Still, it seems a rather poor translation and the authors try to avoid this exact word-by-word variant in the Russian text replacing it with synonymic word combinations which seem more appropriate to them.

weights. When this approach is applied, it makes DALY measure more an economic indicator showing productivity of people who have specific medical condition.

Critics state there are three major ethical problems related to using QALY and DALY measures:

– They don't fully take into account condition of people with poor social status or poor health. Elderly people and people who already have certain healthy disorders make contributions into lower HALY measures since there is only limited potential for improving their health;

– Similarly, these measures discriminate people with limited possibility to be treated or people who are less likely to recover (For example, people with already diagnosed healthy disorders or diseases);

– Both measures don't take into account qualitative differences in outcomes (for example, saving a life against a simple recovery) due to the applied procedure for summarizing mortality and morbidity rates. Health measures and disease measures are combined for all people and for the whole range of health states, starting from its perfect one and down to death. It means that differences between activities aimed at saving a life and those aimed at improving health are neglected. Aggregating as a specific issue also raises a question whether we should estimate insignificant benefits for many people in the same way as significant benefits for just some of them [19].

At present new estimation procedures are being developed which are much better in allowing for social peculiarities and not only can solve the aforementioned ethical issues but also provide a clearer idea of population health.

Therefore, assessment of "disease severity" is the most interesting in terms of scientific research. It can be used as a key parameter for including diseases, injuries, and disabilities into summary health measures which do not result in death but reduce functional abilities, make life shorter and its quality poorer. It is interesting, both theoretically and practically, to search for balance in two directions: 1) balance between health self-assessment and quality of life due to disease, injury or disability and objective health state and functionality, 2) balance between socioeconomic (different social groups have different "value" for a state and its economy[17]) and humanistic (all lives matter equally regardless of sex, age, race, nationality, health or any other social properties) estimates of "significance" assigned to different population groups.

Development of measures for assessing radiation detriment. The TG-102 team presented a report during the 2nd session "Risks and effects" at the International online-conference "The Future of Radiological Protection" which was organized in October 2021 by the ICRP. The report focused on developing a methodology for calculating radiation detriment and specifically outlined how the existing methodology could be improved in future [40]. There were five major spheres for this improvement outlined in the report:

1) update of baseline data and parameters for detriment calculation;

2) revision of "dose – effect" models and the procedure for risk assessment transfer between populations;

3) handling of variation with sex and age in detriment calculation;

4) increasing transparency and comprehensibility of parameters;

5) consideration of non-cancer effect.

The authors outlined three major components for the first sphere: 1) use of actual statistical data on cancer incidence rates and mortality rates; 2) use of data on other populations other than selected Asian and Euro-American

[17] Whether it is ethical to take this factor into account when calculating summary measures of population health is a question to be discussed separately [20]. As a rule, authorities in countries with high income per capita believe all lives are equally valuable whereas authorities in countries where public healthcare budgets are limited have to keep in mind that their possibilities to develop public healthcare are rather limited when determining priority spheres for funding.

ones; 3) adjustment of weighting factors reflecting severity of nonfatal[18] diseases.

The second and fifth items in the list to a greater extent concern summarizing results produced by epidemiological studies whereas the remaining items are more applied and methodological ones. There have been frequent attempts to calculate detriment using more up-to-date medical and demographic data on specific populations (Russian, in particular) [41, 42]; also there have been often changes in some parameters in detriment calculation, such as lethality fraction for cancers etc. [5, 6]. Attempts to take into account risk dependence on sex and age under exposure are also quite frequent, especially when it comes down to assessing risks caused by medical radiation [43–45].

Much less attention has been paid so far to the most fundamental question, that is, the value of detriment, its actual meaning and practical necessity [46]. Meanwhile, as it has been mentioned above, this value needs revising and rethinking; this task is vital due to all the progress which has been achieved recently in population health assessment together with obsolescence of data applied to calculate detriment, medical-demographic and other data as well as due to existing practices in using detriment and its derivatives.

Thus, for example, Shimada K. and Kai M. used DALY in their work as a possible measure for an excess cancer risk following radiation exposure [46]. Based on the results produced by their estimates, they concluded that the IRCP overestimated a contribution made by leukemia risk and underestimated those made by breast cancer and thyroid gland cancer. They also noted that the value of detriment had a drawback and it was that it couldn't be adequately interpreted or applied. Contrary to opinion expressed by many experts, detriment is not a risk for the whole population since it is calculated for a hypothetic population including people of different sexes, different ages, and belonging to different ethnical communities. They also noted that multi-dimensional detriment used in radiation protection was determined as a radiation risk measure, in particular, when it comes down to comparing fatal and nonfatal cancers. They also pointed out that the existing concept of detriment could be used only for comparing effects produced by different exposure doses.

This change in paradigm of assessing detriment to health in the applied sphere should undoubtedly be provided with convicting scientific and practical substantiation. Structural similarities between radiation detriment and DALY measure allow examining several variants for applying the methodology for estimating global burden of diseases in assessing radiation detriment and developing relevant measures:

1) The simplest approach is to directly replace weights assigned to nonfatal cancers in detriment calculation with respective DW measures applied in DALY calculation. This approach would require some changes at the last stage in calculating weighting factors for various organs and tissues since detriment values[19] for nonfatal cancers of specific organs and tissues are already calculated bearing in mind a number of lost years of healthy life whereas fatal cancers are not weighted allowing for this measure.

2) Radiation detriment values are de facto used as a predictive risk rate to solve multiple practical tasks related to providing radiation safety although the ICRP directly pointed out that it wasn't correct to use detriment value in such a way. Given that, it would seem advisable to use actual medical and demographic data on specific populations when calculating numbers of radiation-induced cancers and linear coefficients of radiation detriment for the most significant age-sex-specific population groups. This would make risk assessments based on using them more practically significant even in spite of all well-known uncertainties occurring in such assessments.

[18] Nonfatal diseases in this case are diseases caused by exposure to ionizing radiation and resulting in reducing one's life and making its quality poorer but not in death. This concept is not about a specific nosology in general but only about a share of disease cases that occur among exposed people due to exposure but are not the primary reason for their deaths.

[19] Or detriment-adjusted risk as given in the glossary of the ICRP Publication 103 [14].

3) Finally, calculating DALY linear coefficients per a radiation dose unit and simultaneous use of both these measures in risk assessment could make for gradual implementation of up-to-date radiation detriment measures without violating succession in traditions and the necessity to retrain a great number of experts.

Our analysis of data available in literature assuredly indicates that studies with their focus on developing the risk assessment methodology are vital and also determines the most promising trends in future research.

Conclusions. Based on analysis of all literature sources stated in the references to this article, we can conclude the following:

1. A gradual change in the paradigm of assessing negative influence on population health by various environmental factors, that is, health risk analysis, is an applied aspect in the development of the health assessment. Summary health measures based on population mortality caused by exposure to harmful factors are replaced with measures based on reduction in number of years of healthy life due to the same exposure; this approach should be adopted in decision-making processes in multiple spheres.

2. Implementation of DALY measures into the health risk assessment methodology can provide several advantages in comparison with other existing approaches:

– DALY-based risk assessments allow more correct comparison of negative effects produced by exposure to a harmful factor on population health in case risks realization is distributed differently over time;

– DALY-based risk assessments make comparative risk analysis between different populations simpler since they take into account population differences much more exactly than when risks are comparatively analyzed based on standardization of sex-age-specific medical and demographic parameters;

– procedures for estimating disease severity are being constantly developed and this allows estimating the actual situation with national public healthcare systems and providing their most precise picture in health risk analysis. In particular, it is true for progress in diagnostics and treatment of specific diseases;

– population risk assessments based on lost years of healthy life don't create a false perception of actual death cases in a situation when there is no epidemiological proof of negative effects produced on numerous population groups by exposure to very small doses of a harmful factor, that is, in a situation when negative effects are considered to likely occur only due to extrapolation from higher doses (exposures).

3. A rapid change in the risk assessment paradigm hardly seems feasible and is rather unadvisable. It seems more realistic to gradually change the system of risk measures by applying the methodology for assessing disease severity developed within the GBD project to quantify health risks associated with exposure to various environmental factors. Simultaneously it is possible to use DALY values per a unit of a harmful factor as a measure for assessing harmful effects on health.

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References

1. Demin V.F., Zakharchenko I.E. Risk vozdeistviya ioniziruyushchego izlucheniya i drugikh vrednykh faktorov na zdorov'e cheloveka: metody otsenki i prakticheskoe primenenie [The risk of exposure to ionizing radiation and other harmful factors for human health: assessment methods and practical application]. *Radiatsionnaya biologiya. Radioekologiya*, 2012, vol. 52, no. 1, pp. 77–89 (in Russian).

2. Korenkov I.P., Demin V.F., Soloviev V.Yu. Problems of the establishment of dose – effect relationship for risk assessment under exposure to ionizing radiation and harmful chemical substances. *Gigiena i sanitariya*, 2019, vol. 98, no. 7, pp. 687–700. DOI: 10.18821/0016-9900-2019-98-7-697-700 (in Russian).

3. Cléro E., Bisson M., Nathalie V., Blanchardon E., Thybaud E., Billarand Y. Cancer risk from chronic exposures to chemicals and radiation: a comparison of the toxicological reference value with the radiation detriment. *Radiat. Environ. Biophys.*, 2020, vol. 60, no. 4, pp. 531–547. DOI: 10.1007/s00411-021-00938-2

4. Cléro E., Vaillant L., Hamada N., Zhang W., Preston D., Laurier D., Ban N. History of radiation detriment and its calculation methodology used in ICRP Publication 103. *J. Radiol. Prot.*, 2019, vol. 39, no. 3, pp. R19–R35. DOI: 10.1088/1361-6498/ab294a

5. Zhang W., Laurier D., Cléro E., Hamada N., Preston D., Vaillant L., Ban N. Sensitivity analysis of parameters and methodological choices used in calculation of radiation detriment for solid cancer. *Int. J. Radiat. Biol.*, 2021, vol. 96, no. 5, pp. 596–605. DOI: 10.1080/09553002.2020.1708499

6. Breckow J., Emami S., Amalhaf S., Beshgard A., Buermeyer J., Spruck K. Impact of updating the non-radiation parameters in the ICRP 103 detriment model. *Radiat. Environ. Biophys.*, 2021., vol. 57, pp. 89–98. DOI: 10.1007/s00411-018-0731-z

7. Kobyakova O.S., Deyev I.A., Boikov V.A., Milkevich M.N., Kulikov E.S., Naumov A.O., Golubeva A.A., Shibalkov I.P. Possible application of DALY to health assessment of population in Russia. *Sotsial'nye aspekty zdorov'ya naseleniya*, 2015, no. 2. Available at: http://vestnik.mednet.ru/content/view/660/30/ (12.12.2021) (in Russian).

8. Starodubov V.I., Marczak L.B , Varavikova E., Bikbov B., Ermakov S.P., Gall J., Glenn S.D., Griswold M. [et al.]. The burden of disease in Russia from 1980 to 2016: a systematic analysis for the Global Burden of Disease Study 2016. *The Lancet*, 2018. vol. 392, no. 10153, pp. 1138–1146. DOI: 10.1016/S0140-6736(18)31485-5

9. Publikatsiya 26 MKRZ. Radiatsionnaya zashchita [ICRP Publication 26. Recommendations of the ICRP]. *Trudy MKRZ*. Moscow, Atomizdat, 1978, 88 p. (in Russian).

10. Publikatsiya 60 MKRZ. Radiatsionnaya bezopasnost'. Rekomendatsii Mezhdunarodnoi komissii po radiologicheskoi zashchite 1990 goda. Chast' 2 [ICRP Publication 60. Radiation protection. 1990 Recommendations of the International Commission on Radiological Protection. Part 2]. In: I.B. Keirim-Markus ed. *Trudy MKRZ*. Moscow, Energoatomizdat, 1994, 208 p. (in Russian).

11. Preston D.L., Shimizu Y., Pierce D.A., Suyama A., Mabuchi K. Studies of mortality of atomic bomb survivors. Report 13: solid cancer and noncancer disease mortality: 1950–1997. *Radiat. Res.*, 2012, vol. 178, no. 2, pp. AV146–AV172. DOI: 10.1667/rrav12.1

12. Ozasa K., Shimizu Y., Suyama A., Kasagi F., Soda M., Grant E.J., Sakata R., Sugiyama H., Kodama K. Studies of the mortality of atomic bomb survivors, Report 14, 1950–2003: an overview of cancer and noncancer diseases. *Radiat. Res.*, 2012, vol. 177, no. 3, pp. 229–243. DOI: 10.1667/rr2629.1

13. ICRP Publication 60. Radiation protection. 1990 Recommendations of the International Commission on Radiological Protection. Part 2. In: H. Smith ed. *Annals of the ICRP*, vol. 21, no. 1–3. Oxford, Pergamon Press, 1991, 211 p.

14. ICRP Publication 103. The 2007 Recommendations of the International Commission on Radiological Protection. In: J. Valentin ed. *Annals of the ICRP*, 2007, vol. 37, no. 2–4, 339 p.

15. Repin L.V. On the use of detriment parameters for the quantitative evaluation of radiation exposure consequences. *Radiatsionnaya gigiena*, 2011, vol. 4, no. 1, pp. 35–37 (in Russian).

16. Publikatsiya 103 MKRZ. Rekomendatsii 2007 goda Mezhdunarodnoi komissii po radiatsionnoi zashchite [ICRP Publication 103. The 2007 Recommendations of the International Commission on Radiological Protection]. In: M.F. Kiselev, N.K. Shandala eds. *Trudy MKRZ*. Moscow, OOO PKF "Alana", 2009, 344 p. (in Russian).

17. EPA 402-R-11-001. EPA Radiogenic Cancer Risk Models and Projections for the U.S. Population. *U.S. Environmental Protection Agency*, Washington, D.C., 2011, 175 p.

18. UNSCEAR 2006 Report. Effects of ionizing radiation. Vol. 2. New York, United Nations Publ., 2009, 338 p.

19. Lajoie J. Understanding the Measurement of Global Burden of Disease. *National Collaborating Centre for Infectious Diseases*, 2015, 22 p. Available at: https://nccid.ca/wp-content/uploads/sites/2/2015/03/Global_Burden_Disease_Influenza_ENG.pdf (20.12.2021).

20. Murray C.J.L., Salomon J.A., Mathers C. A critical examination of summary measures of population health. *Bull. World Health Organ.*, 2000, vol. 78, no. 8, pp. 981–994.

21. Gold M.R., Stevenson D., Fryback D.G. HALYs and QALYs and DALYs, Oh My: similarities and differences in summary measures of population health. *Annu. Rev. Public Health*, 2002, vol. 23, no. 1, pp. 115–134. DOI: 10.1146/annurev.publhealth.23.100901.140513

22. Sassi F. Calculating QALYs, comparing QALY and DALY calculations. *Health Policy Plan.*, 2006, vol. 21, no. 5, pp. 402–408. DOI: 10.1093/heapol/czl018

23. Pasport natsional'nogo proekta «Zdravookhranenie» [The profile of the "Healthcare" national project]. Available at: http://static.government.ru/media/files/gWYJ4OsAhPOweWaJk1prKDEpregEcduI.pdf (12.12.2021) (in Russian).

24. Harris E.C., Palmer K.T., Cox V., Darnton A., Osman J., Coggon D. Trends in mortality from occupational hazards among men in England and Wales during 1979–2010. *Occup. Environ. Med.*, 2016, vol. 73, no. 6, pp. 385–393. DOI: 10.1136/oemed-2015-103336

25. Chen Y.-H., Glymour M., Riley A., Balmes J., Duchowny K., Harrison R., Matthay E., Bibbins-Domingo K. Excess mortality associated with the COVID-19 pandemic among Californians 18–65 years of age, by occupational sector and occupation: March through November 2020. *PLoS One*, 2021, vol. 16, no. 6, pp. e0252454. DOI: 10.1371/journal.pone.0252454

26. Popova A.Yu. Working conditions and occupational morbidity in the Russian Federation. *Meditsina truda i ekologiya cheloveka*, 2015, no. 3, pp. 7–13 (in Russian).

27. Onishchenko G.G., Popova A.Yu., Zaitseva N.V., May I.V., Shur P.Z. Health risk analysis in the tasks of improving sanitary and epidemiological surveillance in the Russian Federation. *Health Risk Analysis*, 2014, no. 2, pp. 4–13. DOI: 10.21668/health.risk/2014.2.01.eng

28. EPA 100-B-00-002. Risk Characterization: Science Policy Council Handbook. *U.S. Environmental Protection Agency*. Washington, DC, 2000, 189 p.

29. Thacker S.B., Stroup D.F., Carande-Kulis V., Marks J.S., Roy K., Gerberding J.L. Measuring the public's health. *Public Health Rep.*, 2006, vol. 121, no. 1, pp. 14–22. DOI: 10.1177/003335490612100107

30. Salomon J.A. Disability-Adjusted Life Years. *Encyclopedia of Health Economics*. Elsevier, 2014, pp. 200–203. DOI: 10.1016/b978-0-12-375678-7.00511-3

31. Mathers C.D. History of global burden of disease assessment at the World Health Organization. *Arch. Public Health*, 2020, vol. 78, pp. 77. DOI: 10.1186/s13690-020-00458-3

32. Ustün T.B., Chatterj S., Bickenbach J., Kostanjsek N., Schneider M. The International Classification of Functioning, Disability and Health: a new tool for understanding disability and health. *Disabil. Rehabil.*, 2003, vol. 25, no. 11-12, pp. 565–571. DOI: 10.1080/0963828031000137063

33. The Global Burden of Disease concept. *WHO*. Available at: https://www.who.int/quantifying_ehimpacts/publications/en/9241546204chap3.pdf (12.12.2021).

34. Murray C.J.L., Lopez A.D., Mathers C.D., Stein C. The Global Burden of Disease 2000 project: aims, methods and data sources. *WHO*, 2001, 57 p. Available at: https://www.who.int/healthinfo/paper36.pdf (12.12.2021).

35. Handbook of disease burdens and quality of life measures. In: V.R. Preedy, R.R. Watson eds. New York, Springer, 2010, 4446 p. DOI: 10.1007/978-0-387-78665-0

36. Ruan X., Li Y., Jin X., Deng P., Xu J., Li N., Li X., Liu Y. Health-adjusted life expectancy (HALE) in Chongqing, China, 2017: An artificial intelligence and big data method estimating the burden of disease at city level. *Lancet Reg. Health West. Pac.*, 2021, vol. 9, pp. 100110. DOI: 10.1016/j.lanwpc.2021.100110

37. Lee J.Y., Ock M., Kim S.H., Go D.S., Kim H.J., Jo M.W. Health-Adjusted Life Expectancy (HALE) in Korea: 2005–2011. *J. Korean Med. Sci.*, 2016, vol. 31, suppl. 2, pp. 139–145. DOI: 10.3346/jkms.2016.31.S2.S139

38. Chen A., Jacobsen K.H., Deshmukh A.A., Cantor S.B. The evolution of the disability-adjusted life year (DALY). *Socio-Econ. Plan. Sci.*, 2015, vol. 49, pp. 10–15. DOI: 10.1016/j.seps.2014.12.002

39. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020: summary. In: C.J.L. Murray, A.D. Lopez eds. *WHO*. Boston, Harvard School of Public Health Publ., 1996, 41 p.

40. Ban N., Clero E., Vaillant L., Zhang W., Hamada N., Preston D., Laurier D. Possible Improvements of Methodology for Calculating Radiation Detriment in the Future. *ICRP*. Available at: https://icrp.org/admin/Live%20Sessions/SLIDES_2-2_NobuhikoBan.pdf (12.12.2021).

41. Gorski A.I., Chekin S.Yu., Maksioutov M.A., Menyajlo A.N., Korelo A.M., Tumanov K.A., Zelenskaya N.S., Lashkova O.E., Ivanov V.K. Transfer of ICRP models of radiation risk to the population of the Russian Federation. *Radiatsiya i risk*, 2019, vol. 28, no. 4, pp. 5–15. DOI: 10.21870/0131-3878-2019-28-4-5-15 (in Russian).

42. Ivanov V.K., Chekin S.Yu., Kashcheev V.V., Maksyutov M.A., Korelo A.M., Menyailo A.N. Issledovanie vliyaniya neopredelennosti fonovykh pokazatelei zabolevaemosti na prognoz radiatsionnykh riskov po modelyam MKRZ dlya rossiiskikh populyatsii pri odnokratnom obluchenii [Effect produced by uncertainty of baseline incidence rates on estimating radiation risks with ICRP models for Russian populations following single exposure to radiation]. *Radiatsiya i risk*, 2013, vol. 22, no. 3, pp. 40–56 (in Russian).

43. Andersson M., Eckerman K., Pawel D., Almén A., Mattsson S. Improved radiation risk models applied to different patient groups in Sweden. *Radiation Hygiene*, 2019, vol. 12, no. 2, pp. 44–54. DOI: 10.21514/1998-426X-2019-12-2-44-54

44. Golikov V.Yu., Vodovatov A.V., Chipiga L.A., Shatsky I.G. Evaluation of radiation risk for patients undergoing medical examinations in the Russian Federation]. *Radiatsionnaya gigiena*, 2021, vol. 14, no. 3, pp. 56–68. DOI: 10.21514/1998-426X-2021-14-3-56-68 (in Russian).

45. Ivanov V.K., Tsyb A.F., Mettler F.A., Menyaylo A.N., Kashcheev V.V. Health risks of medical radiation exposure. *Radiatsiya i risk*, 2011, vol. 20, no. 2, pp. 17–28 (in Russian).

46. Shimada K., Kai M. Calculating disability-adjusted life years (DALY) as a measure of excess cancer risk following radiation exposure. *J. Radiol. Prot.*, 2015, vol. 35, no. 4, pp. 763–775. DOI: 10.1088/0952-4746/35/4/763

Repin L.V., Akhmatdinov R.R., Biblin A.M., Repin V.S. On harmonization of health risk indicators caused by ionizing radiation exposure and other harmful factors based on DALY estimates. Health Risk Analysis, 2022, no. 1, pp. 162–175. DOI: 10.21668/health.risk/2022.1.18.eng

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Review

EPIDEMIOLOGIC ASPECTS IN PREVENTION OF THE NEW CORONAVIRUS INFECTION (COVID-19) (LITERATURE REVIEW)

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At the end of 2019 the mankind had to face a new coronavirus infection with higher virulence which resulted in its rapid spread all over the world and in an ultimate pandemic. Initially a new virus which causes COVID-19 was called 2019-nCoV but it soon acquired its well-known name, SARS-CoV-2. We can positively state that this new coronavirus infection will remain in the history of world public healthcare as a disease that caused a collapse in rendering medical aid. Undoubtedly, this new coronavirus infection has changed customary lifestyle of the overall world population.

This review can be considered problematic in its essence and focuses on examining contemporary trends in the official epidemiologic situation in the world regarding the new coronavirus infection (SARS-CoV-2). Having analyzed several foreign and domestic documents, the authors revealed a necessity to enhance levels and quality of COVID-19 epidemiologic diagnostics. There is a suggestion being considered at the moment on including additional clinical and diagnostic activities aimed at preventing further spread of the new coronavirus infection. We should note that data on COVID-19-related mortality and morbidity are renewed every day and every hour. Given that, it seems rather difficult to keep in line with the latest trends in COVID-19 prevention and epidemiologic diagnostics. However, the authors made an attempt to possibly collect all the latest data on epidemiological peculiarities related to the clinical course of the new coronavirus infection. The authors have a hope that this review will be useful for epidemiologists when they detect new cases of the disease as well as for lecturers at medical higher educational establishments when they train students and resident physicians.

***Key words**: new coronavirus infection, SARS-CoV-2, COVID-19, basic reproductive number, pandemic, severe acute respiratory syndrome – SARS, children, pregnant women, fecal-oral transmission, prevention.*

Multiple research papers have been written with their focus on communicable diseases since the history of mankind has seen a great number of pandemics. Primarily, we should mention plague, variola, cholera, and Spanish influenza; these infections caused the longest pandemics that occurred repeatedly and claimed huge numbers of people's lives. At the beginning of the 20th century the Spanish influenza pandemic of 1918 caused as many as 20 million deaths [1, 2]. Given the peculiar features of that period, it is no wonder that the pandemic predominantly spread through trade and communication routes as well as due to military operations (the First World War, 1914–1918). Access to medical aid was limited and sanitary conditions were rather poor thus making for occurrence of factors facilitating the transmission of the disease [3].

A lot of contemporary authors mention in the research works that the mankind has to face a new viral pandemic, the coronavirus

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infection [1, 3–10]. S. Weston with colleagues (2020) emphasize that till the very end of 2019 there were only six coronaviruses which could cause a human disease. Four of them (hCoV-229E, hCoV-HKU1, hCoV-NL63 and hCoV-OC43) can only produce a mild cold and don't cause any special concern of world public healthcare. However, the remaining two viruses caused more severe diseases with typically high case fatality rate. Thus, in 2002 a coronavirus was discovered that caused severe acute respiratory syndrome (SARS-CoV) [11]. From 2002 to 2004 SARS−CoV coronavirus from the Betacorona virus genus (bats are its natural reservoir) caused an epidemic for the first time. The disease was called atypical pneumonia and caused 774 death cases in 37 countries all over the world [11, 12]. Since 2003 there have been no new registered cases of atypical pneumonia caused by SARS−CoV [11]. The second epidemic caused by another coronavirus occurred in 2012 on Arabian Peninsula and was called Middle East respiratory syndrome (MERS-CoV) [11, 12]. SARS-CoV and MERS-CoV outbreaks started with a patient who suffered from pneumonia and both outbreaks resulted from zoonosis [11, 13]. A search for MERS-CoV reservoir was first concentrated on bats since they were considered by many authors [13, 14] to be a natural reservoir for a great variety of coronaviruses, including those similar to SARS-CoV и MERS-CoV. However, serologic tests and enzyme-linked immunoassays (hereinafter ELISA) performed on Arabian camels in Saudi Arabia, Qatar, and the Canary Islands established that MERS-CoV was widely spread in those animals [14–16].

At the end of 2019 the mankind had to face a new coronavirus infection with greater virulence that made for its rapid spreads all over the world and resulted in a pandemic. Initially the new virus was called 2019-nCoV but now its official name is SARS-CoV-2 and it causes the disease called COVID-19. Undoubtedly, this new coronavirus infection has become a significant milestone in the history of the 21st century as it has changed the customary lifestyle of the whole mankind.

This new coronavirus SARS-CoV-2 is a single-stranded RNA-virus that belongs to Coronaviridae family, Beta-CoVB line. The virus is assigned into the pathogenicity group II, similar to some other viruses from this family (SARS-CoV, MERS-CoV). Coronaviruses are the most striking example of a virus that was twice able to overcome the interspecies barrier between wild animals and humans during SARS and MERS outbreaks. SARS-CoV-2 is suspected to possibly overcome this barrier for the third time [17]. SARS-CoV-2 coronavirus is probably a recombinant virus between the bat coronavirus (RaTG13-2013, identity is 96 %) and another coronavirus of unknown origin. The genetic sequence of SARS-CoV-2 is similar to that of SARS-CoV at least by 79 % [17, 18]. To scientists' opinion, it is vital to examine an intermediate host since it. According to provides a better insight into how SARS-CoV-2 became a human virus and how to develop prevention activities in future. It is much safer to create new vaccines for animal hosts thus preventing any infection from spread among people [19].

Sanche S. with colleagues (2020), having generalized their experience in examining the coronavirus infection, noted that at the end of 2019 the municipal public healthcare committee in Wuhan (China) reported 41 cases of "pneumonia with unknown etiology" to the World Health Organization. On January 08, 2020 an infectious agent was successfully identified and shortly after it was established that the virus could be transmitted between people. By January 21, 2020 multiple COVID-19 cases had been registered in most provinces in China. By March 16, 2020 there were more than 170,000 confirmed cases of the disease and more than 6500 deaths all over the world. An outbreak of "pneumonia with unknown etiology" turned into the COVID-19 pandemic in such a short time as 3 months [20].

COVID-19 spread rapidly due to people travelling all over the world (both within a country and between different countries) and the pandemic scales were reached during 2–3 months. Therefore, by November 03, 2020 COVID-19 was detected in more than 210 countries (includ-

ing autonomous areas). The disease was registered on all continents, Antarctica excluded, a number of infected people amounted to 47,327,323; deaths, 1,211,882; 33,942,600 people fully recovered [21].

The basic reproduction number (R_0) is a dimensionless parameter that is used in epidemiology to characterize how contagious a disease is. It is usually determined as a number of people who will be infected by a typical patient who is surrounded by completely non-immunized population and there are no specific epidemiologic measures aimed at preventing this disease from spreading (quarantine, for example) [22]. To estimate COVID-19 spread, a lot of authors apply the basic reproduction number R_0. When $R_0 > 1$, a number of infected people is likely to grow, and if $R_0 < 1$, the transmission is likely to stop [23].

Sanche S. with colleagues [20] point out that the initial values of the basic reproductive number varied from 2.2 to 2.7 at early stages in the COVID-19 outbreak. However, their further studies involved mathematical modeling based on 140 confirmed COVID-19 cases; the authors established that the infection spread was very rapid as R_0 amounted to 5.7 (95 % CI 3.8–8.9) (July 2020). Thus, the basic reproduction number R_0 depends on the exponential growth of an outbreak as well as on latent (a period from contagion to becoming contagious) and infectious periods. The authors concluded that the longer the latent and infectious periods were the higher was R_0 [20]. Ge H. and others gave other data and stated that R_0 varied from 1.4 to 6.49 [24]. We should note that the basic reproduction number might be different in different countries and depend on an applied mathematical model [23] or prevention activities, such as social distancing and facial mask wearing.

Akin L. with colleagues [1] performed a comparative examination of basic reproduction numbers determined for several pandemics including Spanish influenza (1918–1919), 1.7–2.8; Asian influenza (1957–1958), 1.8; Hong Cong influenza (1968–1969), 1.06–2.06; swine influenza (2009), 1.4–1.6; COVID-19 (2019), 5.7.

Therefore, values of the basic reproductive numbers described by several authors [1, 20, 23–25] can possibly indicate that SARS-CoV-2 is highly contagious. The assumption is further confirmed by studies based on analyzing genome parts in the virus; it is assumed that SARS-CoV-2 has much greater affinity with the human receptor ACE2 which is necessary to penetrate a cell than the SARS virus detected in 2003. Thus, high contagiousness of SARS-CoV-2 is provided with a solid molecular basis.

There are some very interesting works on COVID-19 incubation period [26, 27]. Lauer S.A. with colleagues (2020) examined an incubation period in 99 disease cases. The authors took a period of time from the first contact with an infected person and up to the first signs of fever. It was done to exclude a systematic mistake in examining incubation periods caused by calculating them from a moment when cough or sore throat were detected and we should remember that these symptoms can be caused by other, more widely spread microorganisms. The research results showed that average incubation period up to the moment when the fever set in amounted to 5.7 days (CI, from 4.9 to 6.8 days). 2.5 % people had the first fever attack during 2.6 days (CI, from 2.1 to 3.7 days) and 97.5 % during 12.5 days (CI, from 8.2 to 17.7 days) [28]. Ge H. and others reported the longest incubation period that amounted to 24 days [24].

There is an opinion that animals can be a possible source of SARS-CoV-2 [17]. Nevertheless, a man is the primary infection source (the disease is anthroponotic) just as in case of SARS CoV and MERS CoV. The virus is transmitted by droplets of moisture (during talking, coughing, or sneezing), by close contacts, or the transmission can be fecal-oral [24, 29]. Nucleic acids of SARS-CoV-2 are detected in liquid from the bronchial tree, phlegm, nose and throat swabs, feces, blood, and urine at different stages in the clinical course of the disease. Aerosols exhaled from the airways by an infected person can persist in the air and infect people who don't keep a proper social distance in a closed space [30, 31]. SARS CoV-2

virus is detected in the air during three hours in experimental models. However, Cheng V.C.C. with colleagues failed to detect SARS CoV-2 in 8 samples taken at a 10-m distance from the chin of a patient, both wearing a face mask and without it [30]. Similar results were produced by other experts who examined air samples taken at a 5-m distance from patients: no virus detected [29].

Fecal-oral transmission is another topical issue with respect to COVID-19 which hasn't been given an exact answer so far. Diarrhea was among clinical symptoms in a lot of patients with COVID-19 [29, 31]. The virus can probably be transmitted in a direct contact with an infected person as well as with contaminated surfaces or household appliances [32]. SARS CoV-2 has been established to remain viable for 72 hours on plastic and stainless steel; copper, more than 4 hours; and carton boxes, up to 24 hours. However, experts do not have an unambiguous answer to the question whether the virus is able to preserve its virulence when it persists on various surfaces. Another possible transmission route can be associated with the virus penetrating the oral cavity, nose, and eyes form dirty hands [31]. The assumption has been confirmed by Bulut C. with colleagues who detected viable viruses in samples of feces taken from patients with diarrhea [29, 31]. The most indicative data are provided by Dhama K. and others (2020): anal swabs give positive results as opposed to oral cavity swabs at later stages in the infection. This can be used as an additional diagnostic criterion when a patient with COVID-19 is ready to be released from hospital given negative swabs taken from the oral cavity or nasopharynx: there can still be a risk of fecal-oral transmission. The same data were obtained when experts analyzed feces of children infected with SARS-CoV-2 and with mild clinical course of the disease. An oral cavity swab was negative as opposed to anal swab that was SARS-CoV-2-positive during ten days [33]. Medical workers should adhere to strict safety precautions when working with feces samples taken from patients with suspected COVID-19 or already infected ones.

Occurrence of SARS-CoV-2 virus in feces can result in the fecal-oral transmission of the infection. Probably, if we want to prevent SARS-CoV-2 spread, we should believe healthy people to be those who not only have negative oral cavity swabs but also anal ones [33].

Therefore, SARS CoV-2 occurrence in feces can be either due to lesions of the gastrointestinal tract or phlegm digestion and this gives further causes to pay great attention to personal hygiene.

Waste waters are becoming another important aspect in studies focusing on COVID-19 since they can become a factor making for the transmission of the disease. Given that SARS-CoV-2 virus occurs in phlegm, blood, urine, and feces, we can assume that it can also occur in sewerage and waste waters. This requires further investigation due to the fecal-oral transmission being quite possible. Therefore, it seems reasonable to revise the existing procedures and stages in treatment of waste and sewage waters and to implement effective disinfection techniques that can also eliminate SARS-CoV-2 [33].

Previous epidemics of many viral infections could result in pregnancy pathologies, a virus being transmitted from a mother to a fetus, a perinatal infection and even death. Schwartz D.A. (2020) conducted a study where he indicated that COVID-19 didn't cause any pathology in 38 pregnant women. It should also be noted that there have been no confirmed cases when SARS-CoV-2 was transmitted from a mother to a fetus [34–36].

Cheng V.C.C. et al. [30] examined 9 women with diagnosed COVID-19 during the third trimester. The study showed that clinical signs were similar to those detected in women who weren't pregnant: 7 women had fever; 5, lymphopeny; 4, cough; 3, myalgia; 2, sore throat and overall sickness. All the examined women had pneumonia but none of the needed AV; moreover, the outcomes were quite positive in all the examined cases. They all gave birth by cesarean section. Absence of intrauterine or trans-placental transmission was also confirmed by the newborns' Apgar scores: 8–9 after 1 minute and 9–10 after 10 minutes [35].

People with inapparent infection are still its sources and are epidemiologically dangerous for their susceptible counterparts. There have also been some reports on atypical clinical signs of COVID-19 with fatigability being its only symptom. Such respiratory symptoms as fever, cough, and phlegm can be completely absent [33]. Therefore, early diagnostics and detection of patients with inapparent infection can considerably reduce the transmission of the infection to other, more susceptible people. Nevertheless, we should note that experts are still unable to provide exact data on the matter and there is no unified and correct opinion on factors and conditions of SARS CoV-2 transmission.

According to Rasmussen S.A. and others, an average age of hospitalized patients amounted to 49–56 years and 32–51 % of them had another disease [37]. Bulut C. with colleagues [29] concentrated on age-related peculiarities of hospitalized patients in different countries and detected authentically significant differences. Thus, in China 87 % patients were aged 30–39 years; in Italy, 35.8 % and 36 % were aged 50–59 and 70–79 years respectively. However, people aged 20–29 years accounted for more than 70 % of hospitalized patients in Germany [29].

Hospitalized patients tended to have such clinical signs as fever (83–100 %), cough (59–82 %), myalgia (11–35 %), headache (7–8 %), and diarrhea (2–10 %). However, 100 % patients had certain lesions in their lungs detected by chest x-ray examination (ground-glass opacity). Meanwhile, children rarely had COVID-19 and most of them had the disease in its very mild form [37].

Besides age- and sex-related factors, it was also established that middle-age and elderly patients with primary chronic diseases, especially hypertension and diabetes mellitus, were more susceptible to respiratory failure and, consequently, their prognosis could probably be rather unfavorable [33].

According to data provided by the WHO, the overall mortality rate amounted to 6.3 as of April 13, 2020. But there were differences in mortality detected between different countries. This rate tends to be higher in countries with older population. Thus, in Italy average age of people who died from COVID-19 amounted to 78 years and the mortality rate was 12.73 %; France, 15.23 %; Spain, 10.22 %; China, 4.01 %; Germany, 2.28 %; the Russian Federation, 0.81 % [29]. According to data provided by Bulut C. and others, a concomitant disease can increase mortality: cardiovascular diseases, by 10.5 %; diabetes mellitus, by 7.3 %; chronic respiratory diseases, by 6.3 %; hypertension, by 6.0 %; and cancer, by 5.6 % [29].

Experts also note that mortality among men (2.8 %) is higher than among women (1.7 %). ACE2 is known to be located on the X-chromosome which can possibly have some alleles that provide its carrier with resistance to COVID-19 and this fact can explain lower mortality levels among women. Sex hormones might be another reason as it is assumed by Tay M.Z. with colleagues. Estrogen and testosterone have different immune-regulatory functions that can possibly influence both immune protection and severity of COVID-19 [36].

COVID-19 pandemic created a tremendous burden on public healthcare all over the world. A drastic growth in a number of new cases has already exceeded any quantities of available medical consumables thus limiting a capability to provide patients with intensive care and making it available for only a small part of critical ones. This could also make for growing mortality rates during the COVID-19 outbreak [33].

Therefore, it is truly vital to implement effective anti-epidemic, preventive, and sanitary-hygienic activities in order to prevent further spread of the disease and its transmission from person to person.

An epidemic process of any infection, this new coronavirus one among them, includes the epidemiologic triad described by Gromashevskiy: an infectious agent, a transmission mechanism, and a susceptible organism. However, at present we can influence only the first two sections in the epidemic process until a safe and, more importantly, effective vaccine against this new coronavirus infection is created.

Some countries implement various activities aimed at preventing COVID-19 transmis-

sion and spread, some effective, others not [38–40]. Thus, in China many cities were closed and social contacts were seriously limited at early stages in the epidemic. The government made a decision to follow two basic principles, "four early" and "four centralizations" [41]. "Four early" principle included early detection and early isolation of people infected with SARS-CoV-2, early communication and early treatment. All these activities facilitated early diagnostics and treatment and, consequently, prevented further SARS-CoV-2 spread and reduced contagion levels. Contact people were thoroughly traced in order to detect and isolate a source of the infection at an early stage. Any mass events were postponed, schools and industrial enterprises were closed [42, 43].

"Four centralizations" principle meant that patients with the severe clinical course of the disease were placed in the best hospitals with the most effective therapeutic capabilities (centralization of patients). Centralization of doctors, resources, and treatment provided an opportunity to render high quality medical aid to seriously ill patients in accordance with the principle "one person – one strategy". We should note than more than 37,000 thousand medical workers from other provinces of China took an active part in treating patients with SARS-CoV-2 in Wuhan, Hubei province. This fact reflects noble qualities and high professionalism of medical personnel (centralization of doctors). All these aforementioned measures effectively reduced COVID-19 mortality [41].

In the United States, immigration was suspended and certain limitations were imposed on return of American citizens who could create a risk of the new coronavirus infection spread and transmission in the country. However, as it was noted by Patel A. and others, there was practically no quarantine and cities were not closed [44].

The British government adopted another strategy to fight against COVID-19. It was quite distinctive and was aimed at reaching "collective immunity" to SARS-CoV-2 virus. Thus, at least 40 million British citizens "were allowed" to get infected and the government hopes it would be enough to create durable national immunity. However, Yu J. with colleagues (2020) believe this strategy to be "absurd" since vaccination is the only way to create collective immunity whereas the governmental policy in Great Britain sacrifices a lot of people and this is considered to be inhuman in any civilized society. Besides, viruses can mutate and there is no evidence that a recovered person has some sort of durable immunity. Therefore, this strategy to fight the infection hardly seems reasonable [45].

At present most European and American countries haven't still adopted the effective Chinese strategy "to collect as many together as possible" but allow patients with mild clinical course of the disease to isolate themselves at home thus increasing risks of transmission and further spread of the virus.

Isolation and creation of vaccines and antiviral medications are top priorities. In case there is no safe and effective vaccine or a specific drug treatment, the only solution is to prevent the virus transmission, to provide people and medical personnel with basic information and to implement relevant prevention and control activities. Safety precautions can help people to prevent risks of contagion; for example, people should often wash their hands with soap or any alcohol-based disinfectant, cover their mouth with the elbow or a Kleenex when sneezing or coughing, avoid close contacts with people who have apparent symptoms, and apply for a medical aid instantly in case there is fever, cough, or labored breathing [38].

Creating a proper microclimate seems another possibly effective way to prevent SARS-CoV-2 from spreading. In particular, proper temperature and relative humidity can exert significant influence on frequency of COVID-19 cases and SARS-CoV-2 transmission [40].

According to data provided by Harmooshi N.N. (2020), SARS-CoV-2 is not a thermophilic virus; therefore, it becomes inactive just as air temperature drops [40]. However, other experts believe that SARS-CoV-2 disappears at 30 °C, and this is a mistake since the virus can become less viable under this temperature

but this doesn't mean it is eliminated completely [46]. Results produced in some latest research give grounds for an assumption that SARS-CoV-2 virus can survive on a surface during 4–28 days, but if air temperature drops below 30–40 °C, then its life span will decrease. In addition to temperature, coronaviruses are also sensitive to humidity; consequently, it is probable that SARS-CoV-2 virus can live longer under relative humidity being 50 %, than under that equal to 30 % [40].

Therefore, the most effective way to make SARS-CoV-2 virus less active is to use disinfectants which contain 60–70 % of ethanol or 70 % of isopropanol. Also, household detergents or soap can be used for disinfection. If your hands are relatively clean, you can use only a disinfectant, but in case they are dirty, you have to wash them with soap during at least 20 seconds [47].

Greater public awareness should be created by using posters with precise "DO" and "DO NOT DO" lists illustrating symptoms, ways of transmission and prophylaxis activities with a focus on personal hygiene aimed at preventing COVID-19 spread. Any campaigns on organizing physical and social distancing aimed at reducing physical contacts between people should be promoted. Fitbit devices and other applications on smartphones can be used for monitoring over symptoms during such outbreaks [48, 49]. Smartphones and Internet-services can also be used for spreading relevant information on how to prevent the infection from spreading.

Certain issues regarding SARS-CoV-2 still remain without an answer including factors that facilitated the virus overcoming the interspecies barrier and ultimate conclusion on its origin; differences in critical points of mutation in transmission and pathogenesis of the virus; the reason why it occurred; why some infected people die and others only have inapparent infection; repeated cases of the disease among recovered people.

However, one thing is known for sure: we can overcome SARS-CoV-2 virus only by joint efforts made by the whole world society and using lessons that we learned thanks to MERS and SARS outbreaks. Each day brings some new knowledge about the COVID-19 pandemic. It hasn't finished yet, and we should understand that unless we change our attitudes towards SARS-CoV-2 virus and become more demanding to ourselves, the virus will change our everyday life completely what it has been doing rather successfully all this time.

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References

1. Akin L., Gözel M.G. Understanding dynamics of pandemics. *Turk. J. Med. Sci.*, 2020, vol. 50, no. SI-1, pp. 515–519. DOI: 10.3906/sag-2004-133

2. Potter C.W. A history of influenza. *Journal of Applied Microbiology*, 2001, vol. 91, no. 4, pp. 572–579. DOI: 10.1046/j.1365-2672.2001.01492.x

3. Arda B., Acıduman A. Pandemic influenza 1918-19: lessons from 20th century to the 21st from the history of medicine point of view. *Lokman Hekim Journal*, 2012, vol. 2, no. 3, pp. 13–21.

4. Chen B., Tian E.-K., He B., Tian L., Han R., Wang S., Xiang Q., Zhang S. [et al.]. Overview of lethal human coronaviruses. *Signal Transduct. Target. Ther.*, 2020, vol. 5, no. 1, pp. 89. DOI: 10.1038/s41392-020-0190-2

5. Hozhabri H., Piceci Sparascio F., Sohrabi H., Mousavifar L., Roy R., Scribano D., De Luca A., Ambrosi C., Sarshar M. The Global Emergency of Novel Coronavirus (SARS-CoV-2): An Update of the Current Status and Forecasting. *Int. J. Environ. Res. Public Health*, 2020, vol. 17, no. 16, pp. 5648. DOI: 10.3390/ijerph17165648

6. Chen Y., Liu Q., Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. *J. Med. Virol.*, 2020, vol. 92, no. 4, pp. 418–423. DOI: 10.1002/jmv.25681

7. Hassan S.A., Sheikh F.N., Jamal S., Ezeh J.K., Akhtar A. Coronavirus (COVID-19): A Review of Clinical Features, Diagnosis, and Treatment. *Cureus*, 2020, vol. 12, no. 3, pp. e7355. DOI: 10.7759/cureus.7355

8. Zhu N., Zhang D., Wang W., Li X., Yang B., Song J., Zhao X., Huang B. [et al.]. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N. Engl. J. Med.*, 2020, vol. 382, no. 8, pp. 727–733. DOI: 10.1056/NEJMoa2001017A

9. Lu H., Stratton C.W., Tang Y.W. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. *J. Med. Virol.*, 2020, vol. 92, no. 4, pp. 401–402. DOI: 10.1002/jmv.25678

10. Ashour H.M., Elkhatib W.F., Rahman M.M., Elshabrawy H.A. Insights into the Recent 2019 Novel Coronavirus (SARS-CoV-2) in Light of Past Human Coronavirus Outbreaks. *Pathogens*, 2020, vol. 9, no. 3, pp. 186. DOI: 10.3390/pathogens9030186

11. Weston S., Frieman M.B. COVID-19: Knowns, Unknowns, and Questions. *mSphere*, 2020, vol. 5, no. 2, pp. e00203–e00220. DOI: 10.1128/mSphere.00203-20

12. Hijawi B., Abdallat M., Sayaydeh A., Alqasrawi S., Haddadin A., Jaarour N., Alsheikh S., Alsanouri T. Novel coronavirus infections in Jordan, April 2012: epidemiological findings from a retrospective investigation. *East Mediterr. Health J.*, 2013, vol. 19, Suppl. 1, pp. S12–S18.

13. De Wit E., van Doremalen N., Falzarano D., Munster V.J. SARS and MERS: recent insights into emerging coronaviruses. *Nat. Rev. Microbiol.*, 2016, vol. 14, no. 8, pp. 523–534. DOI: 10.1038/nrmicro.2016.81

14. Drexler J.F., Corman V.M., Drosten C. Ecology, evolution and classification of bat coronaviruses in the aftermath of SARS. *Antiviral Res.*, 2014, vol. 101, pp. 45–56. DOI: 10.1016/j.antiviral.2013.10.013

15. Singhal T. A Review of Coronavirus Disease-2019 (COVID-19). *Indian J. Pediatr.*, 2020, vol. 87, no. 4, pp. 281–286. DOI: 10.1007/s12098-020-03263-6

16. Zhou P., Yang X.-L., Wang X.-G., Hu B., Zhang L., Zhang W., Si H.-R., Zhu Y. [et al.]. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature*, 2020, vol. 579, no. 7798, pp. 270–273. DOI: 10.1038/s41586-020-2012-7

17. Shamsheva O.V. New Coronavirus COVID-19 (SARS-CoV-2). *Detskie infektsii*, 2020, vol. 19, no. 1, pp. 5–6. DOI: 10.22627/2072-8107-2020-19-1-5-6 (in Russian).

18. Perlman S. Another Decade, Another Coronavirus. *N. Engl. J. Med.*, 2020, vol. 382, no. 8, pp. 760–762. DOI: 10.1056/NEJMe2001126

19. Haagmans B.L., van den Brand J.M.A., Raj V.S., Volz A., Wohlsein P., Smits S.L., Schipper D., Bestebroer T.M. [et al.]. An orthopoxvirus-based vaccine reduces virus excretion after MERS-CoV infection in dromedary camels. *Science*, 2016, vol. 351, no. 6268, pp. 77–81. DOI: 10.1126/science.aad1283

20. Sanche S., Lin Y.T., Xu C., Romero-Severson E., Hengartner N., Ke R. High Contagiousness and Rapid Spread of Severe Acute Respiratory Syndrome Coronavirus 2. *Emerg. Infect. Dis.*, 2020, vol. 26, no. 7, pp. 1470–1477. DOI: 10.3201/eid2607.200282

21. CORONAVIRUS (COVID-19). Available at: https://coronavirus-monitor.ru (03.11.2020) (in Russian).

22. Li J., Blakeley D., Smith R.J. The failure of R_0. *Computational and mathematical methods in medicine*, 2011. Available at: http://downloads.hindawi.com/journals/cmmm/2011/527610.pdf (17.08.2021).

23. Liu Y., Gayle A.A., Wilder-Smith A., Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J. Travel Med.*, 2020, vol. 27, no. 2, pp. taaa021. DOI: 10.1093/jtm/taaa021

24. Ge H., Wang X., Yuan X., Xiao G., Wang C., Deng T., Yuan Q., Xiao X. The epidemiology and clinical information about COVID-19. *Eur. J. Clin. Microbiol. Infect. Dis.*, 2020, vol. 39, no. 6, pp. 1011–1019. DOI: 10.1007/s10096-020-03874-z

25. Li Q., Guan X., Wu P., Wang X., Zhou L., Tong Y., Ren R., Leung K.S.M. [et al.]. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N. Engl. J. Med.*, 2020, vol. 382, no. 13, pp. 1199–1207. DOI: 10.1056/NEJMoa2001316

26. Rothe C., Schunk M., Sothmann P., Bretzel G., Froeschl G., Wallrauch C., Zimmer T., Thiel V. [et al.]. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. *N. Engl. J. Med.*, 2020, vol. 382, no. 10, pp. 970–971. DOI: 10.1056/NEJMc2001468

27. Cheng Z.J., Shan J. 2019 Novel coronavirus: where we are and what we know. *Infection*, 2020, vol. 48, no. 2, pp. 155–163. DOI: 10.1007/s15010-020-01401-y

28. Lauer S.A., Grantz K.H., Bi Q., Jones F.K., Zheng Q., Meredith H.R., Azman A.S., Reich N.G., Lessler J. The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Re-

ported Confirmed Cases: Estimation and Application. *Annals of internal medicine*, 2020, vol. 172, no. 9, pp. 577–582. DOI: 10.7326/M20-0504

29. Bulut C., Kato Y. Epidemiology of COVID-19. *Turk. J. Med. Sci.*, 2020, vol. 50, no. SI–1, pp. 563–570. DOI: 10.3906/sag-2004-172

30. Cheng V.C.C., Wong S.C., Chen J.H.K., Yip C.C.Y., Chuang V.W.M., Tsang O.T.Y., Sridhar S., Chan J.F.W. [et al.]. Escalating infection control response to the rapidly evolving epidemiology of the coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 in Hong Kong. *Infect. Control Hosp. Epidemiol.*, 2020, vol. 41, no. 5, pp. 493–498. DOI: 10.1017/ice.2020.58

31. Machhi J., Herskovitz J., Senan A.M., Dutta D., Nath B., Oleynikov M.D., Blomberg W.R., Meigs D.D. [et al.]. The Natural History, Pathobiology, and Clinical Manifestations of SARS-CoV-2 Infections. *J. Neuroimmune Pharmacol.*, 2020, vol. 15, no. 3, pp. 359–386. DOI: 10.1007/s11481-020-09944-5

32. Kampf G., Todt D., Pfaender S., Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. *J. Hosp. Infect.*, 2020, vol. 104, no. 3, pp. 246–251. DOI: 10.1016/j.jhin.2020.01.022

33. Dhama K., Khan S., Tiwari R., Sircar S., Bhat S., Malik Y.S., Singh K.P., Chaicumpa W. [et al.]. Coronavirus Disease 2019-COVID-19. *Clinical microbiology reviews*, 2020, vol. 33, no. 4, pp. e00028–20. DOI: 10.1128/CMR.00028-20

34. Schwartz D.A. An Analysis of 38 Pregnant Women With COVID-19, Their Newborn Infants, and Maternal-Fetal Transmission of SARS-CoV-2: Maternal Coronavirus Infections and Pregnancy Outcomes. *Arch. Pathol. Lab. Med.*, 2020, vol. 144, no. 7, pp. 799–805. DOI: 10.5858/arpa.2020-0901-SA

35. Chen H., Guo J., Wang C., Luo F., Yu X., Zhang W., Li J., Zhao D. [et al.]. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet*, 2020, vol. 395, no. 10226, pp. 809–815. DOI: 10.1016/S0140-6736(20)30360-3

36. Tay M.Z., Poh C.M., Rénia L., MacAry P.A., Ng L.F.P. The trinity of COVID-19: immunity, inflammation and intervention. *Nat. Rev. Immunol.*, 2020, vol. 20, no. 6, pp. 363–374. DOI: 10.1038/s41577-020-0311-8

37. Rasmussen S.A., Smulian J.C., Lednicky J.A., Wen T.S., Jamieson D.J. Coronavirus Disease 2019 (COVID-19) and pregnancy: what obstetricians need to know. *Am. J. Obstet. Gynecol.*, 2020, vol. 222, no. 5, pp. 415–426. DOI: 10.1016/j.ajog.2020.02.017

38. Haybar H., Kazemnia K., Rahim F. Underlying chronic disease and COVID-19 infection: A State-of-the-Art Review. *Jundishapur J. Chronic Dis. Care*, 2020, vol. 9, no. 2, pp. e103452. DOI: 10.5812/jjcdc.103452

39. Ghinai I., McPherson T.D., Hunter J.C., Kirking H.L., Christiansen D., Joshi K., Rubin R., Morales-Estrada S. [et al.]. First known person-to-person transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in the USA. *Lancet*, 2020, vol. 395, no. 10230, pp. 1137–1144. DOI: 10.1016/S0140-6736(20)30607-3

40. Harmooshi N.N., Shirbandi K., Rahim F. Environmental concern regarding the effect of humidity and temperature on 2019-nCoV survival: fact or fiction. *Environ. Sci. Pollut. Res. Int.*, 2020, vol. 27, no. 29, pp. 36027–36036. DOI: 10.1007/s11356-020-09733-w

41. Ye Q., Wang B., Mao J., Fu J., Shang S., Shu Q., Zhang T. Epidemiological analysis of COVID-19 and practical experience from China. *J. Med. Virol.*, 2020, vol. 92, no. 7, pp. 755–769. DOI: 10.1002/jmv.25813

42. Chen W., Wang Q., Li Y.Q., Yu H.L., Xia Y.Y., Zhang M.L., Qin Y., Zhang T. [et al.]. [Early containment strategies and core measures for prevention and control of novel coronavirus pneumonia in China]. *Zhonghua Yu Fang Yi Xue Za Zhi*, 2020, vol. 54, no. 3, pp. 239–244. DOI: 10.3760/cma.j.issn.0253-9624.2020.03.003 (in Chinese).

43. Chen S., Yang J., Yang W., Wang C., Bärnighausen T. COVID-19 control in China during mass population movements at New Year. *Lancet*, 2020, vol. 395, no. 10226, pp. 764–766. DOI: 10.1016/S0140-6736(20)30421-9

44. Patel A., Jernigan D.B. 2019-nCoV CDC Response Team. Initial Public Health Response and Interim Clinical Guidance for the 2019 Novel Coronavirus Outbreak – United States, December 31,

2019–February 4, 2020. *MMWR Morb. Mortal. Wkly Rep.*, 2020, vol. 69, no. 5, pp. 140–146. DOI: 10.15585/mmwr.mm6905e145

45. Yu J., Chai P., Ge S., Fan X. Recent Understandings Toward Coronavirus Disease 2019 (COVID-19): From Bench to Bedside. *Front. Cell Dev. Biol.*, 2020, vol. 8, no. 476, pp. 476. DOI: 10.3389/fcell.2020.00476

46. Wang J., Tang K., Feng K., Lv W. High temperature and high humidity reduce the transmission of COVID-19. Available at: https://ssrn.com/abstract=3551767 (17.07.2021).

47. Malik Y.S., Kumar N., Sircar S., Kaushik R., Bhat S., Dhama K., Gupta P., Goyal K. [et al.]. Coronavirus Disease Pandemic (COVID-19): Challenges and a Global Perspective. *Pathogens*, 2020, vol. 9, no. 7, pp. 519. DOI: 10.3390/pathogens9070519

48. Viboud C., Santillana M. Fitbit-informed influenza forecasts. *Lancet Digit. Health*, 2020, vol. 2, no. 2, pp. e54–e55. DOI: 10.1016/S2589-7500(19)30241-9

49. Radin J.M., Wineinger N.E., Topol E.J., Steinhubl S.R. Harnessing wearable device data to improve state-level real-time surveillance of influenza-like illness in the USA: A population-based study. *Lancet Digit. Health*, 2020, vol. 2, no. 2, pp. e85–e93. DOI: 10.1016/S2589-7500(19)30222-5

Butaev T.M., Tsirikhova A.S., Kabaloeva D.V., Kudukhova D.O. Epidemiologic aspects in prevention of the new coronavirus infection (COVID-19) (Literature review). Health Risk Analysis, 2022, no. 1, pp. 176–185. DOI: 10.21668/health.risk/2022.1.19.eng

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COMMENTS AND REVIEWS

THE MONOGRAPH "EVOLUTION OF ARTIFICIAL LIGHTING: A HYGIENIST'S OPINION" BY V. KAPTSOV AND V.N. DEINEGO: AN OUTLINE, MOSCOW, RAS, 2021

Read online

B.A. Revich

Several years ago, a brilliant report on hygienic issues related to lighting was given by Valeriy A. Kaptsov, Doctor of Medical Sciences, Professor, Corresponding Member of RAS. The report was given on the plenary session of the Commission on Environmental Hygiene. And now, after a while, there is a monograph by the same author written in cooperation with an expert in photobiological safety and lighting technologies. Both authors are men of great humanitarian erudition and this enabled them to consider excessive light as a health risk factor within philosophical and historical context, providing multiple poetic and religious citations. As the authors state in their foreword, they "outline the role played by light in the life of the preceding civilizations". This impressive monograph of 632 pages in volume is the first fundamental hygienic work over the last 40 years with its focus on a specific and very complicated health risk factor. Its predecessors are monographs on the environmental hygiene, in particular, a work on the ambient air hygiene which was issued in 1976 by several authors and edited by K.A. Bushtueva and a work on the water supply hygiene by S.N. Cherkinskiy which was issued in 1975. Both these monographs have been widely used in the educational process ever since and have been studied by thousands of students, postgraduates, and experts in various fields. Still, hygienic issues are not considered in them from the general humanitarian point of view. V. Kaptsov has also followed the tradition to cooperate with experts from those fields where hygienic studies are performed, just as our teachers used to do many years ago. For example, Professor K. Bushtueva studied industrial technologies in great detail paying a lot of attention to those of them which created substantial emissions of pollutants into ambient air. Together with production engineers, she searched for ways to minimize them. Professor S. Cherkinskiy had not only medical but also technical education. This helped him to offer the most effective ways to treat sewage waters which were also safe for human health and ecosystems. Therefore, a creative union by the authors of this monograph seems truly logical. Hygienic assessment of light presented in the monograph includes its impacts on biochemical processes in the eye connective tissue and cornea, melatonin synthesis and functions performed by it, oxidative stress and other processes; and this assessment is combined with detailed examination of issues related to lighting technologies. A range of patterns concerning this issue is outlined by the editors in their foreword together with data on the intensive growth of myopia prevalence, both in Russia and in other countries. We can quite agree with the authors that they have been able to develop basic laws in the hygiene of light and provided theoretical foundation for light spectra similarity. We can also share their regrets that the laboratory for lighting hygiene (radiant energy) has ceased its operations. However, we should note that the laboratory of residential and public buildings was also closed down and it's a pity since it dealt with

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hygienic assessment of town planning. As for other closed laboratories, we can mention the laboratory for construction materials hygiene as well as some other laboratories in scientific centers across the country.

Starting from the foreword, the authors study the mythology of light in the ancient Egyptian and Greek culture: “a winner needs a falcon’s health and life-giving light of rising sun”; how sunlight dispersion was discovered by Newton; how the term “myopia” was created; and some other facts regarding the issue.

The first chapter dwells on analyzing and systematizing the results produced by more than 350 studies which revealed variable negative outcomes caused by use of light-emitting diodes; the authors also describe rules of special nutrition necessary for people who spend a lot of time working on a PC and looking at a monitor; they consider an issue related to excessive blue light doses which has already been addressed by them in their previous works. Bearing in mind, that this monograph is distributed free of charge and there is not enough information about its publication, we feel obliged to provide several references to these previous publications: Kaptsov with colleagues, 2013, 2014; Deinego, Kaptsov, 2014; Kaptsov, Deinego, 2016, 2017 and others[1]. A list of headings for the sections in the table of contexts provided for the monograph is almost 2 pages long. This list contains some notes which are utterly interesting for preventive medicine in general, for example, a philosophy of a hygienist and the profile of the lighting environment, hygiene and principles of medical deontology and some others. A small but quite informative section headed “Moonlight and starlight” intertwines scientific data on light with poetic and pictorial examples.

Theoretical aspects of the examined issue (electron deficiency as a basis of oxidative stress pathogenesis, biochemistry of the connective tissue and cornea, etc.) are accompanied with detailed description of preventive activities which are vital in our northern country with huge sunlight and ultraviolet radiation deficiency resulting in relevant protohormone D shortage. Building density now tends to be too high in residential areas and this leads to improper insolation and insufficient open green spaces, especially in megacities; the process is further aggravated with excessive lighting. The authors provide some data that the phenomenon is especially apparent in huge Asian megacities (the first place belongs to Hong Cong where there are no limitations on light pollution). A lot of people living in such cities suffer from insomnia. Therefore, some cities (Shanghai, Sidney, or London, for example) have started to reduce intensive lighting and introduced certain limitations. As the authors put it, “people living in megacities can see only several tens of the brightest starts in the night sky instead of 2500 ones which are always there”. The monograph gives some examples of activities performed in various countries and cities with their aim to reduce light pollution. Nevertheless, in France, for instance, illumination provided for a lot of buildings in downtowns has been only growing and the same is true for architecture monuments and other public places but the process has never been supported with proper hygienic assessment.

The closing chapters in the monograph dwell on health risks caused by some types of LED sources including those influencing the retina. This fundamental work about light is interesting and useful not only for readers mentioned by the authors themselves such as hygienists, occupational pathologies, or experts in labor protection but also for people with a wide range of other occupations including biologists; stage lighting specialists; designers, architects and planners, especially those who design hospitals and children facilities; city developers; power engineering specialists; economists; etc.

[1] Kaptsov V.A., Sosunov N.N., Shishchenko I.I., Viktorov V.S., Tulushev V.N., Deynego V.N., Bukhareva E.A., Murashova M.A. [et al.]. Functional state of the visual analyzer in the conditions of the use of traditional and led light sources. *Gigiena i sanitariya*, 2014, vol. 93, no. 4, pp. 120–123 (in Russian); Kaptsov V.A., Deinego V.N. Blue LED light as a new hygienic problem. *Health Risk Analysis*, 2016, no. 1, pp. 15–25. DOI: 10.21668/health.risk/2016.1.02.eng; Kaptsov V.A., Deinego V.N.. Risks of age related macular degeneration and led lighting. *Health Risk Analysis*, 2017, no. 4, pp. 129–146. DOI: 10.21668/health.risk/2017.4.14.eng; Deynego V.N., Kaptsov V.A. Visual hygiene in led lighting. Modern scientific imaginations. *Gigiena i sanitariya*, 2014, vol. 93, no. 5, pp. 54–58 (in Russian).