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Research article

DEVELOPING MODEL OF RISK-BASED SANITARY-EPIDEMIOLOGICAL CONTROL (SURVEILLANCE) OVER FOOD PRODUCTS IN CONSUMER MARKET

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The relevance of this study arises from products being fixed as an independent object for state sanitary-epidemiological control in law.

The contemporary stage of the public regulation involves the following: administrative pressure on economic entities ought to be easier but the best possible protection of citizens' life and health should be provided.

In this study, our aim was to test approaches to developing the risk-based model for control of food products on the consumer market in the country.

The study relied on using the fundamental methodical approaches to the risk-based control model used by the Sanitary Service of Russia.

A potential health risk was determined as a combination of likely violations of legal requirements to a certain product, severity of health outcomes due to such violations, and coefficients that described a scale of undesirable consequences.

Food products were assigned into one of the following categories as per health risks: objects of extremely high risk, high risk, considerable risk, moderate risk, medium risk, or low risk.

We suggest a fundamental scheme describing how to organize risk-based control of food products as an independent control object. It includes several basic elements, namely, creating a register of consumer food products; identifying priority groups of food products as per risk criteria at the federal level; identifying regional priorities. We provide substantiation for advisability of profound risk assessment performed for food products in each group considering specific frequency of sanitary violations, scales in which a certain food product in consumed in different regions, and priority consumer demands.

Our suggestion is to integrate risk profiles of products and risk-based laboratory support for control into the general model.

We'd like to highlight the relevance of creating a unified database to keep the results of all the control and surveillance activities including data obtained by laboratory tests of products bound to manufacturers, distributors, and sellers. It is also quite relevant to include algorithms and mathematical methods of science-intensive analysis of the data sets into software modules of the Rospotrebnadzor's Unified Information System.

Keywords: *food products, control, safety, risk-based model, risk profile, register of products, violations of mandatory requirements, laboratory control optimization.*

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In 2021, the Federal Law no. 248 On State Control (Surveillance) and Municipal Control in the Russian Federation came into force. The Clause 16 in it establishes that *'the results of economic activities performed by citizens and organizations, including products (goods), works and services covered by mandatory requirements'* are an independent object of the state control. Previously, products were considered a component within control of activities performed by economic entities.

Changes in the legislation have their effect on how control is organized in general whereas its essence remains the same. Control means assessing whether products conform to established requirements to their safety and quality; removing unsafe products from the market; preventing such products from penetrating the market again in future. Requirements to food products as an object of control (surveillance) also remain the same.

The Unified Sanitary-Epidemiological Requirements to Products (Goods) Subject to Sanitary-Epidemiological Surveillance (Control)[1] establish hygienic indicators and safety standards for products (goods) under control.

In particular, they stipulate that:

– products under control should not produce any adverse effects on health of the current and future generations, citizens' property, living conditions, and the environment;

– contents and presentation of consumer product information should allow correct identification of a product and its manufacturer and conform to product requirements established by regulatory documents issued in the member-countries and technical regulations issued for a each type of product.

Russian national requirements, just as requirements of the Eurasian Economic Union, the Russian Federation being its member, are harmonized with the World Health Organization standards according to which 'food safety' is defined as *'assurance that food will not cause adverse health effects to the consumer when it is prepared and/or eaten according to its intended use'*. This safety is provided by *'preventing and eliminating hazards caused by contaminants, admixtures, natural toxins or any other substances, whether chronic or acute, that may make food injurious to the health of the consumer or reducing them to acceptable and safe levels'* [2].

Hazard Analysis and Critical Control Point (HACCP) is the primary and key component in providing food quality and safety [1]. HACCP system is the internationally tested and accepted efficient tool for minimizing risks of contamination in manufactured products, providing their safety and quality, the latter being the primary task that has to be tackled by food industry [2, 3].

HACCP system is the internationally tested and accepted efficient tool for minimizing risks of contamination in manufactured products, providing their safety and quality, the latter being the primary task of food industry [2, 3].

HACCP system was first implemented in Russia in 2001 when the RF State Agency on Standardization and Metrology registered the voluntary certification system that has been functioning successfully ever since. At present, more and more economic entities declare themselves committed to HACCP principles and conform to them when performing their economic activities [4–6].

Nevertheless, state control of products that are already distributed on the consumer market can be and should be considered the primary and integral component in protecting health (and sometimes life) of the population. Even if food products are manufactured in accordance with HACCP principles, they are often delivered to the end consumer after they have been loaded and unloaded several times, stored in warehouses and then put onto shelves in a shop and in some cases processed and packed etc. Due to it, products may lose some

[1] Edinye sanitarno-epidemiologicheskie i gigienicheskie trebovaniya k produktsii (tovaram), podlezhashchei sanitarno-epidemiologicheskomu nadzoru (kontrolyu); utv. resheniem Komissii Tamozhennogo soyuza ot 28 maya 2010 g. № 299 [The Unified Sanitary-Epidemiological Requirements to Products (Goods) Subject to Sanitary-Epidemiological Surveillance (Control); approved by the Decision of the Customs Union Commission on May 28, 2010 no. 299]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/902249109 (August 12, 2023) (in Russian).

[2] Codex Alimentarius. General Principles of Food Hygiene CXC 1-1969. *FAO, WHO*. Available at: https://www.fao.org/fao-who-codexalimentarius/ (June 01, 2023).

of their initial properties and acquire new ones, which are not always safe for the consumer.

The State sanitary control of products sold in retail, food offered by catering organizations and the like is the last and immediate barrier between potentially unsafe and/or low quality food products and their consumers.

It is practically impossible to control all the food products on the market since their range is huge and these products differ considerably as per their physical, chemical and biological properties, initial raw materials they are made of, manufacturers, and many other parameters. Given that, risk-based food control is more justified than in other sphere [7]. International experience gained in application of risk-based control over products on the market proves this point. Thus, the EU Requirements of the General Product Safety Directive (2001/95/EC) establish that *'safe product is … any product which, under normal or reasonably foreseeable conditions of use including duration and, where applicable, putting into service, installation and maintenance requirements, does not present any risk or only the minimum risks …, considered to be acceptable'* (Clause 2, item b). Risk is considered a safety criterion.

Other relevant documents specify that national bodies of the EU countries responsible for control and surveillance over the marketed products are authorized to control any product prior to and after it has been manufactured including even those products that create minimal risks[3]. The essentials the of risk-based food control model were given by the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing at the very start of the administrative reforms in Russia [8]. The Head of the Service, the RF Chief Sanitary Inspector approved the Methodical Guidelines Classification of Food Products on the Marker as per Risks of Health Harm and Property Losses of Consumers for Organizing Scheduled Control and Surveillance Activates[4].

At the same time, the experience of using the risk-based control model [9, 10] and overall changes in the control and surveillance activities call for relevant development of the existing approaches. This development should consider changes in frequency of violations of mandatory requirements to products in dynamics, the current sanitary-epidemiological situation, and specific changes in consumption. Accumulation of digital data on results of product inspections within the Unified Information Analytical System of the Sanitary Service is the key component and solid foundation for the development of the risk-based model [11, 12]. This System is being formed now; however, in future it will make it possible to perform in-depth systemic analysis based on multidimensional and diverse data about safety and quality of products, their manufacturers and sellers.

In this study, our aim was to test approaches to improving the risk-based model for control of food products on the consumer market in the country.

Materials and methods. The study relied on using the fundamental methodical approaches to the risk-based control model used by the Sanitary Service of Russia since they were deemed correct and eligible. A potential health risk was determined as a combination of likely violations of mandatory requirements to a certain product, severity of health outcomes due to such violations, and coefficients that described a scale of undesirable consequences.

Likelihood of violations of mandatory requirements was described by frequency of identified violations in all the RF regions. According to the precaution principle, frequency

[3] Guidance for risk assessment of food and feed from genetically modified plants. *EFSA Journal*, 2011, vol. 9, no. 5. Available at: https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2011.2150 (August 26, 2023); New Legislative Framework. *European Commission*. Available at: https://single-market-economy.ec.europa.eu/single-market/goods/new-legislative-framework_en (August 07, 2017).

[4] Klassifikatsiya pishchevoi produktsii, obrashchaemoi na rynke, po risku prichineniya vreda zdorov'yu i imushchestvennykh poter' potrebitelei dlya organizatsii planovykh kontrol'no-nadzornykh meropriyatii: metodicheskie rekomendatsii; utv. Prikazom Rospotrebnadzora ot 18.01.2016 № 16 [Classification of Food Products on the Marker as per Risks of Health Harm and Property Losses of Consumers for Organizing Scheduled Control and Surveillance Activates; approved by the Sanitary Service Order on January 18, 2016 no. 16]. *Rospotrebnadzor*. Available at: http://61.rospotrebnadzor.ru/files/prikaz_16_18_01_2016.pdf (August 12, 2023) (in Russian).

of violations was taken as 95 % percentile of distribution of regional relative indicators.

Initial data necessary for assessing likelihood of violation of safety requirements were taken from the state departmental statistical reports, the sanitary report form no. 18 Data on the Sanitary Situation in a RF Region (Section 8 Hygienic Characteristics of Food Raw Materials and Food Products).

Severity of health outcomes for consumers caused by exposure to unsafe products was taken as a combination of health outcomes for a specific consumer due to exposure to unsafe products (starting from near-zero values that meant health outcomes were mild and to those close to 0.95 that meant severe health outcomes) and scales of such adverse health outcomes.

The scale of undesirable consequences was determined by using coefficients that described volumes in which food products were consumed considering regional peculiarities and the consumer goods basket. Close attention was paid to the fact that any standards for levels of potentially unsafe impurities in food products were established considering volumes of their consumption.

Scale coefficients were calculated based on initial data taken from the State Statistical Bulletin Consumption of Basic Food Products by the RF Population[5]. Additionally, some data were taken from the reports of the specialized study entitled Food Products Consumption by Households in 2021[6].

Food products were assigned into one of the following categories as per health risks: objects of extremely high risk, high risk, considerable risk, moderate risk, medium risk, or low risk. The categories were identified according to the criteria fixed in the Provisions on Federal State Sanitary Surveillance.

Basic results. In addition to the existing methodical approaches, the study provides a fundamental scheme describing how to organize the risk-based control of products as an independent control object (Figure 1).

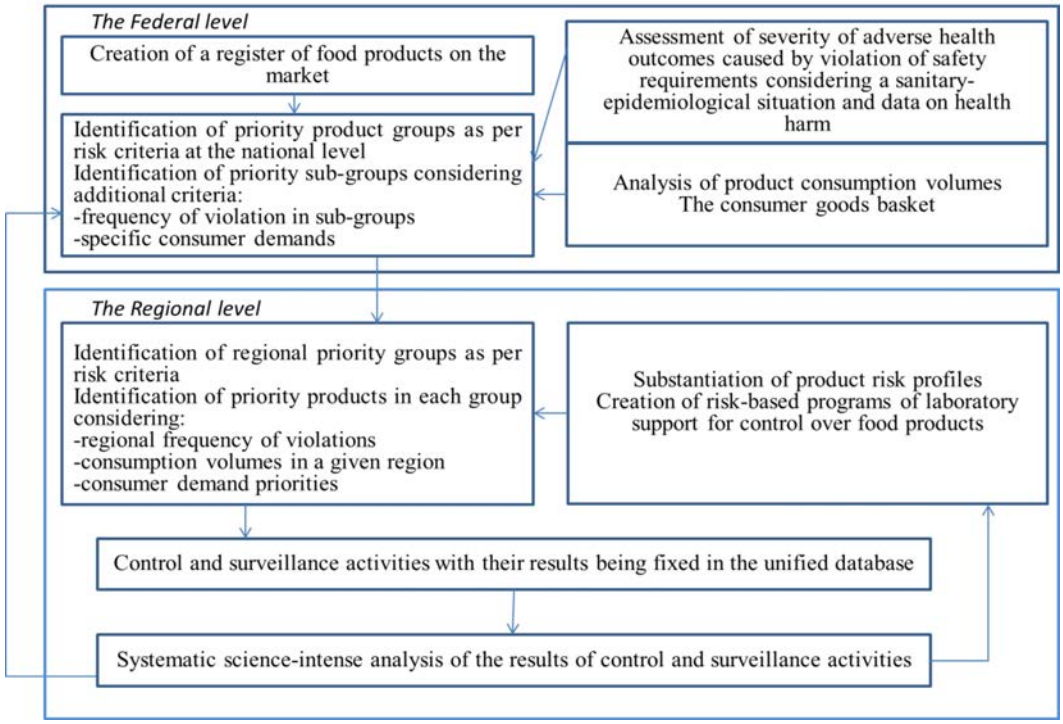


Figure 1. The fundamental scheme showing how to organize the risk-based control of products as an independent control object

[5] Potreblenie osnovnykh produktov pitaniya naseleniem Rossiiskoi Federatsii [Consumption of Basic Food Products by the RF Population]. *Rosstat*. Available at: https://rosstat.gov.ru/compendium/document/13278 (July 19, 2023) (in Russian).

[6] Potreblenie produktov pitaniya v domashnikh khozyaistvakh v 2021 godu po itogam vyborochnogo obsledovaniya byudzhetov domashnikh khozyaistv [Food Products Consumption by Households in 2021 as per the results of sample examination of household budgets]. *Rosstat*. Moscow, 2022, 86 p. (in Russian).

Table 1

Data that may be included into a register of food products as independent objects of sanitary-epidemiological control (surveillance)

No.	Parameter
1	Product code as per CN FEA
2	Product code in accordance with the Russian Classification of Products by Economic Activities
3	Product barcode
4	Product name
5	Code of a region where a product was sampled
6	Manufacturer TIN (in accordance with the Register of Economic Entities (juridical persons/private entrepreneurs, JP/PE) subject to sanitary-epidemiological control (surveillance)
7	Code of a production facility where products have been manufactured in accordance with the Register of Economic Entities subject to sanitary-epidemiological control (surveillance)
8	Identifier of the Certificate on Product State Registration (to connect with the Unified Register of State Registration Certificates)
9	Identifier of assigning a product to 'new product' category (to connect with the Unified Register of New Food Products)
10	Identifier of including a product into the State Register of Food Products, Materials and Articles Permitted to be manufactured on the territory of the Russian Federation or to be imported into the country and distributed on the market
11	Identifier of the State Registration of genetically modified organisms as well as products manufactured with using such organisms or containing them including products imported on the RF territory (https://gmo.rosminzdrav.ru/)
12	Identifier of the State Registration Certificate issued for a specialized food product (to connect with the Unified Register of Specialized Food Products)
13	Identifier of a document(s) stipulating the requirements in accordance to which products have been manufactured (state standards or technical regulations (to connect with the block of regulatory and reference documents (RRD))
14	Essential elements of a document on assessment (confirmation) of conformance (to connect with registers and/or databases containing documents on conformance assessment)
15	Federal risk category (for a product group) (the indicator is connected to the calculation module)
16	Regional risk category (for a product group) (the indicator is connected to the calculation module)
17	Identifiers of regulatory documents stipulating mandatory sanitary-epidemiological requirements to safety and quality of products (to connect with the block of regulatory and reference documents (RRD))
18	Indicators and standards established for this type of products

A complete and continuously updated food products register appears to be the first mandatory component of the suggested model. It should include food products that have mandatory requirements to their safety and quality and are subject to sanitary-epidemiological control (surveillance) as independent objects. This postulate corresponds to the Item 3 in the Provisions on the Federal State Sanitary-Epidemiological Control (Surveillance)[7], which declares that *'Control objects are accounted by the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing … by collecting, analyzing, and keeping data on control objects including information about products (goods) that are subject to the state control (surveillance) performed at the customs border and the customs territory of the Eurasian Economic Union'*. Table 1 provides a tentative structure of such a register.

Figure 2 provides a proposed scheme of a food product register (basic information blocks are colored yellow; Russian classifiers, blue; various registers (register of economic entities, register of state registration certificates, etc.), gray. The main part contains some tables that provide product profiles ('Products' table), product connections with various regulatory

[7] O federal'nom gosudarstvennom sanitarno-epidemiologicheskom kontrole (nadzore): Postanovlenie Pravitel'stva Rossiiskoi Federatsii ot 30 iyunya 2021 goda № 1100 [On the Federal State Sanitary-Epidemiological Control (Surveillance): the RF Government Order on June 30, 2021 no. 1100]. *KODEKS: electronic fund for legal and reference documentation.* Available at: https://docs.cntd.ru/document/607148291 (August 10, 2023) (in Russian).

documents (Sanitary Rules and Norms, EAEU Technical Regulations, Unified Sanitary-Epidemiological and Hygienic Requirements to Products (Goods) subject to Sanitary-Epidemiological Surveillance (Control) in the EAEU Member States[8]), reference documents (the block of regulatory and reference documents), risk levels identified for products, as well as documents regarding product conformance with state standards, technical regulations, and the like, etc. Data are input into the main part considering data exchange with various registers and classifiers by using relevant keys represented by 'P' (primary key) in Figure 2.

The Product Register provides solid basis for filling in results of control and surveillance activities into the unified database. Creation and maintenance of this base will ensure the maximum correct and reliable assessment of how frequently mandatory requirements are violated and identification of certain regularities of these violations, both at the regional and federal levels, including relevant connections with data on manufacturers (sellers) of a product. The latter is extremely important since products are not an independent subject in legal relations and only a juridical person or a private entrepreneur can be held responsible for any violations.

A potential health risk (R^I_{food}) is determined as a combination of likely violations of legal requirements to a certain product, severity of health outcomes due to such violations, and coefficients that describe a scale of undesirable consequences according to the formula 1:

$$R^I_{food} = \sum_i \left(p_i^I \cdot g_i^I \right) \cdot M^I \qquad (1)$$

where p_i^I is likelihood that mandatory safety requirements to food products are violated as per the *i*-th hazard factor during one inspection. Hazard factors include all chemicals, microbial and parasitic agents, radiological indicators, genetically modified organisms, etc., that are covered by control and surveillance activities;

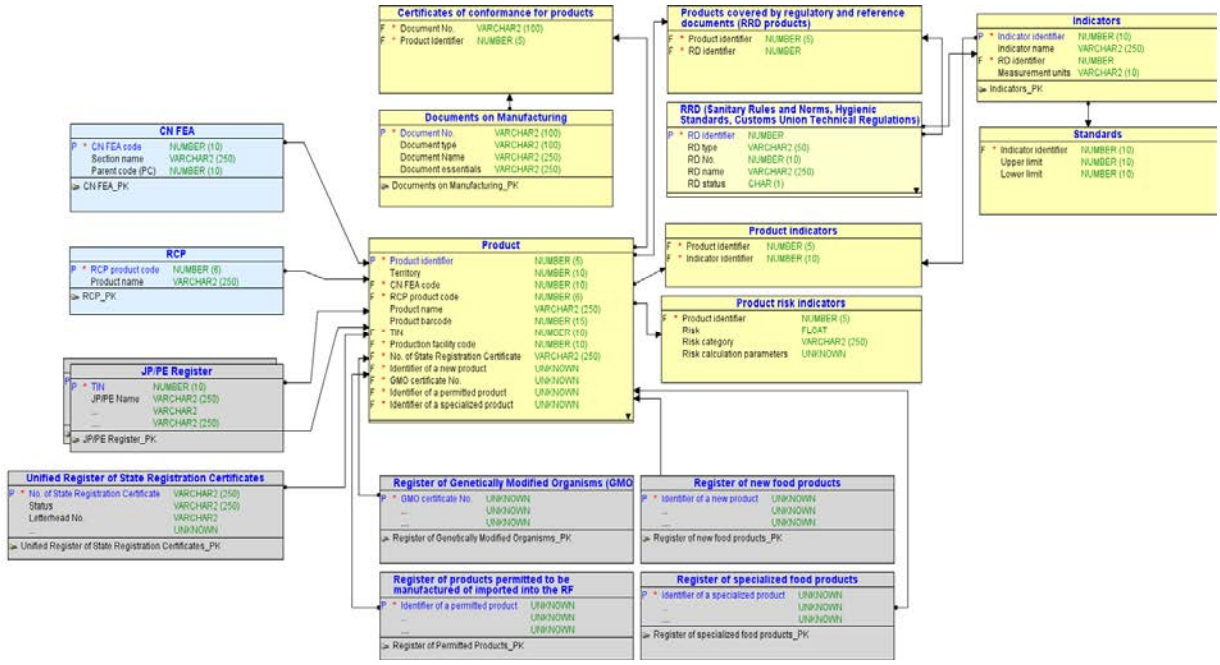


Figure 2. The scheme of the Register of Consumer Food Products in the Russian Federation subject to sanitary-epidemiological control (surveillance)

[8] O primenenii sanitarnykh mer v Evraziiskom ekonomicheskom soyuze: Reshenie Komissii Tamozhennogo soyuza ot 28 maya 2010 g. № 299 [On application of sanitary measures in the Eurasian Economic Union: the Decision of the Customs Union Commission on May 28, 2010 no. 299]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/902227557 (August 10, 2023) (in Russian).

g_i^I is severity of health outcomes due to violation of sanitary-epidemiological requirements to the *i*-th hazard factor of a food product; the value is determined by identifying product hazards and corresponds to the most hazardous (severe) health outcome. Each violation of mandatory requirements is considered to be potentially able to cause relevant adverse health outcomes to a consumer;

M^I is the coefficient that describes a scale of undesirable consequences.

Frequency (likelihood) of violations of mandatory safety requirements to food products as per the *i*-th hazard factor during one inspection (p_i^I) is identified by using statistical reports as a ratio of the number of test results with identified violations to the total number of test results (formula 2):

$$p_i^I = \frac{m_i}{n_i} \quad (2)$$

where m_i is the number of food product samples with values of the *i*-th hazard factor higher than the safety standards per one year;

n_i the total number of tests performed for the i-th hazard factor per one year.

A potential health risk is assessed by using the 95 % percentile of violations as per each analyzed *i*-th factor considering data collected in all RF regions over a 3-year period and recorded in the State Departmental Statistical Form no. 18 Data on the Sanitary Situation in a RF Region (Section 8 Hygienic Characteristics of Food Raw Materials and Food Products).

Severity of health outcomes for a consumer exposed to unsafe products is taken in accordance with the WHO recommendations [13, 14]. For example, severity of rotavirus enteritis is estimated between 0.146 and 0.236 (the mean value is 0.188); *E. Coli*-caused infections, between 0.236 and 0.347 (0.270); salmonellosis, between 0.229 and 0.415 (0.355) etc.

Severity of health outcomes might be adjusted to fit into the Russian risk-based surveillance model considering registered cases of health harm with solid evidence of their association with violations of safety requirements to products [15]. Assessment and evidence-based substantiation of health harm caused by exposure to hazard factors in products, considering its severity, is a relevant trend in hygienic studies and a guarantee that health risks are analyzed adequately.

The coefficient that describes regional consumption of food products *(M)* is determined as the ratio of the actual regional annual consumption of a given product per one person to the physiologically substantiated recommended annual consumption of the same product (the optimal value is consumption that was considered when hygienic safety standards were developed for this product) per one person (formula 3):

$$M = \frac{V}{V_{RF}} \cdot k \quad (3)$$

where V is the actual annual regional consumption of a food product per one person (tons/year, liters/year, items/year and the like);

V_{RF} is the annual consumption of a food product per one person at the country level (tons/year, liters/year, items/year and the like).

k is the multiplying coefficient for food products included into the consumer product basket, k = 10. k = 1 for other types of food products.

At the country level, risk assessment allows establishing the federal priorities and identifying large groups of food products with typically the highest health risks. Such products are subject to stricter control performed in RF regions. Thus, the federal priority groups are milk products, meat products, fish products, and food provided by catering organizations (Table 2).

It is noteworthy that a positive trend has been identified for these product groups since frequency of the detected violations has been declining. Thus, the 95 % percentile of the detected violations was 0.061 for milk and milk products over 2010–2020 at the country level (that is, violations were identified in 6.1 % of the analyzed samples). Over 2020–2022, its value went down to 0.053 (5.3 %). Frequency of violations detected in fish and fish products went down from 0.086 to 0.065 in the same

Table 2

Categories of food product groups considering 2020–2022 data at the national level: a fragment

Food product group (branch classification of the Sanitary Service)	*p*	*g*	*R*	Risk level for scheduled control activities
Meat and meat products*	**0.052**	**0.198**	1.03E-01	Extremely high
Imported meat and meat products	0.071	0.198	1.41E-02	High
Poultry and related products, eggs included	**0.059**	**0.45**	2.66E-01	Extremely high
Imported poultry and related products	0.183	0.45	8.24E-02	High
Milk and milk products	**0.053**	**0.35**	1.86E-01	Extremely high
Imported milk and milk products	0.07	0.35	2.45E-02	High
Fish, fish products, other aquatic organisms	**0.065**	**0.245**	1.59E-01	Extremely high
Imported fish, fish products, and other aquatic organisms	0.086	0.245	2.11E-02	High
Pre-prepared food	0.042	0.18	7.56E-03	Considerable
Non-traditional pre-prepared food	0.333	0.065	2.16E-02	High
Food provided by catering organizations	0.044	0.27	1.19E-01	Extremely high
Flour-based products and cereals	0.026	0.115	2.99E-02	High
Bread and bakery	0.035	0.003	1.05E-03	Considerable
Sugar	0.026	0.002	5.20E-05	Moderate
Fruit and vegetables	0.021	0.152	3.19E-03	Considerable
Non-alcoholic drinks	0.077	0.023	1.77E-03	Considerable
Grain and grain-based foods	0.0001	0.001	1.00E-07	Low
Mineral water	0.057	0.015	8.55E-04	Medium
Salt	0.025	0.001	6.10E-05	Moderate

Note: * products included into the consumer product basket are given in bold (k = 10).

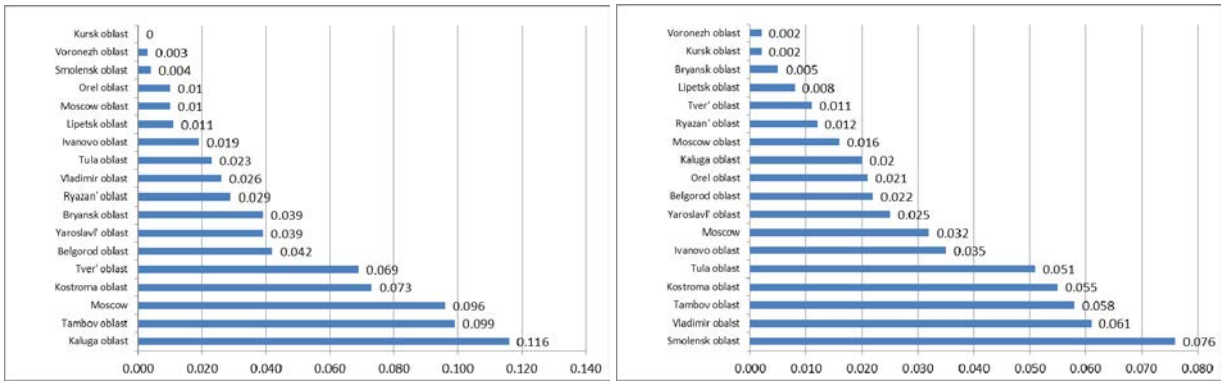
periods. Obviously, the systemic state control motivates manufacturers, distributors, and sellers to comply with the law, to be responsible and conscientious. The latter leads to a decline in frequency of detected violations and ensures quality and safety of food products in the country in general.

Food products established as an independent control object are assigned into specific risk categories according to the Provisions on the Sanitary-Epidemiological Surveillance approved by the Decision of the RF Chief Sanitary Inspector (item 22b). At the same time, it is worth noting that considering regional peculiarities of food product consumption might become an important trend in the development of the risk-based control model. Indicators included into product risk assessment differ considerably from region to region.

Figure 3 provides only two examples of differences in frequency of detected violations. Thus, in the Central Federal District, frequency of meat samples deviating from the hygienic standards varied between 0.0 (0 %) (the Kursk oblast) and 0.116 (11.6 %) (the Kaluga oblast) in 2022; that is, solely this indicator that described frequency of violations was able to multiply health risk levels. The indicator that described frequency of violations for the 'milk and milk products' group also varied considerably, though to a lesser extent.

Frequency of violations of safety requirements to meat products as per sanitary-chemical indicators varied between 0.0 and 0.096 in different RF regions; milk and milk products, between 0 and 0.091; fish and fish products, between 0 and 0.256 (the latter were identified for a rather small sample).

Therefore, history and results of regional control can make substantial corrections into definition of the most important component in health risk, namely, likelihood of an undesirable event (violation of requirements to product safety and, consequently, an adverse health outcome caused by this violation).



a) meat and meat products b) milk and milk products

Figure 3. Frequency of violated requirements to microbiological safety of food products in regions included into the Central Federal District, 2022 (cases of identified unconformity with the standards per 1 analyzed sample)

Volumes of food consumption as a tool to describe a risk scale differ considerably in different regions and depend on a climatic zone, national or religious traditions, availability of certain food products and the like.

Thus, in 2022, meat consumption in the country varied between 62.1 (Chuvashia) and 144.6 kg/person, that is, almost two-fold. Consumption of fish and fish products differed even more drastically and varied between 6.7 kg/person in Tyva and 44.1 kg/person in the Nenets Autonomous Area. Consumption of fruit and berries varied between 39.4 and 125.9 kg/person; vegetables and melons, between 50.4 and 150.2 kg/person; etc.

In addition to the data taken from the State Statistical Bulletin 'Consumption of Basic Food Products by the RF Population[9], it seems advisable to consider materials derived from the reports of the specialized study entitled Food Products Consumption by Households[10]. The latter provides data on a substantially higher range of food products consumed by Russians.

Table 3 compares the results of identifying categories for certain food product groups in the Kaliningrad oblast and Buryatiya.

Risks in these regions were calculated considering the history of inspections in them over the last three years and regional peculiarities of food consumption. The results derived by risk assessment indicate that 10 out of 15 food product groups in Table 3 create extremely high risks and are subject to annual control in Buryatia whereas only 7 such groups are identified in the Kaliningrad oblast.

The analysis indicates that each region should create regional lists of food products with identified risk categories considering specific regional food consumption and the history of regional inspections. Any control (surveillance) activities should be scheduled based on these lists.

The development of the risk-based control model should rely on science-intense systemic analysis of the results of control and surveillance activates. This involves considering not only results obtained by evaluating risks of certain large product groups but also data on their manufacturers and sellers as well as specific consumer demands. Such analysis ensures better targeted and more precise selection of control objects and aims to identify priority groups among all marketed products. A group can be considered a priority if:

- it is in the highest demand by consumers;
- violations are detected most frequently in products from it;
- it is typical for certain manufacturers.

[9] Potreblenie osnovnykh produktov pitaniya naseleniem Rossiiskoi Federatsii [Consumption of Basic Food Products by the RF Population]. *Rosstat*. Available at: https://rosstat.gov.ru/compendium/document/13278 (July 19, 2023) (in Russian).

[10] Potreblenie produktov pitaniya v domashnikh khozyaistvakh v 2021 godu po itogam vyborochnogo obsledovaniya byudzhetov domashnikh khozyaistv [Food Products Consumption by Households in 2021 as per the results of sample examination of household budgets]. *Rosstat*. Moscow, 2022, 86 p. (in Russian).

Table 3

Comparison of risk levels and categories established for certain food product groups in two different RF regions

Food product	Kaliningrad oblast		Buryatiya	
	R	Risk category	*R*	Risk category
Meat and meat products	9.7E-02	High	1.8E-01	Extremely high
Imported meat and meat products	5.2E-03	Considerable	3.9E-02	High
Poultry, eggs and products made of them	1.6E-01	Extremely high	3.8E-01	Extremely high
Milk and milk products	7.9E-01	Extremely high	1.9E+00	Extremely high
Fats and butter	1.7E-02	High	1.2E-01	Extremely high
Fish, other aquatic organisms and products made of them	3.0E-01	Extremely high	4.0E-01	Extremely high
Imported fish, other aquatic organisms and products made of them	1.8E-02	High	2.2E-01	Extremely high
Pre-prepared foods	2.7E-02	High	4.7E-02	High
Non-traditional pre-prepared foods	8.8E-01	Extremely high	4.1E-01	Extremely high
Food provided by catering organizations	1.6E-01	Extremely high	2.4E-01	Extremely high
Flour-based products and cereals	8.7E-04	Medium	6.7E-03	Considerable
Bread and bakery	9.9E-04	Mediaum	8.0E-03	Considerable
Fruits	1.27E-01	Extremely high	4.22E-01	Extremely high
Imported fruits	2.24E-02	High	1.21E-02	High
Vegetables	4.58E-02	Extremely high	1.22E-01	Extremely high

Thus, for example, the analysis of sales on the Russia market performed for the 'milk and milk products' group has revealed that pasteurized milk is in the highest demand by buyers, 28.0 % (as per sales volumes). It is followed by butter and margarine, 17.7 %; sour cream, 14.1 %; curds, 12.1 %; kefir, 9.4 %; sterilized milk, 9.4 %; cream, 3.4 %; other products, 4.0 % [16]. Correspondingly, it seems logical to create a plan for product tests during control and surveillance activities considering levels of demand for a certain product.

History of inspections as per each type of products is another significant criterion eligible for selecting food products for control. The results of laboratory tests of milk products obtained during control and surveillance activities in the Perm oblast over the recent years have established that violations (considering both product safety and quality) are identified most frequently in samples of butter, ice-cream, pasteurized and crude milk. They are identified least frequently in samples of melted cheese, creams, and drinking yogurts. These results can be extremely important for substantiating a selection of a specific product for laboratory tests.

The most significant trend in the developed of the risk-based model is associated with developing approaches that would consider the entire range of criteria when selecting a specific product within a control inspection including a brand and/or manufacturer thereby making this control inspection as targeted as only possible.

The model development also involves optimization of the system for laboratory tests of food products. This trend in research is extremely relevant since results obtained by instrumental examinations are the most informative for product risk assessment. They allow achieving maximum possible objectivity of inspection results [17, 18]. We should bear in mind, though, that only limited resources are usually allocated on laboratory tests within a specific control and surveillance activity. Therefore, tests cannot always cover the entire range of indicators that describe a safety of an object under surveillance [19]. Given that, it is necessary to select those indicators that would be examined with acceptable costs but provide the most informative and reliable support for control activities aimed at revealing unconformity with mandatory requirements. A product risk profile corresponds to these demands since it is usually a typical structure combining frequency of violations of mandatory safety

requirements to specific product parameters and severity of health outcomes due to these violations. Approaches to creating product risk profiles have already been described in several studies; however, they undoubtedly deserve being examined in depth and some methodical development including consideration of new data on products[11] [20]. In general, creating a risk profile can be considered a tool for raising validity and effectiveness of instrumental examinations.

Discussion. Development of the risk-based model for control over food products on the consumer market in the RF fully corresponds to the requirements associated with the contemporary stage in the development of public regulation in the country. Administrative pressure on economic entities ought to be easier but the best possible protection of citizens' life and health as the major country resource should be provided.

Control and surveillance activities (inspections) are the key element in ensuring these requirements are satisfied. They play the most significant role in providing product safety and quality. Inspections should be as targeted as only possible and draw attention of regulatory authorities to the 'most risky' products thereby ensuring removal of unsafe products from the market. Moreover, constant attention a regulatory authority pays to products safety requirements to which are violated most frequently is a strong warning for economic entities and a preventive measure that motivates them to comply with the law. More frequent inspections of the most risky products together with less frequent examinations of indicators that are scarcely informative should ultimately make the consumer market in the country safer for consumers without any growth in total costs spent on instrumental support of control inspections.

Optimization of control over food products is considered important worldwide. Different countries propose their own approaches to how to improve the process. 'Wise recommendations' are proposed on how to give up low-informative tests and examinations [7, 21]. Methodical approaches are being tested with the aim to perform precise expert selection of the most significant hazard factors in certain products in order to control them stricter. Thus, Canadian researchers performed expert estimates in their study; as a result, from the 155 risk factors of food products initially identified, 17 consolidated factors were selected as priority ones and will be considered for the development of the risk assessment model [22]. At the same time, approaches, which are based on objective data and science-intense analysis, seem to be preferable to subjective expert estimates since they ensure systemacy, transparency, and continuity of analytical conclusions.

Conclusion. The contemporary stage of the public regulation as regards providing food products safety calls for relevant development of the risk-based control model. The primary task is to create and maintain a unified and updated database on safety and quality of food products. This database should integrate the results of all the control and surveillance activities including data obtained by laboratory tests of products bound to manufacturers, distributors, and sellers [23]. At present, absence of the complete digital information basis imposes serious limitations on creating product risk profiles. Another limiting factor is incomplete registration of cases when consumers suffer health harm caused by unsafe food products.

The Unified Information System of the RF Sanitary Service, which aims to create a unified information spaces, is being formed at the moment. Experts are going to be given an opportunity to work with relevant data arrays in the nearest future. In-depth analysis is going to require new methodical approaches able to provide uniform and correct:

- substantiation of regional priorities for planning control of food products;

[11] Zaitseva N.V., Alekseev V.B., May I.V., Kleyn S.V., Nikiforova N.V., Chigvintsev V.M., Balashov S.Yu., Sitchikhina L.A. Profil' riska moloka i molochnoi produktsii: baza dannykh [Risk profile of milk and milk products: database], Certificate of Database Registration: 2021620463, March 11, 2021, application no. 2021620323 dated March 01, 2021 (in Russian).

- creation of risk profiles for food products;
- substantiation of optimal volumes and structure of laboratory tests within control of food products as an independent control object.

It is also quite relevant to include algorithms and mathematical methods of these methodical approaches into software modules of the Rospotrebnadzor's Unified Information System. This can be considered a way to develop the model for rick-based sanitary-epidemiological control (surveillance) of food products marketed in Russia.

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Research article

SOME PROPOSALS ON REGULATION OF HIGHLY HAZARDOUS CHEMICALS IN ARTICLES

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When developing safety regulations for chemicals, the international society is constantly searching for safer analogues of highly hazardous chemicals to use as alternatives in various products. Within the Scientific Research Work under the State Program 'Provision of Chemical and Biological Safety in 2021–2024', The Russian Register of Potentially Hazardous Chemical and Biological Substances of the Federal Scientific Center of Hygiene named after F.F. Erisman of Rospotrebnadzor has developed a concept on replacement of highly hazardous chemicals in various products (food products, synthetic detergents and household chemicals, pesticides, paints and varnishes, basic chemicals) with their safer analogues. Still, we should highlight that regulation of highly hazardous chemicals in articles has not been developed sufficiently in the RF. Therefore, the purpose of the study was to provide scientific substantiation for criteria and rules for assigning chemicals in articles as prohibited and (or) restricted.

Materials this study is based on are represented by the regulatory legal acts of the Russian Federation, EEC and the EU (in particular, Decrees, Resolutions, Technical Regulations, Directives, Regulations, etc. in the field of safe management of substances of concern), as well as domestic and international databases, scientific articles and monographs containing information on the toxic properties of chemicals.

In order to develop effective measures to minimize the risk of exposure to chemicals in articles and their safe management at all stages of a life cycle, the study provides substantiation of criteria and rules for assigning chemicals in articles as prohibited and (or) restricted and proposes a mechanism for the creation of a National list of chemicals of concern in articles. When created, this List will allow monitoring of their circulation on the territory of the Russian Federation, proper waste disposal, and stimulating research work to find alternatives.

Keywords: *chemical safety, regulation, highly hazardous chemicals, articles, materials, prohibition, restriction, analogues.*

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Searching for alternatives and substituting highly hazardous chemicals in articles with their safer analogues is a key trend in international regulation of chemicals safety[1]. In the Russian Federation, the Eurasian Economic Commission (EEC) Decision dated 21 April 2015 no. 30 'On Non-Tariff Regulation' regulates circulation of ozone depleting substances and articles containing them, hazardous wastes, crop protection chemicals and other persistent organic pollutants covered by Annexes A and B of the Stockholm Convention, narcotics, psychotropic drugs and their precursors. Apart from the aforementioned conventional chemicals regulated by the EEC documents, the Russian Federation lacks legally established mechanisms for identifying, prohibiting or restricting production and consumption of highly hazardous chemicals.

Within the Scientific Research Work under the State Program 'Provision of Chemical and Biological Safety in 2021–2024', the Russian Register of Potentially Hazardous Chemical and Biological Substances of the Federal Scientific Center of Hygiene named after F.F. Erisman of Rospotrebnadzor has developed a concept on replacement of highly hazardous chemicals in various products (food products, synthetic detergents and household chemicals, pesticides, paints and varnishes, basic chemicals) with their safer analogues. Scientific substantiation has been provided for a National List of chemicals of concern, 1480 compounds overall; 630 of them are mutagens, 320 are carcinogens, 271 are toxic for reproduction[2], 502 are endocrine disruptors[3]. Criteria have been developed to classify substances as candidates for prohibition and (or) restriction and proposals have been formulated on relevant amendments into the methodological and regulatory framework on chemical safety of the Russian Federation [1–7].

At the same time, it cannot be stated that enough attention has been paid in the RF to such important issues as regulation of highly hazardous chemicals in articles including their prohibition and (or) restriction; monitoring of such chemicals at all the stages in the article lifecycle (from raw materials to production and consumer wastes); proper waste classification and utilization considering their hazardous properties; searching for alternatives to substitute highly hazardous chemicals with their safer analogues [8, 9].

The aim of the study was to provide scientific substantiation for criteria and rules for assigning chemicals in articles as prohibited and (or) restricted.

Material and methods. Materials this study is based on are represented by the regulatory legal acts of the Russian Federation, EEC and the EU (in particular, Decrees, Resolutions, Technical Regulations, Directives, Regulations, etc. in the field of safe management of substances of concern), as well as domestic and international databases, scientific

[1] Ob Osnovakh gosudarstvennoi politiki Rossiiskoi Federatsii v oblasti obespecheniya khimicheskoi i biologicheskoi bezopasnosti na period do 2025 goda i dal'neishuyu perspektivu: Ukaz Prezidenta RF ot 11.03.2019 № 97 [On the basics of the RF state policy in the sphere of providing chemical and biological safety for the period up to 2025 and beyond: The RF President Order dated March 11, 2019 no. 97]. *Prezident Rossii: official Internet portal*. Available at: http://www.kremlin.ru/acts/bank/44066 (July 01, 2023) (in Russian); Chemicals in products. *SAICM: Knowledge Platform of the Strategic Approach to International Chemicals Management*, 2022. Available at: https://saicmknowledge.org (July 03, 2023); Synthesis Report: OECD Workshop on Approaches to Support Substitution and Alternatives Assessment. Series on Risk Management no. 51. *OECD*, 2019. Available at: https://images.chemycal.com/Media/Files/env-jm-mono(2019)3_synth.pdf (July 03, 2023).

[2] MR 1.2.0321-23. Otsenka i klassifikatsiya opasnosti reproduktivnykh toksikantov: Metodicheskie rekomendatsii, utv. rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii A.Yu. Popovoi 4 aprelya 2023 g. [Assessment and classification of substances toxic for reproduction: Methodical guidelines, approved by A.Yu. Popova, Head of the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing, the RF Chief Sanitary Inspector, on April 4, 2023]. Moscow, the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2023, 32 p. (in Russian).

[3] MR 1.2.0313-22. Otsenka i klassifikatsiya opasnosti endokrinnykh razrushitelei: Metodicheskie rekomendatsii, utv. rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii A.Yu. Popovoi 30 dekabrya 2022 g. [Assessment and classification of endocrine disruptors: Methodical guidelines, approved by A.Yu. Popova, Head of the Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing, the RF Chief Sanitary Inspector, on December 30, 2022]. Moscow, the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2022, 86 p. (in Russian).

articles and monographs containing information on the toxic properties of chemicals.

Results and discussion. According to the State Standard GOST 32419-2022 Chemical Hazard Classification. General Requirements[4], articles are ready items that have passed through all the technological stages in production, during which they have been given a specific shape, surface, or design that determine their functional purpose to a greater extent than their chemical composition; such items are ready for private use or use in other production in a form they have been produced by their manufacturer. In Russia, requirements to safety of chemical products, including classification of their hazards and elements of information system (labeling and safety data sheet) are established by the Technical Regulations of the Eurasian Economic Union 'On the Safety of Chemical Products' (TR EAEU 041/2017, has not come into force yet)[5] and the National Technical Regulations 'On the Safety of Chemical Products' (draft). In contrast to chemical products, articles are not regulated by the foregoing regulations. Meanwhile, many articles contain highly hazardous chemicals that can pose serious threats for human health and the environment both in short- and long-term prospect. It is noteworthy that information about such chemicals is not usually provided on labels and (or) in supporting documents and this creates certain difficulty in, for example, monitoring over circulation of highly hazardous chemicals as well as hazard classification and proper utilization of consumer waste.

In the Russian Federation, the following Technical Regulations (TR) establish safety requirements for different articles:

– TR CU 003/2011 On safety of railroad Infrastructure;

– TR CU 005/2011 On safety of package;

– TR CU 007/2011 On safety of products for children and adolescents;

– TR CU 008/2011 On safety of toys;

– TR CU 010/2011 On safety of machinery and equipment;

– TR CU 014/2011 Motorways safety;

– TR CU 017/2011 On safety of light industry products;

– TR CU 018/2011 On safety of wheeled vehicles;

– TR CU 019/2011 On safety of personal protection equipment;

– TR CU 025/2012 On safety of furniture;

– TR CU 026/2012 On safety of small vessels;

– TR CU 031/2012 On safety of agricultural and forestry tractors and trailers for them;

– TR CU 032/2013 On safety of equipment operating under excessive pressure;

– TR CU 035/2014 Technical Regulations for tobacco products;

– TR EAEU 037/2016 On restricting the use of hazardous chemicals in electric and electronic items;

– TR EAEU 038/2016 On safety of attractions;

– TR EAEU 050/2021 On safety of produces used in civil defense and protection against natural or technogenic emergencies;

– TR EAEU 052/2021 On safety of metro rolling stock.

The task was to substantiate criteria and rules for assigning chemicals in articles as prohibited and (or) restricted. To do that, the foregoing regulations were analyzed considering an article's name, a type of a material it was made of (polymer, glass, ceramics, metal, alloy, etc.), controlled chemicals, safety requirements to articles including prohibitions and restrictions,

[4] GOST 32419-2022. Klassifikatsiya opasnosti khimicheskoi produktsii. Obshchie trebovaniya, vved. v deistvie 01.01.2023 [Chemical Hazard Classification. General Requirements, introduced on January 01, 2023]. Moscow, Russian Standardization Institute, 2022, 40 p. (in Russian).

[5] TR EAEU 041/2017. O bezopasnosti khimicheskoi produktsii: Tekhnicheskii reglament Evraziiskogo ekonomicheskogo soyuza, prinyat Resheniem Soveta Evraziiskoi ekonomicheskoi komissii ot 3 marta 2017 goda № 19 (ne vstupil v silu) [On the Safety of Chemical Products: the Technical Regulations of the Eurasian Economic Union, approved by the Decision of the Council of the Eurasian Economic Commission on March 3, 2017 no. 19 (has not come into force yet)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/456065181 (July 04, 2023) (in Russian).

levels of chemicals migration into various media (air, water, a model environment, etc.).

One hundred and twenty-four chemicals were identified after requirements to chemical safety were analyzed. These chemicals are regulated by Technical Regulations of the Customs Union (TR CU) in light industry articles, articles for children and adolescents, toys, furniture, tobacco articles, personal protection equipment as well as in electric and electronic articles. Fifty of them (40.3 %) are volatile organic compounds (VOCs); 33 (26.6 %) are heavy metals and their salts. Chemicals that are subject to the strictest regulation include formaldehyde (213 indicators in TR CU), acetaldehyde (116), methanol (96), phenols (77), acetone (64), lead and its compounds (58), butanol (55), toluene (50), zinc and its compounds (45), and mercury and its compounds (37). Chemicals in articles regulated by TR CU (the first 10 positions) are given in Table 1 together with a type and category of hazards they pose according to the GHS (Globally Harmonized System of Classification and Labelling of Chemicals).

The analysis of the TR CU requirements revealed that the main criteria for chemicals in articles hazardous for human health include such indicators as mutagenic and carcinogenic effects, toxicity for reproduction, effects on the endocrine system, as well as some additional hazards including acute toxicity by inhalation or skin contact (hazard category 1 and 2), irritation of the respiratory tract, narcotic effect; impacts on target organs and (or) systems under single and (or) multiple (long-term) contacts with a chemical, respiratory and (or) skin sensitization, skin and eye damage (hazard category 1). At the same time, it is not advisable to take into account such type of hazards as acute toxicity caused by swallowing or aspiration in the case of articles due to the impossibility and (or) low probability of the process.

Figure 1 shows distribution of hazardous properties of chemicals in articles regulated by TR CU.

Table 1

Chemicals in articles regulated by TR CU (the first 10 positions)

CAS name	Number of indication in TR CU	Hazard category				Additional hazard
		M	C	R	E	
Formaldehyde 50-00-0	213	2	1A	1	2	skin (category 1B) and eye (category 1) burns, skin sensitization (category 1), after repeated / long-term inhalation exposure: the respiratory system (category 1)
Acetaldehyde 75-07-0	116	-	2	-	3	respiratory tract irritation (category 3), narcotic effect (category 3)
Methanol 67-56-1	96	-	-	2	2	under single exposure: the central nervous system, eyes (category 1)
Phenol 108-95-2	77	2	-	1	-	skin (category 1B) and eye (category 1) burns, after repeated / long-term inhalation exposure: the nervous and respiratory systems (category 2)
Acetone 67-64-1	64	-	-	2	-	respiratory tract irritation (category 3), narcotic effect (category 3)
Lead* 7439-92-1	58	-	2	1A	-	after repeated / long-term exposure: the hematopoietic and nervous systems, kidneys (category 1)
Butanol 71-36-3	55	-	-	-	-	respiratory tract irritation (category 3), narcotic effect (category 3)
Toluene 108-88-3	50	-	-	1B	2	aspiration hazard (category 1); after repeated / long-term inhalation exposure: the nervous system (category 2)
Zinc* 7440-66-6	45	-	-	-	-	eye damage (category 1), after repeated / long-term exposure: the respiratory and hematopoietic system (category 1)
Mercury* 7439-97-6	37	-	-	1	-	acute inhalation toxicity (category 1), after repeated / long-term inhalation exposure: the nervous system (category 1)

Note: *This position includes both a metal and its ion forms and classification can be different for each specific case; M is mutagen; C is carcinogen; R is toxic for reproduction; E is endocrine disruptor; hazard categories are given in accordance with the GHS classification.

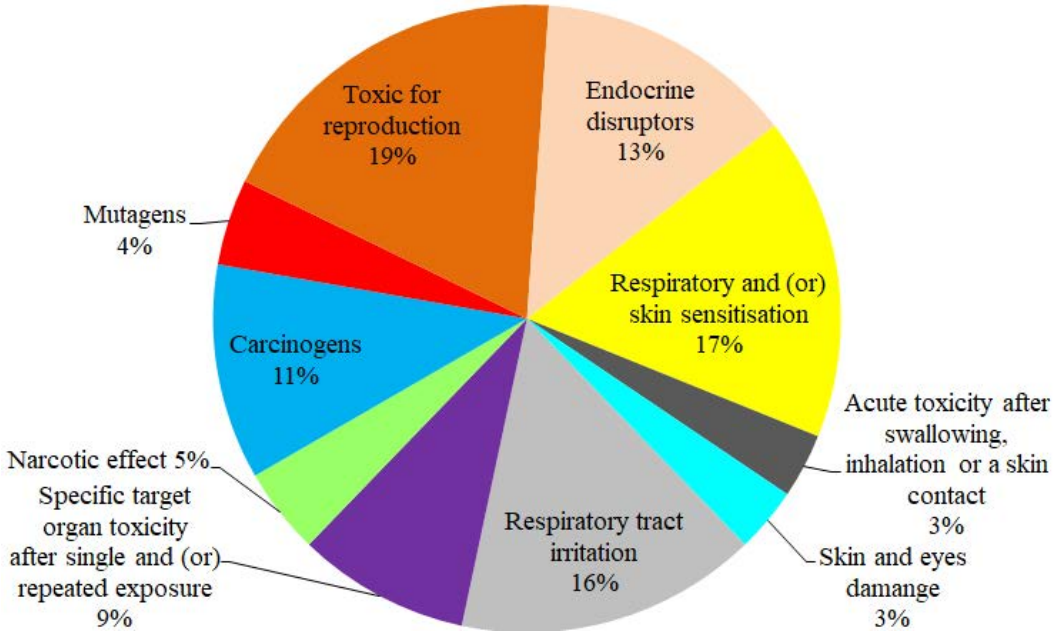

Figure 1. Distribution of hazardous properties of chemicals in articles regulated by TR CU

Major hazards posed by chemicals in articles are reproductive and developmental toxicity (19 % of the chemicals regulated by TR CU are toxic for reproduction, categories 1 and 2 according to the GHS), respiratory and (or) skin sensitization (17 %), irritation of the respiratory tract (16 %), and effects on the endocrine system (13 %).

Since approximately 40 % of the chemicals in articles regulated by TR CU are VOCs and are represented by, for example, monomers of polymers (vinyl acetate, methyl methacrylate, formaldehyde, chloroprene and others) or solvents (toluene, hexane, heptane, and others), it is possible to assume that VOCs levels in articles are going to decline over time of use and, consequently, hazards posed by them will also decrease. Irritation of the respiratory tract, respiratory and (or) skin sensitization, and narcotic effect are intrinsic mostly to VOCs; consequently, in long-term prospect, the greatest hazards will be posed by chemicals in articles that do not belong to VOCs and are able to produce some specific and delayed effects, including mutagenic and carcinogenic ones, reproductive toxicity, and effects on the endocrine system. Among such chemicals, it can be mentioned, for example, heavy metals and their organic compounds able to modify some properties of materials applied to manufacture articles (photoinitiators, stabilizers, flame retardants, hardeners, accelerants, preservatives, and others). It is noteworthy that for chemical products released into circulation on the territory of the Russian Federation, the legislation requires the preparation of a safety data sheet containing information about the hazardous components of the product, as well as the classification and labeling of hazards. This allows monitoring hazardous chemicals in products at any stage in the lifecycle (from raw materials to production and consumer waste) and provides safety when dealing with them. However, when it comes down to articles, such data is not provided and this creates serious difficulties not only for proper waste disposal including possible recycling and reuse but also for studies with their focus on searching for alternatives to substitute highly hazardous chemicals in articles with their safer analogues.

At present, the list of chemicals in articles regulated by TR CU includes, in addition to VOCs and heavy metals, a few other substances used as additives to polymer materials. They include antioxidants, such vulcanization accelerants as thiazole and thiuram, tin and its compounds, polybrominated diphenyls, and diphenyl ethers. Still, a wide range of highly hazardous chemicals is practically not regulated in the RF at all and this is contrary to in-

ternational trends as regards regulation of their safety.

For example, the European list of substances in articles of very high concern for human health and the environment (so called Candidate List)[6] currently consists of 235 positions including:

– category 1A or 1B carcinogens according to the GHS;

– category 1A or 1B mutagens according to the GHS;

– category 1A or 1B reproductive toxicants according to the GHS;

– persistent, bioaccumulative and toxic substances (PBT);

– very persistent and very bioaccumulative (vPvB);

– endocrine disruptors;

– respiratory sensitizers;

– chemicals with specific target organ toxicity after repeated exposure;

– other chemicals, for which scientific evidence is provided confirming likelihood of considerable health outcomes or effects on the environment comparable with those listed above (Article 57, REACH).

Since the chemicals from the Candidate List are considered those that might be prohibited and (or) restricted in the nearest future, a chemical having one or several of the enlisted hazard types is the necessary, but not sufficient, condition for it to be included into the Candidate List. It is also important to study a possibility whether this component could be substituted in an article with its safer alternative considering technical feasibility and assessment of involved socio-economic risks.

All the companies operating in the EU countries that produce, import, or deliver goods (articles) onto the EU market containing chemicals from the Candidate List, that is chemicals of very high concern, in quantity exceeding 0.1 % as per an article mass, are obliged to provide information about such goods (articles) in specific notifications submitted to the European Chemicals Agency (ECHA). This makes it possible to monitor hazardous chemicals at all the stages in the article life cycle.

The Substances of Concern In Product as such or in complex objects (Articles) database (SCIP)[7] was created by the European Chemicals Agency in 2021. It contains data on hazardous chemicals in articles and goods distributed on the European Union market. Analysis of this database revealed chemicals that were the most frequent to be detected in articles and goods. They include lead and its compounds, boron and its compounds, ethylene thiourea, bisphenol A, siloxanes, chlorinated paraffins C_{14}-C_{17}, chromium (VI) compounds, phthalates, and ethoxylated nonylphenols (Table 2 and Figure 2). Table 2 provides the first 25 positions as per the number of notifications submitted by companies between 01 January 2021 and 01 August 2023 as well as the reason why a chemical in an article is considered of concern, the exact number of notifications, and a range of use. As for the latter, the leading place in the Candidate List belongs to additives to polymers (photoinitiators, stabilizers, and flame retardants). It is noteworthy that the European Candidate List does not include any VOCs and the emphasis is on hazards posed by chemicals in articles in the long term.

The European approach to creating groups of articles that cause concern for human health and the environment allows identifying several categories: articles made of ceramics; glass; metal; leather; paper and board; plastic and polymers; rubber and elastomers; stone, plaster, and cement; fiber include textile; wood; others (mixed materials). The chemicals included in the Candidate List are most frequently identified in articles made of metal (39 % of the submitted notifications), mixed materials (21 %), glass (11 %), rubber and elastomers (10 %), plastic and polymers (9 %) (Figure 3).

[6] Candidate List of substances of very high concern for Authorization. *ECHA: European Chemicals Agency*. Available at: https://echa.europa.eu/candidate-list-table (July 03, 2023).

[7] SCIP Database. *ECHA: European Chemicals Agency.* Available at: https://echa.europa.eu/scip-database (July 03, 2023).

Table 2

Chemicals in articles notified within the SCIP 2021–2023 (the first 25 positions)

No.	Name	CAS No.	The reason for inclusion into the Candidate List	Number of notifications*	Range of use
1.	Lead and its compounds	7439-92-1 and others	Toxic for reproduction	9852535	Electric and electronic equipment, vehicles, batteries and accumulators
2.	Boron and its compounds	7440-42-8 and others	Toxic for reproduction	1716812	Articles made of stone, plaster, cement, glass, ceramics, plastic, leather, textiles, electric and electronic equipment, construction materials
3.	Imidazolidine-2-thione (ethylene thiourea)	96-45-7	Toxic for reproduction	1228390	Accelerator of neoprene rubber vulcanization
4.	4,4'-Isopropylidenediphenol (bisphenol A)	80-05-7	Toxic for reproduction, endocrine disruptor	1102646	Manufacture of plastic, polycarbonate plastic, epoxy resins; electric and electronic equipment, thermal paper
5.	Decamethylcyclopentasiloxane	541-02-6	PBT; vPvB	1085887	Used in manufacture of plastic articles and rubber articles
6.	Octamethylcyclotetrasiloxane	556-67-2	PBT; vPvB	1073677	Used in manufacture of plastic articles and rubber articles
7.	2-Methyl-1-(4-methylthiophenyl)-2-morpholinopropan-1-one	71868-10-5	Toxic for reproduction	852311	Photoinitiator of polymerization
8.	Tris (nonylphenyl) phosphite	26523-78-4, 3050-88-2, 31631-13-7, 106599-06-8 and others	Endocrine disruptor	822419	Plastic and rubber manufacture; food contact packaging
9.	1,6,7,8,9,14,15,16,17,17,18,18-Dodecachloropentacyclo [12.2.1.16,9.02,13.05,10] octadeca-7,15-dien ("Dechlorane plus"™)	13560-89-9	vPvB	764317	Flame retardants for thermoplastic materials
10.	2-Benzyl-2-dimethylamino-4'-morpholinobutyrophenone	119313-12-1	Toxic for reproduction	749979	Photoinitiator of polymerization, pigmentation of US-hardened systems, photoresistors, print plates
11.	1,1'-Azobiscarboxamide	123-77-3	Respiratory sensitizing properties	748211	Foaming agents, manufacture of textile articles, plastic, rubber, construction materials
12.	1,2-Dimethoxyethane	110-71-4	Toxic for reproduction	686611	Electric and electronic equipment, batteries
13.	2-Methylimidazole	693-98-1	Toxic for reproduction	686337	Epoxy resin hardener
14.	6,6'-Di-tret-butyl-2,2'-methylendi-p-cresol	119-47-1	Toxic for reproduction	683227	Antioxidant, manufacture of rubber, oil articles, fiber, varnishes and paints
15.	Chlorinated paraffins C_{14}-C_{17}	85535-85-9	PBT; vPvB	672779	Electric and electronic equipment
16.	Dodecamethylcyclohexasiloxane	540-97-6	PBT; vPvB	616328	Articles made of rubber and plastic
17.	1,3,5-Tris(oxirane-2-methyl)-1,3,5-triazin-2,4,6-(1H,3H,5H)-trion	2451-62-9	Mutagen	598114	Polyether powder paints hardener
18.	2-Ethylhexyl-2-{[({2-[(2-ethyl-hexyl)oxi]-2-oxoethyl}sulfanyl) dioctilestannil]sulfanyl}acetate	15571-58-1	Toxic for reproduction	577018	Thermal stabilizer of polyvinylchloride in food package
19.	Dicyclohexyl phthalate	84-61-7	Toxic for reproduction, endocrine disruptor	574011	Articles made of polyvinylchloride, rubber, plastic; textiles, electric and electronic equipment, vehicles
20.	Chromium (VI) compounds	1333-82-0, 24613-89-6 and others	Mutagen, carcinogen	484806	Electric and electronic equipment, vehicles
21.	Ethoxylated nonylphenol	-	Endocrine disruptor	473720	Non-ionic surfactant, textiles, leather articles, metal processing
22.	Bis(2-ethylhexyl)phthalate	117-81-7	Toxic for reproduction, endocrine disruptor	455496	Plasticizer, manufacture of plastic and rubber, vehicles, textiles, electric and electronic equipment, construction materials, batteries and accumulators
23.	Bis(2-(2-methoxyethoxy) ethyl)ether	143-24-8	Toxic for reproduction	442439	Electric and electronic equipment
24.	2,2',6,6'-Tetrabromo-4,4'-isopropylidenediphenol	79-94-7	Carcinogen	404195	Flame retardants for resins and polymer materials
25.	Benzene-1,2,4-tricarboxylic acid 1,2-anhydride	552-30-7	Respiratory sensitizing properties	382426	Epoxy resin hardener and inhibitor in PVC-pastes used in linoleum manufacture; electric and electronic equipment, vehicles

Note: * EU companies have submitted 10,592,895 notifications between January 01, 2021 and August 01, 2023; PBT means persistent, bioaccumulative and toxic substances; vPvB means very persistent and very bioaccumulative.

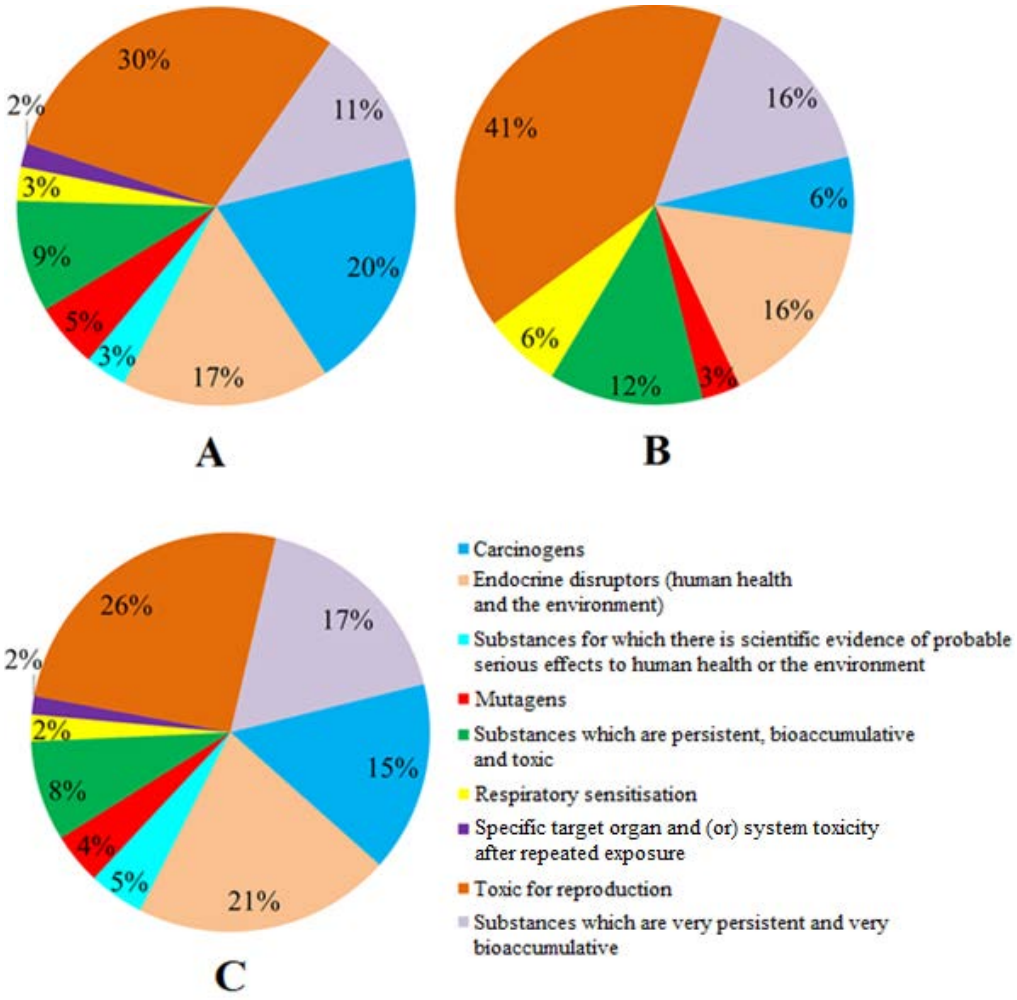

Figure 2. Distribution of hazardous properties of chemicals in articles subject to notification being submitted to SCIP considering all the notifications submitted between 01 January 2021 and 01 August 2023 (A), considering the most frequent 25 (B); included into the Candidate List (C)

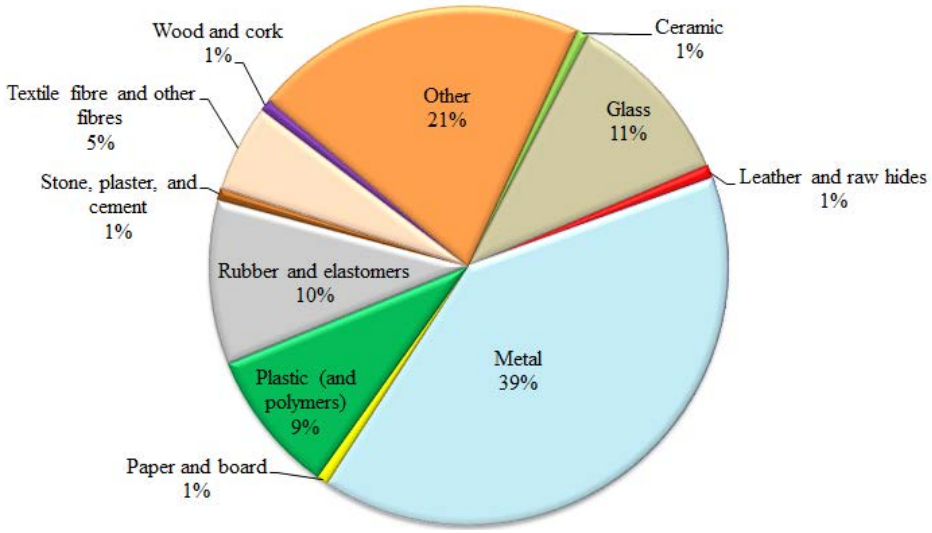

Figure 3. Distribution of notifications on chemicals from the Candidate List as per categories (groups) of articles

The analysis of distribution of hazardous properties of chemicals included in the Candidate List and chemicals in articles notified to the SCIP showed that the main types of hazards are reproductive toxicity (26–30 % of chemicals have this type of hazard), carcinogenicity (15–20 %), endocrine disrupting (17–21 %), very persistent and highly bioaccumulative (11–17 %).

In order to develop effective measures to minimize the risk of exposure to chemicals in articles and its safe management at all stages of the life cycle, including prohibition and (or) restriction, proper waste disposal, stimulating research to find alternatives, as well as creating a transparent mechanism that allows the chemical to be classified as prohibited and (or) restricted, it is considerable to create and maintain a National List of chemicals of concern in articles.

Such a List should include both substances that have acute (e.g., VOCs) and delayed effects. The European approach to creating a Candidate List, which excludes VOCs from consideration, is inapplicable in the Russian Federation, because VOCs are:

– highly hazardous chemicals (for example, formaldehyde is a mutagen category 2, carcinogen – 1A, toxic for reproduction – 1, endocrine disruptor – 2; benzene is mutagen – 1B, carcinogen – 1A, toxic for reproduction – 1; vinyl chloride is carcinogen – 1A, endocrine disruptor – 2, toxic for reproduction – 2);

– widely used in synthesis of polymer materials of articles most people come in contact with;

– pollute the environment by migrating into ambient air and water. This is becoming an acute problem especially for sensitive population groups (for example, formaldehyde migrates into ambient air from construction materials).

It is necessary not only to control VOCs levels in articles and check whether they comply with TR CU requirements but also to search for ways to decrease these levels and (or) to substitute VOCs in articles with safer alternatives.

Candidates for inclusion in the National List of chemicals of concern in articles are chemicals classified in accordance with the GHS:

– carcinogens (hazard categories 1 and 2);

– mutagens (hazard categories 1 and 2);

– toxic for reproduction (hazard categories 1 and 2);

– endocrine disruptors (hazard categories 1 and 2);

– acutely toxic by inhalation and skin contact (hazard categories 1 and 2);

– skin and eye damage (hazard category 1);

– respiratory and (or) skin sensitization (hazard category 1);

– chemicals with specific target organ and (or) system toxicity after single and (or) repeated (long-term) exposure (including those able to produce narcotic effect and irritating the respiratory tract);

– acute (hazard category 1) and chronic (hazard categories 1 and 2) toxicity for aquatic biota [10]; as well as chemicals, which are

– persistent, bioaccumulative and toxic substances

– very persistent and very bioaccumulative.

Chemicals classified as carcinogens, mutagens, toxic for reproduction, and endocrine disruptors of hazard categories 1 and 2 according to the GHS are included into the National List of chemicals of concern that consists of 1480 positions. Of them, 630 chemicals are mutagens; 320 are carcinogens; 271 are toxic for reproduction; 502 are endocrine disruptors (12 chemicals have all four effects and 29 chemicals have three of them). Comparison of the National List of chemicals of concern with the RF Inventory List of Chemicals obtained as part of the inventory and posted on the State Industry Information Website (as of July 2023) showed that 1295 items (87.5 %) are circulating in the Russian Federation.

In addition to evaluating and classifying hazards for human health and the environment, the following points are to be considered prior to including a chemical into the National List of chemicals of concern in articles:

– risk of exposure,

– a number of person in contact,

– production volumes,

– application area,

– migration from articles into ambient air and water,

– method of disposal (recycling),

– possibility to substitute a chemical with its safer alternatives considering the international experience in the sphere.

Some alternatives have already been developed or (are) being developed now for many chemicals enlisted in international conventions (Stockholm and Rotterdam Conventions) as well as for chemicals from the European Candidate List. These alternatives consider an application area for a specific chemical (Table 3) [11, 12].

The creation of a National List of chemicals of concern in articles will make it possible to organize monitoring of their circulation on the territory of the Russian Federation. Within implementation of the National Technical Regulations 'On the Safety of Chemical Products' permissive registration might be introduced for such chemicals. In addition, with the involvement of manufacturers, it is possible to form a database 'Substances in articles', which will facilitate establishing the composition of consumption and production waste as well as their proper classification and disposal.

An ultimate decision on assigning a chemical in an article as prohibited and (or) restricted should be based on an expert report issued with the participation of representatives from Federal Service for Surveillance on Consumer Rights Protection and Human Wellbeing, the RF Ministry of Health, the RF Ministry of Industry and Trade, the RF Ministry of Natural Resources and Environment, the RF Ministry of Agriculture, and the RF Ministry of Economic Development. The report should cover the following points:

– assessment and classification of hazards and risks of exposure to a chemical for human health and the environment;

– substantiation of its permissible levels in an article, levels of its migration into ambient air and water;

– information about alternatives including safer chemical analogues, technological alternatives, a possibility to apply organizational measures as a substitute for a hazardous chemical;

Table 3

Some examples of substituting hazardous chemicals in articles [13–20]

№	Name	Substitute (alternative)
1	Lead and its compounds	– magnesium and aluminum hydrates in manufacturing rubber and plastic articles, – synthetic hydrotalcit as thermal stabilizer in PVC manufacture
2	Bisphenol A	– polyamide in children bottles made of transparent hard plastic; – so-polymer of dimethyl terephthalate, cyclohexanedimethanol, and 2,2,4,4-tetramethyl-1,3-cyclobutandiol in bottles for drinks; – a mixture based on vegetable oil and resin as an inner surface of a package
3	Di(2-ethylhexyl)phthalate	– diisononyl adipate, acetyltirbutylcitrate, diisononyl cyclohexane1,2-dicarboxilate, di(2-ethylhexyl)terephthalate, phenyl ethers of C_{10}-C_{18}-alkyl-substituted sulfonic acids as plasticizers in toys and childcare items; – copolymer of ethene-1-acetene to substitute a basis of PVC carpet and phthalate plasticizer; – dimethyl siloxane and methyl hydrosiloxane in plastisol printing and textile manufacturing
4	2,2',6,6'-Tetrabromo-4,4'-isopropylidenediphenol	– aluminum hydroxide, melamine polyphosphate, aluminum salt of diethyl phosphine acid, boehmite
5	Perfluorooctanesulfonic acid	– paraffins in textiles and carpets; siloxanes modified with alpha-olefin; polyurethanes modified with fatty acids

– assessment of alternatives;

– assessment of socioeconomic risks associated with prohibition and (or) restriction of a chemical;

– an overall conclusion whether a chemical can be assigned as prohibited and (or) restricted.

Conclusion. Upon completion of the present study, the following results have been achieved. The criteria and rules for assigning chemical substances in articles as prohibited and (or) restricted have been substantiated; a mechanism has been proposed for the creation of a National List of chemicals of concern in article. When created, this List will allow monitoring of their circulation on the territory of the Russian Federation, proper waste disposal, and stimulating research work to find alternatives.

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Research article

AGE DYNAMICS OF CANCER INCIDENCE INTENSITY INDICATES EXISTENCE OF SOME FRAILTY SUBROUPS

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The problem of managing population and occupational risks of cancer incidence or mortality presupposes knowledge on biological mechanisms of their formation. These mechanisms determine dynamics of mass processes recorded by statistics. However, there is still no clear understanding of the causal relationship between possible factors of cancer incidence and its real dynamics. The article analyzes a hypothesis about significant influence on dynamics of incidence rates between 'health' and 'disease' states exerted by an intermediate transitional and objectively existing 'frailty' state, which is characterized by accelerated withdrawal from observation compared with the intensity associated with the general variability of individual properties of a population.

It has been statistically established that the dynamics of such common diseases as stomach cancer, lung cancer, breast cancer, prostate cancer, and thyroid cancer can be explained by the fact that almost all diagnosed cases are observed after an individual enters a vulnerable group long before the diagnosis itself. From this point of view, two fundamentally different biological mechanisms of occurrence of neoplasms should be distinguished: induction as a transition from the state of 'health' to the state of 'frailty', as well as promotion as a transition from 'frailty' to 'disease'. Each of these transformations should be characterized in a population by their intensity and their dependence on endogenous or exogenous risk factors.

It is shown that some known facts of paradoxical changes in radio-sensitivity indicators can be satisfactorily interpreted within the concept of a frailty subgroup by using numerical modeling on the example of modifying the dynamics of thyroid cancer incidence under influence of ionizing radiation. The facts were established in 1994–2006 and have not yet received a proper explanation since the concept discussed by the authors of the studies has not been involved.

Keywords: *frailty, compartment, intensity, heterogeneity, survival, rate, risk, cohort, population.*

The concept of frailty (vulnerability) is a clear way to describe unobservable reasons for occurrence of random effects. First of all, it applies to oncology in cases when there are signs of hidden heterogeneity detected in a cohort when analyzing data on survival rates in it. Inherently, the concept takes its origin in the study by Greenwood and Yule on 'proneness to accidents'[1]. The term 'frailty' was obviously first introduced in the study [1] when the authors were describing longitudinal analysis of survival rates in cohorts. Later on, the concept of frailty was successfully promoted by several other researchers [2–4]. Russian scientists have made their contribution to its development as well [5, 6].

The main difficulty typical for analysis within the 'frailty' concept is that there are no reliable indicators of individual frailty that would facilitate observation of biomedical effects in an association with their signaling signs. This would allow establishing cause-effects relations directly in case there were objectively any. On the one hand, this fact stimulates the researchers to actively look for frailty indicators but on the other hand it makes the very concept of frailty vapid since it replaces working with some informative markers with analyzing a set

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[1] Greenwood M., Yule G.U. An inquiry into the nature of frequency distributions representative of multiple happenings with particular reference to the occurrence of multiple attacks of disease or of repeated accidents. *Journal of the Royal Statistical Society*, 1920, vol. 83, no. 2, pp. 255–279. DOI: 10.2307/2341080

Table 1

Thyroid cancer incidence among women in Russia [8]

Age group (years)	Rate ($\times 10^5$ year^{-1})	Age group (years)	Rate ($\times 10^5$ year^{-1})	Age group (years)	Rate ($\times 10^5$ year^{-1})
0–4	0.00	30–34	7.58	60–64	22.29
5–9	0.05	35–39	10.61	65–69	24.21
10–14	0.76	40–44	13.95	70–74	14.86
15–19	2.04	45–49	15.86	75–79	11.90
20–24	3.05	50–54	18.47	80–84	7.75
25–29	5.73	55–59	21.72	85+	5.52

of concomitant (secondary) signs, either physiological or even sociological ones. This creates multiple surrogate predictive models for ranking patients with the use of various clinical predictors (GRACE, TIMI, PAMI, PURSUIT, CADILLAC and the like [7]).

Materials and methods. Meanwhile, it is sometimes still possible to gain direct evidence of vulnerable subgroups existing objectively in cohort or population studies. For example, this can be achieved by analyzing age-specific dynamics of annual cancer incidence rates or cancer mortality rates, both indicators being monitored in the Russian Federation by experts from the P.A. Herzen's Moscow Scientific Research Oncological Institute [8]. It is worth noting that in this case an analysis will be based on indirect observations since the tables created in the Institute do not contain any unobservable or hidden variables able to describe elevated frailty for a part of an analyzed population. Let us provide more detailed data on thyroid cancer incidence among women in Russia in various subgroups where age dependence is substantially nonmonotonic growing up to 65 years of age approximately according to the power-level law and then showing a paradox decline almost down to zero in the subgroup aged 85 years and older (Table 1).

This analysis can be performed by using mathematical modeling. In contrast to traditional description of conditional survival rates that implies a homogenous group of individuals with the same chances to drop out of epidemiological observations, we are going to consider a heterogeneous cohort that consists of two subgroups, the basic one and the frailer one.

We confine ourselves to analyze cancer incidence that is usually established in the Russian Federation when a patient is examined after applying for medical aid or, much less frequently, during screening activities. Medical reports primarily include cancer incidence as new cancer cases, which actually become completed for observation right away. A patient's death is a competing process for such accounting. As a result, the analysis allows assuming that the following Markov's compartment scheme is quite eligible (Figure 1).

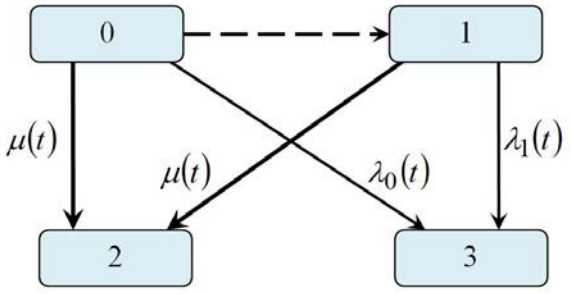

Figure 1. The compartment scheme for modeling cancer incidence intensity: 0 is the basic part of the cohort; 1 is the frailer part of the cohort; 2 is people who died due to other causes; 3 is people who dropped out of epidemiological observation due to an analyzed cancer; $\mu(t)$ is the competing intensity of mortality due to all other causes; $\lambda_0(t), \lambda_1(t)$ is intensity of incidence in the homogeneous subgroups 0 and 1

In the scheme, there is a hidden (uncontrollable) transition between the cohort states 0 and 1 by which some individuals can move from one conditionally homogeneous subgroup into another. Any person can likely die or fall sick with an analyzed cancer regardless of an initial state. According to the methodology de-

scribed in [8], only the number of people in the compartment 3 (diseased) and the total number of lived person-years of observations are traced in a cohort or a population. Collected data are then used to estimate [8] dynamics of the descriptive function *h(t)*, which depends on an age *t* and is usually called an annual incidence risk rate. The risk is measured as an expected number of cases per a year of cohort observation for an allegedly homogeneous group made of 100,000 people who have survived until the registration moment *t*.

If the transition 0–1 occurs earlier and faster than the compartments 0 and 1 become empty, this process can typically manifest itself exactly as it has been shown in Table 1. Although available data are limited, a mathematical model for dynamics in the compartments 0 and 1 can be made quite complete in this case so that we could consider the initial share of population in the basic compartment 0, that is, the parameter β_0 $(0<\beta_0<1)$ practically a constant provided that there are no external risk factors. Then, the dynamics of the registration process can be described with the following system of equations:

$$\begin{aligned} \frac{dS_0}{dt} &= -\left(\mu(t)+\lambda_0(t,\boldsymbol{\beta})\right)\cdot S_0(t); \\ \frac{dS_1}{dt} &= -\left(\mu(t)+\lambda_1(t,\boldsymbol{\beta})\right)\cdot S_1(t); \\ S_\Sigma(t) &= S_0(t)+S_1(t). \end{aligned} \qquad (1)$$

Let us write down the solution to it for the following initial conditions: $S_0(0)=\beta_0$, $S_1(0)=1-\beta_0$, $S_2(0)=0$, $S_3(0)=0$, neglecting the inertia of the transition 0–1. Here $S_i(t)$ is likelihood of filling the compartments; $S_\Sigma(t)$ is 'apparent' (descriptive) likelihood of conditionally 'healthy survival' in the heterogeneous two-compartment cohort; $\lambda_0(t)=\lambda_0(t,\boldsymbol{\beta})$ and $\lambda_1(t)=\lambda_1(t,\boldsymbol{\beta})$ are parameterized incidence intensities in the homogeneous subgroups 0 and 1. It is essential to parameterize them in this case because none of the conditional incidence rates have been measured and are known due to the subgroups 0 and 1 not being determined clearly. Nevertheless, the essence of their specific age dependence is quite clear; it is power-law, similar to Weibull approximation of intensity typical for analogies with technical systems with a weak link[2] [9] or to a sequencing (or even branching) chain of transformable states [6]. Empirical facts of the type have already been known for more than 70 years [10]. They are usually associated with Armitage – Doll compartment model of carcinogenesis [11]. There is also direct evidence in the literature that 'the law of 4–7 degree' is likely associated with the number of stages in tissue transformation of altered cells occurring at the spontaneous initiation stage [12]. This is typical for genesis of epithelial tumors that account for approximately 70 % in the total cancer mortality. We can take $\lambda_0=\beta_1(t/70)^{\beta 2}$ and $\lambda_1=\beta_3(t/70)^{\beta 2}$ with quite good accuracy, where new components of the parameter vector $\boldsymbol{\beta}$ are also positive, for a wide range of attained ages (between 0 and ~70 years). In contrast to incidence rates, the total mortality intensity $\mu(t)$ does not need similar parameterization. In case some specific events due to which a person drops out of observation, are relatively rare and have weak influence on mortality rates, data on the total mortality can be derived by analyzing demographic data in reports of the Federal Statistics Service[3]. In other words, the function $\mu(t)$ can be considered known or we can use its known approximations such as Gompertz or Gompertz – Makeham formulas [9]. The very system of equations (1) can be easily integrated in quadratures, the numeric values of

[2] Weibull W. A statistical distribution function of wide applicability. *ASME J. Appl. Mech.*, 1951, vol. 18, no. 3, pp. 293–297.

[3] Tablitsa smertnosti naseleniya Rossii dlya kalendarnogo goda 2014 [The RF population mortality table in the calendar year of 2014]. *Demoskop Weekly*. Available at: www.demoscope.ru/weekly/ssp/rus_lt.php?year=56 (December 29, 2022) (in Russian).

which are directly calculated under the given set of parameters $\boldsymbol{\beta}$ using such up-to-date mathematical software packages as MathCAD or Wolfram Mathematica. Moreover, since $S_0(t) \sim \exp(-M(t))$ and $S_1(t) \sim \exp(-M(t))$, where $M(t) = \int_0^t \mu(\tau)\, d\tau$ obviously have the same proportionality, we should expect very weak physical dependence of the descriptive incidence rate $h(t, \boldsymbol{\beta})$ on the competing influence of mortality $\mu(\tau)$:

$$h(t,\boldsymbol{\beta}) = -\frac{10^5}{S_\Sigma(t,\boldsymbol{\beta})}\frac{dS_\Sigma(t,\boldsymbol{\beta})}{dt} = \\ = 10^5 \cdot \frac{\lambda_0(t,\boldsymbol{\beta})\cdot S_0(t,\boldsymbol{\beta}) + \lambda_1(t,\boldsymbol{\beta})\cdot S_1(t,\boldsymbol{\beta})}{S_0(t,\boldsymbol{\beta}) + S_1(t,\boldsymbol{\beta})} \quad (2)$$

This allows linking the scheme shown in Figure 1 to observations of specific annual cancer risk rates [8] by calculating their expected values in accordance with the definition of descriptive incidence intensity in the cohort and performing acceptable approximation by varying the vector $\boldsymbol{\beta}$ components within the 4-parameter model (formula 1).

Results and discussion. Approximation results turn out to be quite consistent with observations [8] within a wide age range, approximately between 30 and 85+ years, for some cancer sites that occupy leading places in cancer incidence and mortality. Figure 2 shows the results of comparing population data provided by the P.A. Herzen's Moscow Scientific Research Oncological Institute [8] and calculations as per the cohort formula (2) for thyroid cancer incidence among women; Figure 3, stomach cancer incidence among women.

In the considered cases, we should not be skeptical about a slight difference in the meaning of two concepts, cohort incidence intensity and population rate of annual incidence risk since both indicators are estimated in practice using the same techniques in case of observations [8] accomplished within short five-year strata[4]. Age strata in the population study [8] differ only per their belonging to different cohorts due to different years of birth.

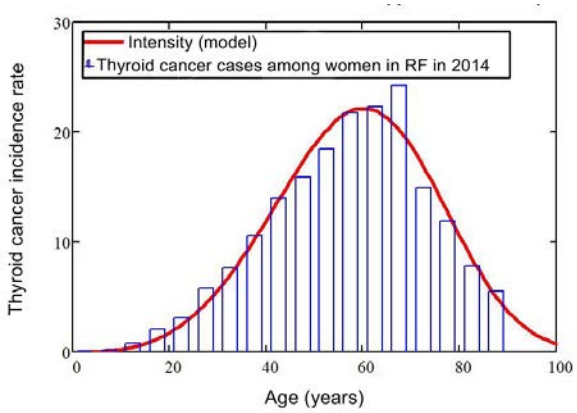

Figure 2. Compared model (age-specific) and actual (2014) dynamics of thyroid cancer incidence rates among women in Russia (per 100,000 survived people per year)

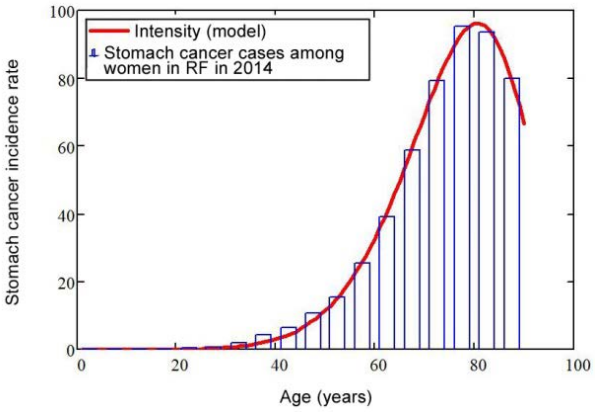

Figure 3. Compared model (age-specific) and actual (2014) dynamics of stomach cancer incidence rates among women in Russia (per 100,000 survived people per year)

An assumption that the initial share of the frailty subgroup $1 - \beta_0$ is practically constant in different calendar sub-cohorts of the Russian population seems rather fantastic. Despite that, approximations, which were similar as per quality of description, were obtained also for thyroid cancer and stomach cancer among men, prostate cancer (men), lung cancer (both men and women), and even for breast cancer (men and women). Moreover, as we can see

[4] A Dictionary of Epidemiology, 4th ed. In: J.M. Last ed. Oxford University Press, 2001, 196 p.

from Table 2, the most plausible estimates of the model parameters are reproduced quite stably in all the described cases of successful approximation despite different cancer sites. They also allow evaluating the share of the frail people ($1 - \beta_0$) and correctly recovering empirical risk rates (the annual risk rate, Nelson – Aalen cumulative hazard rate, radiation-attributed decrease of survival (RADS) [13] and the actual observed lifetime risk). The most interesting thing is a possibility to assess ratios of flows of events measured in 'persons/year' under transitions between the compartments 0–3 and 1–3. This value has turned out to be considerably lower than 1, even at its maximum, despite greater absolute and relative population in the compartment 0. This fact means that practically all diagnosed cases of a specific cancer are observed after people have moved into the compartment 1, that is, into the frailty subgroup even prior to cancer being diagnosed in them. The transition 0–3 is actually negligibly unlikely and this justifies the very concept of a 'frailty group'. It is also worth noting that even if it was not so, than, due to the formula (2) being weighted average in its essence and together with the apparent first maximum $h(t, \beta)$, an additional peak in the rate would exist in the age group 85+. Obviously, nothing alike has been registered empirically so far.

We should also note that conditional risk rates N-A and RADS, which are essentially descriptive and based on integration of the annual descriptive rate $h(t, \beta)$, give somewhat overestimated cumulative evaluations in comparison with the number of people in the frailty group if this comparison is made in identical units. At the same time, an actual observed descriptive cumulative cancer risk turns out to be half the share of the frailty group since not every potentially frail person in it survives until a cancer is diagnosed due to competition by mortality caused by all other reasons.

Another important point is that an attempt to use the concept of the fixed number of people in the 'frailty group' for providing simple explanation of dynamics of age dependence with respect to incidence rates of some other spontaneous cancer has been unsuccessful. This primarily concerns malignant neoplasms of lymphoid, hematopoietic and related tissue (C81–C96) that have apparent bimodal or even trimodal dependence between incidence rates and age, especially the 'youth component'. Incidence rates had similar multi-modal behavior in case of malignant neoplasms of lip, oral cavity and pharynx and malignant neoplasms

Table 2

Estimated cancer incidence rates in Russia in 2014

Cancer site	ICD-10	The share of 'frailty' (%)	Estimation of β_2 degree	Standardized annual rate	N-A	RADS	LR	Flow ratio (0–3 to 1–3)
Stomach (men)	C16	4.4	6.5	25.2	5650	5494	2063	~ 0.14
Stomach (women)	C16	2.9	6.2	11.4	2514	2482	1493	$\sim 10^{-5}$
Trachea, bronchi, and lungs (men)	C33,34	8.3	6.6	53.4	10,931	10,354	4505	~ 0.11
Trachea, bronchi, and lungs (women)	C33,34	2.2	4.8	8.1	1718	1703	1070	$\sim 10^{-5}$
Breast (men)	C50	0.45	4.3	0.69	163	163	56	$\sim 5 \cdot 10^{-3}$
Breast (women)	C50	7.3	4.1	52.9	8049	7734	5878	~ 0.11
Prostate (men)	C61	8.5	9.4	47.1	11,758	11,093	3937	~ 0.13
Thyroid (men)	C73	0.27	3.3	2.03	253	253	140	$\sim 10^{-15}$
Thyroid (women)	C73	0.94	3.0	8.3	919	915	752	$\sim 10^{-6}$

Note: all cumulative rates (N-A, RADS and LR) are given per 100,000 people a year for the age ranges up to 90 years; direct standardization is performed as per the world standard population [14]; Nelson – Aalen rate (the area under the hazard curve) is given as N-A; radiation-attributed decrease in survival is given as RADS; actual conditional lifetime risk rate is given as LR.

of digestive organs (C00–C15; C17–C21), malignant neoplasms of bone and articular cartilage (C40, 41), malignant neoplasms of eye, brain and other parts of central nervous system (C69–C72). However, it is hardly possible to deny the very fact that frailty subgroups are likely to exist in these cases as well. Obviously, dynamic changes in the share of frail people in a population or a cohort are typical for the aforementioned wide range of cancer sites together with a shorter hidden period of cancer development both under endogenous spontaneous reasons and due to exposure to external carcinogenic factors.

Finally, let us mention an important indirect sign. The objective existence of an internal frailty compartment in a cohort or a population inevitably causes observable peculiar modifications of age-specific dynamics of cancer incidence under exposure to external carcinogenic risk factors. The process can be registered by using statistical-epidemiological methods. Among the most well-known factors, special attention should be paid to effects produced by ionizing radiation on body cells and tissues. Almost a century has passed since German Mueller published his findings (1927) that evidenced genetic effects of radiation exposure. In 1928, the International X-ray and Radium Protection Committee was founded as a prototype of the existing permanent International Commission on Radiological Protection (ICRP). It coordinates radiation epidemiology and radiobiology research on the international level. Huge amounts of statistical data have been accumulated over years. In particular, there is the commonly accepted and known concept that a cumulative dose of any absorbed ionizing radiation can directly result in descriptive annual intensity of cancer incidence and an individual lifetime cancer risk growing approximately as per the linear law [15, 16]. This is the so called linear no-threshold (LNT) model or the proportionate risk concept. All international radiation safety standards are LNT-based; but at the same time the documents [15, 16] and several other publications do not always provide officially recognized mentions of slightly different dose trends, identified, at least, for some cancer sites.

The ‘frailty group’ concept turns out to be able to explain the existing differences between commonly recognized concepts and observable facts. To do that, we should pay attention to the fact that the transition between the compartments 0 and 1 in the scheme shown in Figure 1 corresponds to the induction of malignant neoplasms and the transition 1–3 corresponds to their promotion under exposure to ionizing radiation. That is, we should distinguish between at least two biologically different radiation-oncological effects in case we neglect the existence of the third, though weaker, dose-related dependence of mortality intensity due to all the other causes $\mu(t|D)$.

Let us show what consequences can be expected within this assumption. We can identify them by performing numeric modeling, for example, for thyroid cancer, spontaneous incidence rates of which have already been studied in dynamics in this work (Figure 2). Still, according to the recommendations provided in [15, 16], we are not going to step over the LNT model boundaries spreading them onto each of the transitions 0–1 and 1–3. In this case, to consider dose dependence in the analyzed models, we should only formally replace the share of frail people $(1-\beta_0)$ with $(1-\beta_0)\cdot(1+k_1D)$, and the β_3 multiplier in the intensity λ_1 with $\beta_3\cdot(1+k_2D)$, where k_1, k_2 are coefficients that describe radio-sensitivity. Age-specific dependence of potentially observable cohort annual incidence rate has been evaluated under different levels of radiation exposure (the background level and exposure to 1 Sv). The results are shown in Figure 4 for a subgroup of women who had their thyroid exposed to radiation at the age of 0–9 years and the exposure was single and acute.

Obviously, the ratio between descriptive risk rates in two dose groups changes substantially due to the existing subgroup of frail people. It can be both higher than one (up to 50 years of age) and lower than one (for elderly women). Therefore, if the LNT model is applied correctly, the proportionate risk concept

is violated together with the descriptive LNT model itself. Lifetime risk can have a significantly weaker dose trend in comparison with that of the annual risk rate; we cannot consider the annual risk rate trend a linear one either (Figure 5). The graph makes it quite easy to conclude that the calculated-nominal value of excess relative risk on a unit dose of 1 Sievert (ERR/Sv) can vary between 8.8 Sv^{-1} in younger age groups (without considering the reducing DDREF = 2 [15]) and negative values in older ones (older than 55 years) if the calculations are based on analysis of annual

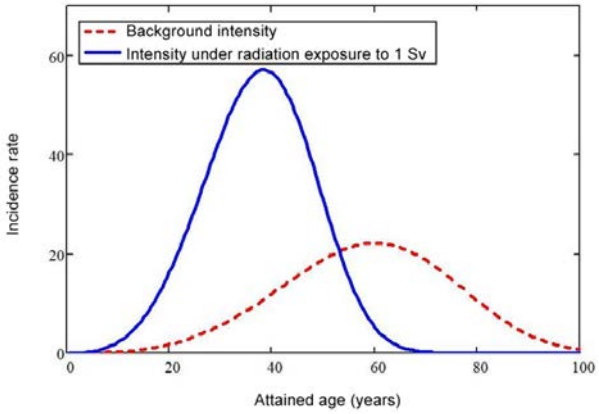

Figure 4. Age-specific dependence between thyroid cancer incidence (per 100,000 a year) among unexposed women and women who were exposed to radiation at the age of 0–9 years, a dose of 1 Sv (calculations rely on the following coefficients of radio-sensitivity: $k_1 = 0.5\,Sv^{-1}$ and $k_2 = 5.0\,Sv^{-1}$)

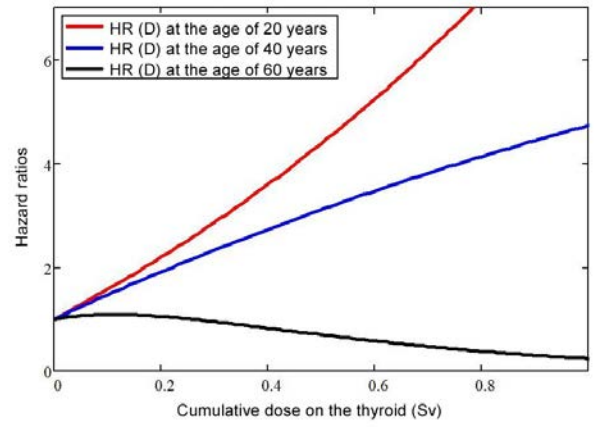

Figure 5. Apparent non-linearity of dependence between annual hazard ratio and a dose, which give evidence of the proportionate risk concept being ineligible for describing radiation effects

risk rates. But if we analyze excess dose dependence of the standardized incidence ratios (SIR), then the evaluation goes down to approximately 2.3 Sv^{-1} due to age-specific averaging. However, it does not correspond to the true value of 5.0 Sv^{-1} predetermined within the modeling process in either case. Even a lower descriptive coefficient of radio-sensitivity, approximately 0.87 Sv^{-1}, can be derived from our preset model, if the evaluation is based on a dose trend identified for the actual lifetime risk of thyroid cancer among women who underwent acute radiation exposure when they were younger than 15 years. The last evaluation is astonishingly consistent with the opinions of the ICRP experts [17].

Meanwhile, the proportionate risk concept is a quite stable mental construction with some other concepts being based on it, such as the concept of nominal risk coefficient [15] and even the conventional concept of the effective doze of ionizing radiation [18]. Moreover, use of excess relative risk per dose unit (ERR/Sv) as the basic characteristic of a dose trend in radiation harm nowadays has become the conventional ‘golden standard’ of the UNSCEAR and IAEA [16, 19] as well as of many studies on radiation epidemiology. This concept has become so prevailing that the document [16] incorrectly mentions the radio-sensitivity value ERR/Sv in most cases as excess relative risk itself. Therefore, it would be useful to have some actual data confirming existing heterogeneities in analyzed cohorts since it would disprove the proportionate risk concept. The most interesting thing is that such data have long been available in studies, especially as regards thyroid cancer [20–22]. In particular, the study [20] involved examining a substantially big sample made of children who had their thyroid gland exposed to gamma radiation due to various reasons at the age younger than 15 years. As a result, long-term observations established that the linear ‘dose – effect’ model worked effectively only until a dose was lower than 0.1 Gy. Moreover, either the proportionate risk model or additive risk model was not effective within a wider dose range; the ERR/Gy value was 7.7 Gy^{-1} (95 %

CI: 2.1–28.7) for younger age groups; radio-sensitivity did not keep its value within wide observation ranges as it declined with age and a growing dose down to zero under ≈ 10 Gy. In their turn, the authors of the study [21] examined cancer incidence in the cohort made of atomic bomb survivors in Hiroshima and Nagasaki and concluded that a risk of thyroid cancer due to radiation exposure was negligible, if even existing, 20 years after the bombing. In particular, they pointed out that the ERR/Sv value went down with attained age from 9.47 Sv^{-1} for the age group of 0–9 years down to negative 0.23 Sv^{-1} for the age group of 40+ years (at the moment of radiation exposure). That is, this excess relative risk could change its sign in the same way as it has been shown in Figures 4 and 5. The radio-sensitivity rate ERR/Sv turned out to behave in a similar way in the cohort made of people living in the Bryansk, Kaluga, Orel, and Tula oblasts in 1981–2008 who were exposed to radionuclides fall caused by the Chernobyl disaster. Still, negative radio-sensitivity to thyroid cancer together with elevated standardized (cumulative for the analyzed population) annual ratios could be simultaneously and, apparently, controversially observed in the age group of people older than 18 years [22]. Despite available evidences, even those provided in the document [16], the very fact that a nonmonotonic dose- and age-specific trend of the descriptive hazard ratio exists has been stimulating heated discussions in the expert society over the period between 2017 and 2021. Their ultimate result was that ICRP Publication 147 [17] was issued in a substantially cut version (13 pages) as opposed to its initial draft one (69 pages). A decision was made not to mention any peculiarities as regards how the hazard ratio behaved itself depending on an attained age of exposed groups. The document contained only the description of ERR/Sv radio-sensitivity depending on an age when radiation exposure started; its value was based on a cumulative lifetime risk. Undoubtedly, this political decision was made to preserve the effective dose concept that directly relied on the linear no-threshold model and the ‘dose – effect’ principle of analysis that were now applicable only to a lifetime risk rate or any other cumulative analogue. In contrast to it, the ‘frailty group’ concept corresponds to another principle, namely, ‘dose – time – effect’, even if its form is a bit curtailed and not able to disclose the biological mechanism of carcinogenesis. Nevertheless, the document [17] still fixed the fact that the descriptive radio-sensitivity ratio ERR/Sv dropped manifold with an age when radiation exposure started and not only for thyroid cancer but also stomach cancer, rectum cancer, bone marrow cancer, urinary bladder cancer, liver cancer, and some other cancer sites. The described character of influence exerted by external ionizing radiation on cancer incidence by no means can be explained by the existing concepts of prevailing effects produced on induction of malignant neoplasms by external radiation exposure. However, it does not contradict some concepts that imply existence of a relatively rapidly reducing frailty group among members of a cohort who are of the same age; intensity of reduction in this group can depend on a xenobiotic dose.

To conclude our discussion, we would like to give a reference to a study that has not been reviewed so far[5]. It reports a mutual intersection between curves of age-dependent annual risk rates for different dose groups (similar to Figure 4). This mutual intersection appeared in studies of lung cancer mortality among personnel employed at a facility with radiation hazards and this definitely indicates more rapid reduction in a cancer-frail group due to more deaths. In addition to that, the authors of this report published the results of a study with its focus on prostate cancer incidence [23] where they stated directly that “…radiation-induced risk of the disease [ERR/Gy] … equaled 5.24 … per 1 Gy in the

[5] Vliyanie uslovii truda na sostoyanie zdorov'ya personala v proizvodstve po utilizatsii vooruzhenii i voennoi tekhniki: Otchet o NIR po kontraktu № 11.312.09.1 (shifr «Personal-1») [Effects produced by working conditions on personnel employed at a weaponry and military equipment utilization facility: Reports on R&D work under the contract no. 11.312.09.1 (‘Personnel-1’ code)], State Registration Number 01200952999. Ozersk, SUIBPh, 2009, 166 p. (in Russian).

Mayak PA personnel cohort aged 50 years and then declined drastically as this age was attained …", notably, almost down to zero already at the age of 60 years. Negative values were likely to be achieved for the age groups 70+ but the authors humbly neglected them. That is, age-specific distribution of the annual risk rate had a bias towards early ages together with the graph being stretched vertically when a gamma radiation dose grew. We cannot explain why the risk rate behaves in this way if we use the traditional LNT model but we can easily do it using the 'frailty group' concept.

Conclusion. Therefore, relying on comparison of the results obtained by numeric modeling of cancer incidence in dynamics and analysis of statistical epidemiological data, we can almost surely ascertain that dynamics of risk rates is determined for many cancer sites by cancer-frail groups existing in a population. These groups are formed predominantly during a period when a body grows intensively, up to the age of 15–20 years. Cancer is diagnosed in a considerable part of this group (approximately a half of it) when a patient is alive. External exposures to xenobiotics and carcinogens can accelerate the transition from the 'frailty' compartment to the 'disease' compartment and this should be taken into account when developing occupational safety standards.

The established fact highlights relevance of studies aimed at early preventive establishment of reliable specific biomarkers eligible for determining whether a specific person belongs to an objectively existing cancer-frail group. Still, not every tissue hyperplasia or hypertrophy can be considered an actual transition into a cancer-frail group. We can make such judgments if we compare, for example, prevalence of frailty-states with respect to prostate cancer (see Table 2) and prevalence of benign prostate hyperplasia among men, which can reach 80 % in older age groups. Moreover, a correct prediction requires markers that describe both early and late stages of an individual pre-cancer state in a frail group.

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Research article

ANALYSIS OF CARCINOGENIC RISK AND DYNAMICS OF POPULATION MORBIDITY AND MORTALITY IN THE IRKUTSK REGION DUE TO MALIGNANT NEOPLASMS AND CARCINOGENIC RISK FACTORS

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Morbidity and mortality caused by malignant neoplasms (MNs) is a priority challenge for health care.

We analyzed some rough and standardized levels (oncological morbidity and mortality) over 2009–2018 based on official statistics. We ranked the RF regions as per the standardized morbidity level and established that the Irkutsk region took the 1st rank place among 85 RF regions as per it; it took the 16th rank place as per the 'rough' level. Morbidity and mortality levels that were higher in the Irkutsk region than the national average were established for such localizations as trachea, bronchi and lung cancer; prostate cancer; cervical cancer. The mortality to morbidity ratios were on average equal to 0.45 in the Irkutsk region and 0.49 in the RF as a whole; we identified a certain decrease in them, by 19.3 % and 20.0 % accordingly. We provided evidence of unacceptable individual carcinogenic chemical risk for people in cities with developed chemical industry and non-ferrous metallurgy. High carcinogenic radiation risks were caused by natural radon levels in soils. We calculated some prognostic morbidity and mortality levels: in 2021, the standardized morbidity level would be between 270.9 and 329.8 cases per 100 thousand people; the 'rough' level, between 372.7 and 532.4. The 'rough' mortality level would be between 220 and 230 cases per 100 thousand people.

We determined some priority tasks for future research aimed at identifying adverse effects produced by environmental factors and lifestyle-related factors as well as some tasks related to developing relevant targeted activities aimed at eliminating and mitigating cancer-inducing exposures.

Keywords: *carcinogenic risk, morbidity, mortality, malignant neoplasms, population, chemical factor, radiation factor, prognosis.*

Cancer morbidity and mortality are growing in many regions of the world and this fact highlights medical and social significance of the issue [1–3]. A trend of growing prevalence of chronic non-communicable diseases, cancer included, is associated with various factors such as changes in the age structure of population that involve longer life expectancy and

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ageing, chemical and physical contamination of the environment, and behavioral risk factors [4]. Among basic causes of malignant neoplasms (MNs), we should mention not only genetic factors, exposure to chemical carcinogens in ambient air or food but also working conditions [5–9]. The National Goals of the RF development[1] and targets stipulated by the Cancer Control Federal Project include growing life expectancy at birth of the RF population up to 78 years (by 2030), a decrease in mortality among working age population, a decrease in mortality caused by neoplasms, malignant ones included (down to 185.0 cases per 100,000 people by 2024). To achieve them, it is necessary to know how population levels as regards MNs are formed in different regions in the country, the Irkutsk oblast included. MNs morbidity is known to be mostly concentrated and growing among people of older ages (the highest share of cancer incidence is identified in the age group of 65–69 years) [10]. Therefore, considering the ongoing population ageing in Russia, we can assume a further growth in the number of MNs cases as well as their greater significance as a major reason for disability among the RF population [11].

Several studies have been accomplished with their focus on epidemiological aspects of oncological pathology in Siberian regions where morbidity has been established to grow; this growth was more apparent among urban population [12–14]. MNs morbidity among population in the Irkutsk oblast is one of the highest in the Siberian Federal District [15]. According to statistics, malignant neoplasms occupy the first rank place among reasons for disability in adult population of the Irkutsk oblast; the 2nd rank place, in the total mortality; 4th rank place, in the mortality of working age population[2]. All this highlights specific relevance of the issue for the region. Therefore, it is necessary to prevent and reduce incidence of malignant neoplasms in the Irkutsk oblast and provide scientific substantiation for development of the most effective preventive activities.

The aim of this study was to evaluate carcinogenic risk levels and accomplish profound analysis and prediction of morbidity and mortality caused by malignant neoplasms among the Irkutsk oblast population.

Materials and methods. Individual and population carcinogenic risks associated with chemical pollution in ambient air were calculated according to the methods stipulated in the Guide Human Health Risk Assessment from Environmental Chemicals (R 2.1.10.1920-04)[3]; when calculating risk levels, we relied on average annual data of social and hygienic monitoring (SHM) over 2000–2018. MNs morbidity and mortality among the Irkutsk oblast population was analyzed in 2009–2018 by using official statistical reports (From no. 7 Data on Incidence of Malignant Neoplasms), materials from the annual data collections Malignant Neoplasms in Russia and Socially Significant Diseases among the RF Population, and official data provided in the UIISS (Unified Interdepartmental Information Statistic System)[4].

We analyzed morbidity and mortality in the Irkutsk oblast in comparison with their national rates in the Russian Federation. The analysis covered ‘rough’ and standardized morbidity rates, including men and women separately, in 10-year dynamics; structure of the

[1] O natsional'nykh tselyakh i strategicheskikh zadachakh razvitiya Rossiiskoi Federatsii na period do 2024 goda: Ukaz Prezidenta RF ot 07.05.2018 № 204 [On national goals and strategic tasks of the Russian Federation development for the period up to 2024: the RF President Order dated May 07, 2018 no. 204]. *Prezident Rossii: the official web-site of the RF President*. Available at: http://www.kremlin.ru/acts/bank/43027 (April 12, 2023) (in Russian); O natsional'nykh tselyakh razvitiya Rossiiskoi Federatsii na period do 2030 goda: Ukaz Prezidenta RF ot 21.07.2020 № 474 [On national goals and strategic tasks of the Russian Federation development for the period up to 2030: the RF President Order dated July 21, 2020 no. 474]. *GARANT: information and legal support*. Available at: https://base.garant.ru/74404210/ (April 12, 2023) (in Russian).

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

[4] Ofitsial'nye statisticheskie pokazateli [Official statistical indicators]. *EMISS: state statistics*. Available at: https://www.fedstat.ru (May 04, 2023) (in Russian).

MNs morbidity; 'rough' and standardized (the world standards, WHO, 2001) mortality rates. We identified a rank place that belonged to the Irkutsk oblast among 85 RF regions as per its 'rough' and standardized MNs morbidity rates. The rates were analyzed in dynamics and correlations between morbidity and mortality as well as their correlations with the age structure of the population were evaluated in the Statistica 6.0 software package (Pearson's correlation and regression analysis (r)). Statistical significance was taken at $p < 0.05$.

Specific territories in the Irkutsk oblast were combined into several clusters by k-mean clustering considering average long-term morbidity as per priority cancer sites. We calculated and compared potential carcinogenic risk rates caused by chemical and radiation exposure on territories with the highest morbidity rates (Cluster 1).

Predictive estimates of morbidity and mortality rates are based on statistical models that cover data collected over a 10-year period and this allows considering the latest trends. 2021 indicators were calculated relying on estimated population number in 2021 so that we could derive a calculated number of new MNs cases and deaths caused by them.

We calculated ratios between standardized morbidity and mortality rates to assess effectiveness of healthcare provided for MNs patients. This allows removing influence of differences in age and sex structure of the population living on the analyzed territories. Moreover, this ratio is considered an index that describes validity of registration: when it is qualitative, the number of deceased, even for cancer sites with high fatality rates, should not be higher than the number of diseased [16]. These ratios were compared by using a share of ratio differences (RDS), which determines a difference between two ratios in percent. It was calculated as per the following formula:

$$\text{RDS} = (R_1 - R_2 / R_1) \cdot 100,$$

where R_1, R_2 are compared ratios. In most cases, R_1 should represent a higher ratio; however, R_1 represented national RF ratios in this study and they were higher than R identified for the Irkutsk oblast in most cases.

Results and discussion. More than 10,000 MNs cases are registered annually in the Irkutsk oblast. In 2018, 11,999 MNs cases were registered in the Irkutsk oblast for the first time (including 5559 among men and 6440 among women) (Table 1).

Obviously, average long-term morbidity rate (ALM) equals 432.44 among the Irkutsk oblast population over 2009–2018 and this was 11.7 % higher than the national average (387.12 in the RF). If taken in dynamics, the morbidity rate has an apparent ascending trend. It grew by 68.7 % in the Irkutsk region between 2003 and 2018 (the national average rate grew slower and increased only by 19.6 %). Over the last decade, the growth has been 33.9 % (it is 19.6 % in the RF). By the end of 2018, 60,052 patients with cancer were registered in the region (the 'rough' morbidity rate was 499.1 in the Irkutsk oblast, which was 17.3 % higher than the national average (425.46). MNs prevalence equaled 2497.8 per 100,000 people in the Irkutsk oblast (2562.3 in the RF).

Standardized ALM was 292.36 in the Irkutsk region over 2009–2018 and this was 24.1 % higher than the national average (235.58 in the RF). The standardized morbidity rate has an apparent ascending trend in the analyzed period. Over the last decade, this rate has grown by 18.2 % in the Irkutsk oblast (the national average rate grew slower and increased by 8.5 %). In 2018, the standardized MNs morbidity rate was 320.2 ± 3.07 in the Irkutsk oblast and was 29.8 % higher than the national average (246.77 ± 0.33).

We ranked 85 RF regions as per the standardized morbidity rate and established that the Irkutsk oblast was among the top five regions with the highest cancer morbidity for many years. In 2018, the Irkutsk oblast took the 1st rank place among 85 RF regions (the 1st rank place for men and 2nd rank place for women) and the 16th rank place as per the 'rough' morbidity rate.

Cluster analysis results indicate that the highest primary MNs morbidity as per the

Table 1

MNs morbidity rates in dynamics identified among the Irkutsk oblast population and in the RF over 2009–2018

Year	Absolute number		Primary morbidity (actual incidence) (per 100,000)					
			'Rough'		Rank place*	Standardized		Rank place *
	Registered MN patients	First diagnosed cases	Irkutsk oblast	RF		Irkutsk oblast	RF	
2009	41,396	9332	372.7	355.8	34	270.9	227.4	3
2010	43,438	9595	383.4	364.2	33	275.5	231.1	6
2011	44,874	9955	410.0	365.4	23	286.7	228.1	4
2012	46,280	10,021	413.3	367.3	23	283.2	227.6	5
2013	48,020	10,275	424.2	373.4	25	288.0	229.2	3
2014	50,174	10,389	430.2	388.0	31	287.9	235.2	3
2015	52,148	10,804	447.4	402.6	28	296.4	241.4	3
2016	54,635	11,122	461.0	408.6	26	302.9	242.6	3
2017	57,536	11,626	483.1	420.3	19	311.9	246.6	2
2018	60,052	11,999	499.1	425.5	16	320.2	246.8	1
ALM**	**49,855**	**10,512**	**432.4**	**387.1**		**292.4**	**235.6**	

Note: * means the rank place of the morbidity rate in Irkutsk oblast among all RF regions (ranking is performed as per descending in the rate), **ALM is average long-term morbidity.

leading cancer sites is identified in Cluster 1 that includes Irkutsk, Bratsk, Sayansk, Usolie-Sibirskoe, Ust-Ilimsk, Cheremkhovskoe municipal settlement, Svirskoe municipal settlement, Angarskoe municipal settlement as well as Slyudyanskii and Shelekhovksii districts (1.4 million people overall). In addition to that, high primary morbidity rates are established on territories included in Clusters 2 and 3. Cluster 2 (482 thousand people) includes seven administrative districts. Cluster 3 (165 thousand people) includes nine administrative districts. The lowest primary morbidity rates as per the leading cancer sites are identified in 10 administrative districts included in Cluster 4 (162 thousand people overall): Balaganskii, Zhigalovskii, Olkhonskii, Ust-Udinskii, Alarskii, Bayandaevskii, Bokhanskii, Nukutskii, Osinskii, and Ekhirit-Bulagatskii districts.

High cancer incidence rates can be explained not only by qualitative diagnostics and treatment but also effects produced by technogenic factors. In this study, we considered some environmental factors that could have certain significance for occurrence and progression of blastoma-causing processes including adverse chemical exposures as well as radiation exposure such as radon occurrence in housing and public buildings. Natural ionizing radiation sources are the leading factor causing radiation exposure of the Irkutsk oblast population. According to data derived by long-term observation (over 2001–2017), the Irkutsk oblast population tend to be exposed to elevated (more than 5.0 mSv/year) doses created by natural ionizing radiation sources (5.1 mSv/year). Several zones with elevated radon emissions are registered in the Irkutsk oblast including those located in towns included in Cluster 1: Ust-Ilimsk (the average dose is 7.34, the critical one is 17.32 mSv/year) and Irkutsk (the average dose is 2,93, the critical one reaches 18,61 mSv/year). Elevated radon levels, including those identified in housing and public buildings as well as water supply sources, are caused by geological peculiarities of the earth crust in the Irkutsk oblast. We have not established any critical zones in other towns and settlements in Cluster 1. Table 2 provides data on average annual individual and population carcinogenic risk rates caused by chemical and radiation exposure identified on the most risky territories.

Levels of ambient air pollution tend to be very high in the Irkutsk oblast due to emissions from industrial enterprises and motor transport. This includes pollution with carcinogenic chemicals. Along with thermal

Table 2

Individual and population carcinogenic risks caused by chemical and radiation exposure

Territories in Cluster 1	Individual risk		Population carcinogenic risk (the number of additional MNs cases)	
	chemical (ICR)	average annual radon levels, mSv/year	chemical	radiation
Angarsk	6.50E-04	1.72	154.9	22.5
Shelekhovkii district	1.00E-03	2.13	64.9	7.6
Irkutsk	7.31E-04	2.93	449.8	99.2
Bratsk	1.06E-03	2.56	249.6	33.1
Sayansk	8.01E-05	1.93	3.1	4.1
Usolie-Sibirskoe	1.25E-04	2.29	9.9	9.9
Ust-Ilimsk	1.03E-06	7.34	0.1	33.5
Cheremkhovo	2.50E-05	2.15	1.3	6.1

Table 3

'Rough' and standardized mortality rates due to MNs among the Irkutsk oblast population and in the RF in 2009–2018

Years	Absolute number	Mortality rate per 100,000 people					
		'Rough'		Rank place*	Standardized		Rank place*
		Irkutsk oblast	RF		Irkutsk oblast	RF	
2009	4751	194.4	204.9	43	135.4	125.2	17
2010	4682	185.3	204.4	55	131.7	124.0	25
2011	4759	194.9	202.5	49	133.5	120.2	16
2012	4604	190.0	201.0	54	126.1	117.7	31
2013	4916	203.1	201.1	43	134.0	116.8	11
2014	4885	201.8	199.5	44	130.3	114.6	13
2015	4953	205.2	202.5	42	131.4	114.8	16
2016	5015	208.0	201.6	37	131.9	112.8	9
2017	5166	214.7	197.0	32	132.9	109.0	5
2018	5080	211.6	200.0	39	129.0	108.6	11
AMR	**4881**	**200.9**	**201.5**		**131.6**	**116.3**	

Note: * means the rank place of the mortality rate in Irkutsk oblast among all RF regions (ranking is performed as per descending in the rate).

power stations, various industrial enterprises emit carcinogenic chemicals in ambient air such as aluminum production in Bratsk and Shelekhov, petrochemical and electrolysis-chemical plants in Angarsk, and vinyl chloride production in Sayansk. Productions with carcinogenic hazards have long been functioning on territories where health risks were accumulated due to previous economic activities (including Svirsk, Usolie-Sibirskoe, and Baikalsk).

Obviously, the highest individual carcinogenic risks under potential chemical exposure are established for people living in large industrial centers such as Bratsk (1.06E-03) and Shelekhovskii district (1.00E-03); these risk rates are considered unacceptable. They are followed by Irkutsk (7.31E-04), Angarsk (6.50E-04), and Usolie-Sibirskoe (1.25E-04). The risk is considered acceptable in Sayansk (8.01E-05), Cheremkhovo (2.50E-05), and Ust-Ilimsk (1.03E-06). The highest average annual radon level (7.34 mSv/year) was identified in Ust-Ilimsk; these levels did not exceed 2.93 mSv/year on all the other territories in Cluster 1. Population risk rates are associated not only with ambient air being polluted with carcinogens but also with the number of exposed population; therefore, the most risky territories primarily include cities with population higher than 200 thousand people (Angarsk and Bratsk) as well as the oblast center Irkutsk (more than 600,000 people).

Average annual mortality rate equaled 200.9 in the Irkutsk region over 2009–2018 (201.5 in the RF) (Table 3).

In 2018, the 'rough' mortality rate equaled 211.6 in the Irkutsk oblast, which was 5.8 % higher than the national average (200.03).

The mortality rate tended to grow over the analyzed period. It grew by 8.8 % in the Irkutsk oblast between 2009 and 2018 (the growth was negative in the country as the national average mortality rate dropped by 2.4 %).

In 2018, the standardized mortality rate equaled 129.0 ± 1.89 and was 18.8 % higher than the national average (108.56 ± 0.21). Over 2009–2018, the long-term average standardized mortality rate equaled 131.6 in the Irkutsk oblast, which was 13.1 % higher than the national average (116.3). Over 2009–2018, a descending trend occurred in the standardized mortality rate as it went down by 4.7 % in the Irkutsk oblast (the national average declined faster and went down by 13.3 %).

We ranked RF regions as per the standardized mortality rate due to MNs and established that the Irkutsk oblast was among those with the highest standardized MNs mortality rate in 2018 as it held the 11th rank place out of 85 regions (13th rank place for men and 15th rank place for women) and the 39th rank place as per the rough mortality rate (39th rank place for men and 31st rank place for women).

Next, we calculated mortality / morbidity ratios as per their standardized rates; this made it possible to assess healthcare quality in the Irkutsk oblast and the RF in general by eliminating influence of different age structure. On average, the ratio was 0.45 in the Irkutsk oblast and 0.49 in the RF over 2009–2018; we also established a decline in the ratios, by 19.3 % and 20.0 % accordingly. This dynamics is easily described by linear regression equations: R (Mr/Mb) = -0.0085x + 0.4983 (R^2 = 0.880) for the Irkutsk oblast; R (Mr/Mb) = -0.0128x + 0.5655 (R^2 = 0.987) for the RF. Therefore, we assume that a growth in the morbidity rate with a simultaneous decline in the mortality rate indicates that cancer is identified more effectively and more qualitative healthcare is provided for cancer patients.

Predicted MNs morbidity and mortality rates in the Irkutsk oblast were calculated by using the following equations that reflect the identified trends: the standardized rate y = 4.964x + 265.06 (R^2 = 0.931) and the 'rough' rate y = 13.326x + 359.15 (R^2 = 0.979). The prediction periods were substantiated considering the following: polynomial trends had somewhat better approximation properties than linear equations; for the standardized rate, $y = 0.114x^3 - 1.540x^2 + 9.901x + 262.7$ (R^2 = 0.977); for the 'rough' rate, $y = 0.194x^3 - 2.849x^2 + 24.213x + 350.3$ (R^2 = 0.991). Since the 'rough' rate describes an actual situation considering age- and sex-related characteristics of a population, it is advisable to make predictions relying on it. In addition, analysis of polynomial dynamics allows identifying a correct prediction 'range'. Basing on our analysis of a 16-year trend, we established that a 'step' of change equaled 7 years. Consequently, we can make 7-year predictions taking a time moment when a rise in a rate begins as our starting point. In our case, this is a medium-term prediction for the period up to 2021 (3 years).

Given all the aforementioned, we established that in 2021 the predicted standardized morbidity rate would be within 270.9–329.8 cases per 100,000 people with 95 % certainty; the 'rough' morbidity rate would very within 372.7–532.4 cases. We applied the following equations to predict dynamics of MN mortality in the Irkutsk region: y = 133.12 – 0.273x (R^2 = 0.095), which described a trend in the standardized mortality rate; and y = 185.22 + 2.851x (R^2 = 0.904), which described a trend in the 'rough' mortality rate. According to prediction calculations, in 2021 the standardized mortality rate would equal 127.1–132.2 cases per 100,000 people; the 'rough' mortality rate, 220.0–230.0 cases per 100,000 people.

We analyzed prevalence of cancer sites relying on 2018 data and established three groups of malignant neoplasms that were the most significant in the overall (both men and women) structure of cancer morbidity: malignant neoplasms of digestive organs (C15–C26), 24.2 %; melanoma and other malignant neo-

plasms of skin, 13.1 %; malignant neoplasms of respiratory organs (trachea, bronchi, lungs, and larynx), 12.8 %. Priority cancer sites included trachea, bronchi, and lungs (11.8 %) (9.9 % in the RF), skin (11.5 %; 13.1 % including melanoma) (12.6 % in the RF; 14.4 % including melanoma); breast, 10.9 % (11.4 % in the RF); prostate (7.3 %) (6.8 % in the RF); stomach (6.5 %) (5.9 % in the RF); colon (5.9 %) (6.9 % in the RF); kidney (4.8 %) (3.9 % in the RF); lymphoid and hematopoietic tissue (4.6 %) (4.8 % in the RF); rectum, rectosigmoid junction, and anus (4.4 %) (5.0 % in the RF); cervix uteri (3.7 % (2.8 % in the RF); corpus uteri (3.4 %) (4.3 % in the RF); pancreas (3.3 %) (3.1 % in the RF); urinary bladder (2.5 %) (2.8 % in the RF); ovary (2.3 %) (2.3 % in the RF); and esophagus (1.5 %).

The morbidity rates were established to be higher in the Irkutsk oblast than the national average for almost all the analyzed cancer sites (Table 4).

In 2018, the morbidity rates identified in the Irkutsk oblast were higher than the national average for 10 cancer sites: cervix uteri (the Irkutsk oblast rate is 59.4 % higher than the national average); trachea, bronchi, and lungs (55.8 % higher); kidney (54.0 % higher); prostate (49.7 % higher); esophagus (45.9 % higher); stomach (43.5 % higher); pancreas (41.7 % higher); liver and intrahepatic bile ducts (35.6 % higher); thyroid (31.1 % higher); and lymphoid and hematopoietic tissue (30.2 % higher than the national average). The morbidity rates identified for the next five cancer sites were 15–30 % higher than the national average: ovary; female breast; other malignant neoplasms of skin; urinary bladder; rectum, rectosigmoid junction, and anus. The morbidity rates identified for four following

Table 4

Standardized mortality and morbidity rates for the most common cancer sites in the Irkutsk blast and in the RF, 2018

Cancer sites	Rate per 100,000 people				Mortality / morbidity ratio		Share of differences in the rates (of the RF)
	mortality		morbidity				
	Irkutsk oblast	RF	Irkutsk oblast	RF	Irkutsk oblast	RF	
Esophagus	3.12	2.65	4.64	3.18	0.67	0.83	19.3
Stomach	11.86	9.94	19.45	13.55	0.61	0.73	16.9
Colon	8.5	7.73	17.87	15.58	0.48	0.50	4.1
Rectum, rectosigmoid junction, and anus	5.92	5.66	13.7	11.63	0.43	0.49	11.2
Liver and intrahepatic bile ducts	4.41	3.66	4.49	3.31	0.98	1.11	11.2
Pancreas	8.52	6.59	9.95	7.02	0.86	0.94	8.8
Larynx	1.5	1.58	3.29	2.91	0.46	0.54	16.0
Trachea, bronchi, and lungs	25.99	19.08	36.82	23.64	0.71	0.81	12.5
Skin melanoma	1.65	1.44	4.99	4.73	0.33	0.30	-8.6
Other malignant neoplasms of skin	0.47	0.48	33.33	27.46	0.01	0.02	19.3
Female breast	16.01	14.02	63.26	51.63	0.25	0.27	6.8
Cervix uteri	8.87	5.07	25.18	15.8	0.35	0.32	-9.8
Corpus uteri	3.9	3.98	18.7	18.79	0.21	0.21	1.5
Ovary	5.8	4.92	13.97	11.14	0.42	0.44	6.0
Prostate	17.68	12.11	62.06	41.45	0.28	0.29	2.5
Kidney	3.1	4.02	15.42	10.01	0.20	0.40	49.9
Urinary bladder	2.01	2	7.66	6.41	0.26	0.31	15.9
Brain and other and unspecified parts of central nervous system	3.54	3.61	4.92	4.45	0.72	0.81	11.3
Thyroid	0.43	0.37	8.34	6.36	0.05	0.06	11.4
Lymphoid and hematopoietic tissue	6.4	6.39	18.43	14.16	0.35	0.45	23.0
Total MNs:	**129**	**108.6**	**320.2**	**246.77**	0.40	0.44	**8.5**

cancer sites were less than 15 % higher than the national average: colon; larynx; brain and other and unspecified parts of central nervous system; skin melanoma.

The mortality rates that were higher in the Irkutsk region than the national average were identified for the following 12 cancer sites: cervix uteri; prostate; trachea, bronchi, and lungs; pancreas; liver and intrahepatic bile ducts; stomach; ovary; esophagus; thyroid; skin melanoma; female breast; colon. The highest difference between the mortality rate in the Irkutsk oblast and the national average was identified for cervix uteri cancer (75 % higher than the national average); prostate cancer (46 % higher in the Irkutsk oblast than the national average); trachea, bronchi, and lungs cancer (36.2 % higher).

Maximum mortality / morbidity ratios, both in the Irkutsk oblast and the RF in general, are typical for malignant neoplasms of liver and intrahepatic bile ducts (0.98 and 1.11 respectively), which indicates high cancer fatality rate together with ineffective detection; probably, in some cases the disease is diagnosed in the RF after a patient's death. High ratios were also identified for the following cancer sites: pancreas (0.86 and 0.94); trachea, bronchi, and lungs (0.71 and 0.81); brain (0.72 and 0.81); esophagus (0.67 and 0.83); stomach (0.73 and 0.61). Although the cancer mortality and morbidity rates tend to be higher in the Irkutsk oblast than the national average over the analyzed 10 years, their ratios are still lower than in the RF in general for most cancer sites. And although the difference is rather low if we take total MNs (8.5 %), it can reach 15–50 % for such cancer sites as kidney, lymphoid and hematopoietic tissue, esophagus, other skin MNs, urinary bladder, stomach, and larynx.

Population cancer morbidity rates are established to also depend on the age structure of population [4]; to eliminate influence of the factor, rates are usually standardized when analyzed comparatively. MNs morbidity tends to grow in the Irkutsk oblast, including both the standardized and 'rough' rate. This fact provides a relevant trend in future research, namely, identification of cause-effect relations within the 'environmental factors – cancer prevalence' system.

D.G. Zaridze and others think [3] that cancer morbidity grows in Russia due to, among other things, growing prevalence of some risk factors. Use of highly sensitive screening technologies and early diagnostics also facilitate this growth in morbidity rates, cancer morbidity included [17]. Medium or even low MNs mortality rates have been established on territories with higher living standards, available and widely applied up-to-date techniques of early diagnostics and high-tech healthcare even though cancer morbidity rates were rather high there [18]. An inverse correlation has been identified between population mortality and the number of healthcare workers (doctors) and in-hospital 'cancer' beds per capita (Buryatiya) [7].

We have analyzed the existing negative situation in the Irkutsk oblast associated with high cancer mortality and morbidity among population. So, we assume that a high morbidity rate and its growth can be caused not only by more effective detection and growing morbidity in older age groups due to population ageing and longer life expectancy but also by an actual growth in morbidity due to exposure to carcinogenic factors.

Some carcinogenic risk factors can be considered manageable, both at the individual and group or population level. According to the World Health Organization materials and data obtained in Russian research works, a substantial share of deaths due to cancer (more than 30 %) is caused by manageable (modifiable) risk factors, including tobacco smoking, alcohol abuse, low physical activity, and insufficient consumption of fruit and vegetables [4, 17, 19]. In addition, environmental exposures, occupational ones included, can also act as carcinogenic risk factors [6, 8, 20]. However, we have not found any studies with their focus on influence exerted by the whole set of factors on cancer prevalence in the Irkutsk oblast. Given that, issues of establishing carcinogenic factors become vital for the region within development and implementation of primary cancer

prevention. The latter is achieved by reducing or eliminating adverse effects of factors manageable at the population, group, and individual levels. The aforementioned tasks are ranked as the priority ones to be tackled by the Sanitary Service, the Center for Hygiene and Epidemiology, and the East-Siberian Institute of Medical and Ecological Research.

Conclusion. Therefore, assessment of individual carcinogenic risks caused by potential chemical exposure gives evidence of the existing unacceptable risk levels in Bratsk, Shelekhov, Irkutsk, Angarsk, and Usolie Sibirskoe. Risks are assessed as acceptable in Sayansk, Cheremkhovo, and Ust-Ilimsk. At the same time, the highest average annual radon dose is detected in Ust-Ilimsk (7.34 mSv/year), which calls for the risk-based approach as a basis for periodical medical examinations of workers exposed to carcinogenic occupational factors in their workplaces and mass health examinations of population. Basically, MNs morbidity and mortality rates can be considered unfavorable among the population in the Irkutsk oblast. Their values, long-term trends taken in dynamics, and cancer mortality to morbidity ratios give evidence of sufficient healthcare provided for cancer patients in the Irkutsk oblast. Predictive values that were calculated by analyzing long-term trends in the rates are going to be within the following ranges in 2021: the standardized morbidity rate, within 270.9–329.8; the 'rough' morbidity rate, within 372.7–532.4 per 100,000 people living in the Irkutsk region; the 'rough' mortality rate, within 220.0–230.0 cases.

This study allowed identifying priority tasks for the development of targeted activities aimed at eliminating or reducing adverse effects produced by carcinogenic factors on human health.

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Research article

THE THRESHOLD OF TOXICOLOGICAL CONCERN FOR INSUFFICIENTLY EXPLORED CHEMICALS OCCURRING IN DRINKING WATER DURING TRANSPORTATION

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Finding solutions to issues of drinking water safety is a significant component in activities aimed at public health protection. In accordance with sanitary-epidemiological requirements, drinking water, in particular, should be harmless as regards its chemical composition and have favorable organoleptic properties. It is especially vital to identify risk factors for public health associated with drinking water quality. Supplying high-quality drinking water to population is a relevant problem associated, among other things, with use of new materials and reagents. The major challenge posed by their hygienic assessment is a potential growth in human health risks caused by consuming tap drinking water contaminated with migrating organic compounds. Although each of them has been detected in low concentrations, they can cause adverse chronic health outcomes.

The Threshold of Toxicological Concern (TTC) is a powerful tool of risk assessment. It is based on identifying a threshold value of effects produced on human health by chemicals for which no hygienic standards have been developed so far. Below such a threshold, there is very low (95 %) likelihood of a health risk being higher than its acceptable levels. An idea of some exposure levels unable to cause adverse health outcomes is embedded in establishing maximum permissible levels (MPLs) for chemicals with known toxicological profiles. The TTC enlarges this concept by assuming that the minimum value can be identified for many chemicals based on their composition even if there is no comprehensive database on their toxicity. The TTC can be used for evaluating up-to-date materials applied in drinking water supply in order to detect risks for human health caused by consumption of drinking water that had contacts with them. Such risk assessment relies on the results of examining water extracts and involves identifying priority chemicals for their further investigation and control.

Keywords: *water supply, drinking water, hygienic assessment of polymer materials, threshold of toxicological concern, polymers, migration, water-related risk.*

Exposures to environmental factors are considered a strategic social risk in Russia. But quite often they are either neglected or comprehended incorrectly by the society due to absence of adequate and reliable data on them.

Multiple studies have established anthropogenic pollution of drinking water, together with ambient air and soil pollution, to be a substantial factor able to affect human health [1–7]. Ongoing pollution and constant development of analytical methods result in discovering new anthropogenic chemicals in drinking water sources as well as in water that has been treated until it is safe for drinking. Finding solutions to issues of drinking water safety is a significant component in activities aimed at public health protection. In accordance with sanitary-epidemiological requirements, drinking water, in particular, should be harmless as regards its chemical composition and have favorable organoleptic properties. It is especially vital to identify risk factors for public health associated with drinking water quality [1, 7]. At present, supplying high-quality drinking water to population is a relevant problem associated, among other things, with use of new materials and reagents in drinking water supply. Drinking water contains some admixtures represented by a heterogeneous group of anthropogenic compounds (for example, alkylphenols, pharmaceuticals, and microplastics); although each compound is usually identified

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in low concentrations, exposure to such mixtures can cause chronic adverse health outcomes [8–11]. In fact, even if all the components of a mixture occur in quantities, which separately are unable to cause any observed adverse effects, people still might be affected due to chronic low-level exposures able to produce additive effects thereby becoming more toxic [12, 13].

At present, the system for hygienic regulation exists in the Russian Federation. Within the system, the threshold principle covers all the exposure effects and compliance with the hygienic standards (maximum permissible levels or MPL, some others) guarantees absence of any adverse effects on human health. However, more and more chemicals are being identified worldwide, which are not covered by the established hygienic standards (they have no MPL determined for them). The concept that exposure thresholds or safe exposure levels can be identified for certain chemicals is widely used nowadays in routine practices of regulatory authorities in western countries. They rely on it when establishing acceptable daily intakes for chemicals with known chemical structure [14, 15]. The concept proposes that a low level of exposure with a negligible risk can be identified for many chemicals, including those of unknown toxicity, based on knowledge of their chemical structures [16]. Munro with colleagues used a database containing information about 613 chemical compounds explored in sub-chronic and chronic animal studies including certain industrial chemicals, pharmaceuticals, food chemicals, protection chemicals, and consumer chemicals. Later on, new studies were added into the database and now it is employed in software tools such as Toxtree (TT) and OECD Toolbox. The database is used to identify a threshold of acceptable human exposure for three structural classes and can be applied in the absence of specific toxicity data on a substance within one of them. The Threshold of Toxicological Concern (TTC) method was first introduced in the 90ties last century to facilitate assessment of hazards and risks caused by chemicals [17, 18].

The threshold of toxicological concern (TTC) is a risk assessment tool that is based on the principle of determining a human exposure threshold value for all chemicals, which do not have hygienic standards established for them. Below such a threshold, there is a very low probability of an appreciable risk to human health (95 % likelihood that any chemical belonging to a specific class does not produce any adverse effects on human health) [19, 20]. The concept that there are levels of exposure that do not cause adverse effects is inherent in setting acceptable daily intakes (ADIs) for chemicals with known toxicological profiles. The TTC principle extends this concept by proposing that a *de minimis* value can be identified for many chemicals, in the absence of a full toxicity database, based on their chemical structures and the known toxicity of chemicals, which share similar structural characteristics [21]. The TTC method compares information about a chemical dose with a threshold, below which any observed adverse effects are highly unlikely. Some chemical groups are excluded from the TTC approach, namely, heavy metals, compounds with extremely long half-life time, chemicals that have huge interspecies differences in bioaccumulation and are strong genotoxic carcinogens (aflatoxin-like substances, N-nitrosamines, azoxy compounds, steroids and polyhalogenated dibenzo-p-dioxins, polyhalogenated dibenzofurans), and proteins [20–22].

The TTC approach employs Cramer classification of chemicals to assign a chemical into one of three structural classes depending on its structure. Initially, the approach relied on a database [23] that contained results obtained for 613 chemicals in subchronic and chronic animal studies. For each substance, the 5^{th} percentile was calculated from the empirical cumulative distributions of No observed (adverse) effect level (NOAEL) (concentration) values. Subsequent application of an uncertainty factor of 100 accounting for inter- and intraspecies differences and a default adult body weight of 60 kg resulted in TTCs representing exposure levels at which a 95% chance exists that any chemical belonging to the same

class does not elicit adverse human health effects. The threshold human exposure levels identified for these three structural classes are 1800, 540 and 90 μg/person per day respectively [24–26] (Table 1).

That is, if a chemical belongs to Class 1, exposure to it in a dose lower than 1800 μg/day does not create any health risks even if there are only limited data on toxicological properties of this chemical. Body weight of an adult person is assumed to equal 60 kg; therefore, the threshold value can also be given as 30 μg/kg of body weight per day.

Exposure thresholds identified for each TTC level are based on evaluations of available data on chemicals toxicity at each level. However, it is generally accepted that those chemicals without any available data on their toxicity can be assigned to a relevant TTC level based on their chemical structure.

Researchers determined the lowest TTC levels to be equal to 0.15 μg/day (0.0025 μg/kg of body weight per day). Any chemical, for which there is information about its toxicity / mutagenic effects, is assigned into this category [24, 27].

Chemicals that are not potential mutagens and / or carcinogens, organic fluorine compounds or carbamates are assigned into one of three structural classes based on Cramer Decision tree[1]. The tree includes 33 questions that employ established ways of metabolic deactivation and activation and data on toxicity. The Decision tree was created in such a way so that chemicals not covered by the TTC approach are excluded at an early stage. Use of the Decision tree ensures the well-structured approach that makes it possible to sequentially apply the TTC method to assess chemical risks. The databases are constantly updated [28, 29] but since they can fail to include certain chemicals, the latter should not be considered as per this principle.

Cramer structural classes were identified in the following way: Cramer class 1 includes substances of simple chemical structure with known metabolic pathways and low potential toxicity. Cramer class 2 includes substances that are intermediate; they possess structures that are less innocuous than those in Class 1 but they do not contain structural features that are suggestive of toxicity like those in Class 3. Cramer class 3 contains substances with chemical structures that permit no strong initial impression of safety and may even suggest a significant toxicity. Therefore, assigning a chemical into one of these three Cramer classes is an important step in maintaining risk assessment reliability.

Several software platforms were based on the obtained information. They allow achieving minimal subjectivity and sequentially applying Cramer Decision tree for any chemical that should be assessed. The Decision tree was employed in software tools including Toxtree (TT) [30] and OECD Toolbox (TB) [31]. There were certain inconsistencies between TT and TB. In total, 165 chemicals (16 %) turned out to have different results in these two programs. Crucial control points are being revealed in the Decision tree; there are ongoing discussions as regards strategies and recommendations on how to identify a Cramer class for various chemicals [31, 32].

Table 1

TTC values within classification of chemicals

Classification	TTC, μg/day	TTC, μg/kg of body weight per day
Potential mutagens and /or carcinogens	0.15	0.0025
Organic fluorine compounds and carbamates with anti-cholinesterase activity	18	0.3
Cramer class 3	90	1.5
Cramer class 2	540	9.0
Cramer class 1	1800	30

[1] TOXNET Databases. Available at: https://toxnet.nlm.nih.gov/cpdb/ (February 15, 2023).

Toxtree is a user-friendly open source application. Its development was ordered by the European Chemical Agency of the Joint Research Center of the European Commission exclusively for determining a Cramer class of a chemical substance and estimating its relative toxic hazard. Later Toxtree versions included some additional options such as mucosa irritation, BfR / SICRET and Verhaar [33].

OECD QSAR Toolbox was ordered by the Organization for Economic Cooperation and Development (OECD). Cramer classification was included into it as a module. Although both these systems were developed based on the same Cramer Decision tree, each rule might be interpreted differently in each of them[2].

Some foreign organizations such as Health Canada[3], Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS)[4], and Food Standards Australia New Zealand (FSANZ) [34] consider TTC a powerful tool for identifying priorities and performing risk-based screening. The Toxic Substances Control Act (TSCA) obliges the US Environmental Protection Agency (US EPA) to determine priority of chemicals in trade based on risks posed by them and then assess health risks caused by high-priority substances. Such assessments combine data obtained by toxicological studies and information about exposures [22]. The TTC approach can be used as a filter to determine the necessity of a toxicological study and its order of priority and avoid conducting such studies if an exposure level of a chemical in humans is far below the concentration needed for it to have any biological effect. Such a situation is labeled as 'negligible exposure' in the REACH legislation. The studies [19, 35] highlight a likely decrease in animal studies as a result of active TTC use.

The TTC approach is applied to evaluate safety of cosmetic ingredients and ingredients in personal and household products [36–38]. The European Food Safety Agency relies on TTC to evaluate levels of pesticides in groundwater [39]. Independent non-food Scientific Committees (SCCP, SCHER, and SCHENIHR) assessed potential TTC use and concluded that the approach was scientifically eligible for assessing non-carcinogenic risks for human health caused by exposure to chemicals in trace quantities [40]. The TTC approach is also used to assess food products safety (flavoring agents); for mixtures of substances; to identify internal exposure to chemicals (iTTC) [41]; for plant extracts (Botanical-TO); to identify the ecological threshold of toxicological concern (eco-TTC) [42–44].

In the Netherlands a clear and consistent approach called 'Drinking Water Quality for the 21st century (Q21)' has been developed within the joint research program of the drinking water companies. Target values for anthropogenic drinking water contaminants were derived by using the Threshold of Toxicological Concern (TTC) approach [45]. The target values for individual genotoxic and steroid endocrine chemicals were set at 0.01 μg/l. For all other organic chemicals the target values were set at 0.1 μg/l. The target value for the total sum of genotoxic chemicals, the total sum of steroid hormones and the total sum of all other organic compounds were set at 0.01, 0.01 and 1.0 μg/l, respectively.

The studies [46, 47] set the following chemical levels for drinking water supply: 37 μg/l for Cramer class 1 substances and 4 μg/l for Cramer class 3 substances; for Cramer class 3 substances with reproductive toxicity, 3 μg/l. The authors believe it is essential to assess toxicological risks posed by pollutants in drinking water sources since it helps identify potential health risks and determine priority of chemicals for further investigation and monitoring. Calculations performed in the studies [45–47] either rely on a person consuming 2 liters of water per day, or consider 10 % admissible daily contribution made by water for substances with threshold effects, or non-threshold lifetime risk of cancer reaching $10^{(-6)}$.

[2] The OECD QSAR Toolbox. Available at: https://www.oecd.org/chemicalsafety/oecd-qsar-toolbox.htm (March 17, 2023).
[3] Health Canada. *Government of Canada*. Available at: https://www.canada.ca/en/health-canada.html (March 18, 2023).
[4] Australia's National Industrial Chemicals Notification and Assessment Scheme (NICNAS). Available at: https://www.nicnas.gov.au/ (March 18, 2023).

Therefore, **the aim of this study** was to test whether it was possible to apply the TTC approach to evaluate materials used in drinking water supply. The task was to reveal likely risks for public health caused by consumption of drinking water that had contacts with a polyethylene coated woven hose used within reconstruction of drinking water pipelines. To do that, we evaluated the results yielded by examining water extracts.

Materials and methods. In this study, we examined a polyethylene coated woven hose designed for reconstruction of drinking water pipelines, thermal water supply, communal and industrial sewage networks. Its use was examined by analyzing water extracts derived from samples under aggravated conditions.

Ready samples were represented by white hose cuts with a smooth inner polyethylene coated surface and an outer surface made of a synthetic woven material. The samples were evaluated considering the Unified Requirements[5]; we also examined some indicators that were not mandatory within assessment of polymer materials used in drinking water supply.

Prior to any tests, the samples were prepared in accordance with the Methodical Guidelines MU 2.1.4.2898-11 Sanitary-Epidemiological Examinations (Tests) of Materials, Reagents, and Equipment used for Water Treatment[6]. The ratio of a surface of an examined material and a contacting water volume was 1 cm^2 per 1 cm^3. Distilled water was used as initial one to prepare water extracts. The extracts were derived under +20 °C and +37 °C. The aforementioned water types were used as controls to ensure adequacy of hygienic assessment. Samples of test (water extracts) and control water were examined to identify and quantify low volatile organic compounds on the 5th and 7th day of the experiment by using chromato-mass-spectrometry.

Results and discussion. Our analysis of a 5-day water extract from a polyethylene coated woven hose identified 22 organic compounds under 37 °C and 15 organic compounds under 20 °C. Most compounds were identified in low concentrations; maximum permissible levels in water were not established for some of them. The identified compounds mostly belonged to oxygen-containing ones; it is noteworthy, that we detected phenols and aldehydes, ketones, organic acids, complex ethers, and phthalates. Moreover, we identified nitrogen- and fluorine-containing compounds used in chemical industry, such as benzotiazol in a level equal to 0.102 mg/l. According to chromato-mass-spectrometry data, the following substances were identified in the highest concentrations, apart from benzotiazol: tetrahydrofurfuryl ether (0.437 mg/l under 37 °C and 0.088 mg/l under 20 °C) and di-tert-butyl-oxaspiro-decadiendion (0.345–0.136 mg/l), both substances not standardized in drinking water.

Our analysis of a 7-day water extract identified 15 organic compounds under

37 °C and 12 organic compounds under 20 °C. The identified substances were in low concentrations and maximum permissible levels in drinking water were not established for most of them. According to chromato-mass-spectrometry data, the following substances were identified in the highest concentrations: pentadecanols, hexadecanols, 2,4 di-tert-butylphenol, di-tert-butyl-oxaspiro-decadiendion, di-tert-butyl benzochinon; all these substances were not standardized in drinking water.

Therefore, chromato-mas-spectrometry identified a wide range of chemicals in water extracts, most of them though in low levels; still,

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[5] Edinye sanitarno-epidemiologicheskie i gigienicheskie trebovaniya k produktsii (tovaram), podlezhashchei sanitarno-epidemiologicheskomu nadzoru (kontrolyu), utv. Resheniem Komissii Tamozhennogo soyuza ot 28 maya 2010 goda № 299 [The Unified Sanitary-Epidemiological and Hygienic Requirements to products (goods) subject to sanitary-epidemiological surveillance (control), approved by the Decision of the Customs Union Commission on May 28, 2010 No. 299]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/902249109 (April 11, 2023) (in Russian).

[6] MU 2.1.4.2898-11. Sanitarno-epidemiologicheskie issledovaniya (ispytaniya) materialov, reagentov i oborudovaniya, ispol'zuemykh dlya vodoochistki i vodopodgotovki: metodicheskie ukazaniya, utv. Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii i vvedeny v deistvie 12.07.2011 [Sanitary-Epidemiological Examinations (Tests) of Materials, Reagents, and Equipment used for Water Treatment: Methodical Guidelines, approved by the Head of the Federal Service for Surveillance over Consumer Rights Protection, the RF Chief Sanitary Inspector; came into force on July 12, 2011]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200089967 (April 11, 2023) (in Russian).

it is noteworthy that maximum permissible levels in drinking water are not established for most of them. Our tests also showed that intensity of migration is influenced by many factors; in our case, the experiment involved different time of contacts with water and different temperatures.

The next task was to determine possible effects on health produced by the chemicals identified in water extracts from a polyethylene coated woven hose designed for reconstruction of drinking water pipelines. To do that, we determined Cramer classes of the identified chemicals without any hygienic standards established for their level in drinking water using Toxtree and OECD Toolbox software (Table 2).

Table 2

Cramer's classes of the chemicals identified in the analyzed water extracts determined by using Toxtree and OECD Toolbox

No.	Chemical	CAS	Cramer class, Toxtree	Cramer class, Toolbox
1.	Tetradecene	1120-36-1	Low (Class 1)	Low (Class 1)
2.	Trimethyl-1-dodecanol	6750-34-1	No data available on the chemical	No data available on the chemical
3.	Phenoxyethanol	122-99-6	Intermediate (Class 2)	Intermediate (Class 2)
4.	2,4- di-tert-butylphenol	96-76-4	Low (Class 1)	Low (Class 1)
5.	Cyclopentanone	120-92-3	Intermediate (Class 2)	Intermediate (Class 2)
6.	2-cyclopentyl cyclopentanone	4884-24-6	No data available on the chemical	Intermediate (Class 2)
7.	2-cyclopentiliden-cyclopentanone	825-25-2	No data available on the chemical	Intermediate (Class 2)
8.	Tributyl acetylcitrate	77-90-7	Extended Cramer rules with Low (Class 1). Updated Cramer Decision tree High (Class 3)	Low (Class 1)
9.	Methyl ether of 3-oxo-2-pentylcyclopentane-acetic acid	24851-98-7	Intermediate (Class 2) Updated Cramer Decision tree Low (Class 1)	High (Class 3)
10.	Diisobutyl phthalate	84-69-5	Low (Class 1) skin-irritating	Low (Class 1)
11.	Oxaspirodecadiendion-di-tert-butyl	82304-66-3	No data available on the chemical	No data available on the chemical
12.	2,5-di-tert-butyl-1,4-benzochinon	2460-77-7	No data available on the chemical	Intermediate (Class 2)
13.	4-methyl-8-aminochinoline	62748-01-0	No data available on the chemical	High (Class 3)
14.	Tetramethylindol	27505-79-9	No data available on the chemical	No data available on the chemical
15.	Nitrosomethane	865-40-7	No data available on the chemical	High (Class 3)
16.	(3 5-dimethyl-1-piperidinyl) (4-mopholil)methanone	349118-92-9	No data available on the chemical	No data available on the chemical
17.	Benzotiazol	95-16-9	High (Class 3) Updated Cramer Decision tree Intermediate (Class 2)	High (Class 3)
18.	Tetradecane	629-59-4	Low (Class 1)	Low (Class 1)
19.	5-tridecene	25524-42-9	No data available on the chemical	No data available on the chemical
20.	2,4-di-tert-butylphenol	96-76-4	Low (Class 1)	Low (Class 1)
21.	3,5-di-tert-butyl-4-hydroxybenzaldehyde	1620-98-0	No data available on the chemical	High (Class 3)
22.	Hexadecane acid	57-10-3	Low (Class 1)	Low (Class 1)
23.	Butoxyethoxy ethyl acetate	124-17-4	Low (Class 1)	Low (Class 1)
24.	Propylene carbonate	108-32-7	High (Class 3) Revised Cramer Decision tree Low (Class 1)	High (Class 3)
25.	Complex ether of propionic acid	74381-40-1	No data available on the chemical	No data available on the chemical
26.	1 6-dioxacyclododecane-7 12-dione	777-95-7	No data available on the chemical	Low (Class 1)

We did not find any information about 6 substances that would allow assigning them into one of the aforementioned classes. These chemicals are not included into the IARC classification of carcinogens either.

Tables 3 and 4 provide results of comparisons between the levels of the chemicals identified in the analyzed water extracts and the threshold of toxicological concern, below which there is a very low probability of an appreciable risk to human health. The detected concentrations (mg/l) were recalculated into dose values (μg/day) basing on the assumption that a person on average consumes 3 liters of water per day (as established in the Methodical Guidelines MU 2.1.5.720-98 Substantiation of Hygienic Standards for Chemicals in Drinking and Household Water[7]). The concentrations of the identified chemicals were taken from the series of tests conducted under 37 °C as the most aggravated conditions. In a situation, when use of two different software packages, Toxtree and OECD Toolbox, yielded different results, a substance was assigned into a higher Cramer class out of two.

Table 3

Indicators that describe quality of water (water extracts) in a statics experiment in comparison with the threshold of toxicological concern for these substances (distilled water; in a contact with the analyzed material for 5 days; water temperature is 37 ± 0.5 °C)

No.	Chemical	CAS	Level, mg/l	Cramer class	TTC, μg/day, not higher than	Intake with drinking water, μg/day
1	Tetradecene	1120-36-1	0.005	Low (Class 1)	1800	15
2	Trimethyl-1-dodecanol	6750-34-1	0.008	No data available on the chemical		
3	Phenoxyethanol	122-99-6	0.023	Intermediate (Class 2)	540	69
4	2,4- di-tert-butylphenol	96-76-4	0.014	Low (Class 1)	1800	42
5	Cyclopentanone	120-92-3	0.007	Intermediate (Class 2)	540	21
6	2-cyclopentyl cyclopentanone	4884-24-6	0.092	Intermediate (Class 2)	540	276
7	2-cyclopentiliden-cyclopentanone	825-25-2	0.046	Intermediate (Class 2)	540	138
8	Tributyl acetylcitrate	77-90-7	0.012	High (Class 3)	90	36
9	Methyl ether of 3-oxo-2-pentylcyclopentane-acetic acid	24851-98-7	0.015	High (Class 3)	90	45
10	Diisobutyl phthalate	84-69-5	0.051	Low (Class 1)	1800	153
11	Oxaspirodecadiendion-di-tert-butyl	82304-66-3	0.345	No data available on the chemical		
12	2,5-di-tert-butyl-1,4-benzochinon	2460-77-7	0.014	Intermediate (Class 2)	540	42
13	4-methyl-8-aminochinoline	62748-01-0	0.032	High (Class 3)	90	96
14	Tetramethylindol	27505-79-9	0.017	No data available on the chemical		
15	Nitrosomethane	865-40-7	0.01	High (Class 3)	90	30
16	(3 5-dimethyl-1-piperidinyl) (4-mopholil)methanone	349118-92-9	0.091	No data available on the chemical		

[7] MU 2.1.5.720-98. Obosnovanie gigienicheskikh normativov khimicheskikh veshchestv v vode vodnykh ob"ektov khozyaistvenno-pit'evogo i kul'turno-bytovogo vodopol'zovaniya, utv. i vved. v deistvie Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii 15 oktyabrya 1998 goda [Substantiation of Hygienic Standards for Chemicals in Drinking and Household Water, approved and put in force by the RF Chief Sanitary Inspector on October 15, 1998]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200006903 (April 12, 2023) (in Russian).

Table 4

Indicators that describe quality of water (water extracts) in a statics experiment in comparison with the threshold of toxicological concern for these substances (distilled water; in a contact with the analyzed material for 7 days; water temperature is 37 ± 0.5 °C)

No.	Chemical	CAS	Level, mg/l	Cramer class	TTC, µg/day, not higher than	Intake with drinking water, µg/day
1	Tetradecene	629-59-4	0.015	Low (Class 1)	1800	45
2	5-tridecene	25524-42-9	0.028	No data available on the chemical		
3	Pentadecanols (3 isomer compounds)	629-76-5	0.050	Low (Class 1)	1800	150
4	Hexadecanol (2 isomer compounds)	36653-82-4	0.049	Low (Class 1)	1800	147
5	2,4- di-tert-butylphenol	96-76-4	0.034	Low (Class 1)	1800	102
6	3,5-di-tert-butyl-4-hydroxybenzaldehyde	1620-98-0	0.008	High (Class 3)	90	24
7	6,8-dioxapentadecane	-	0.018	No data available on the chemical		
8	Hexadecane acid	57-10-3	0.043	Low (Class 1)	1800	129
9	Butoxyethoxy ethyl acetate	124-17-4	0.012	High (Class 3)	90	36
11	Propylene carbonate	108-32-7	0.037	High (Class 3)	90	111
12	Complex ether of propionic acid	74381-40-1	0.033	No data available on the chemical	-	-
13	Methyl ether of 3-oxo-2-pentylcyclopentane-acetic acid	24851-98-7	0.032	High (Class 3)	90	96
14	Oxaspirodecadiendion-di-tert-butyl	82304-66-3	0.050	No data available on the chemical	-	-
15	2,5-di-tert-butyl-1,4-benzochinon	2460-77-7	0.037	Intermediate (Class 2)	540	111
16	1 6-dioxacyclodo-decane-7 12-dione	777-95-7	0.005	Low (Class 1)	1800	15
17	Hexadecane acid	57-10-3	0.014	Low (Class 1)	1800	42

Our analyses of the test data revealed that levels of some chemicals in water extracts, including 4-methyl-8-aminochinoline (in tests on 5-day extracts), propylene carbonate, and methyl ether of 3-oxo-2-pentylcyclopentane-acetic acid (in tests on 7-daty extracts) were higher than the threshold of toxicological concern after the identified concentrations were recalculated into dose values. These findings are evidence of likely health risks. Chemical concentrations higher than TTC indicate the necessity to search for new data and to conduct toxicological experiments to collect an evidence base proving their safety. Therefore, our study findings do not allow absolute certainty in confirming it is safe to use the examined polyethylene coated woven hose in drinking water supply.

Conclusion. The major challenge in hygienic assessment of up-to-date materials is a potential growth in health risks associated with drinking tap water, which is polluted with migrating organic compounds [48, 49]. It is impossible to achieve complete absence of any pollutants in supplied drinking water since modern analytical procedures allow identifying even very low concentrations; it hardly seems possible to prevent migration completely either given the contemporary levels of industrial development. New plasticizers are being developed at the moment; there is ongoing search for compounds able to provide good mechanical properties of a material but with limited or even zero migration, resistance to extraction, and low volatility.

At present, the TTC use to evaluate materials applied in drinking water supply allows identifying possible health risks for human health caused by consuming drinking water that had contacts, among other things, with polymers. Such evaluations are based on analyzing results obtained by examining water extracts.

The issue of calculating a dose of a chemical intake with water remains open for discussion. In this study, we calculated intake doses relying on likely consumption equal to 3 liters of water per day in accordance with the Methodical Guidelines MU 2.1.5.720-98 Substantiation of Hygienic Standards for Chemicals in Drinking and Household Water[7]. Therefore, the upper limit of TTC-based levels in drinking water is 30 μg/liter for chemicals assigned into the high Class 3. Given possible effects on the reproductive function and likely long-term health outcomes, the threshold for drinking water should be set at 0.03 μg/liter. The Guide Human Health Risk Assessment from Environmental Chemicals (R 2.1.10.1920-04[8]) calculates health risks relying on daily water consumption of 2 liters, therefore, the upper limit of chemical levels will grow.

In this study, we conducted hygienic assessment of a polyethylene coated woven hose; as a result, it is not deemed to comply with the EAEU Unified Sanitary-Epidemiological and Hygienic Requirements to Goods Subject to Sanitary-Epidemiological Surveillance (Control). It is not safe to use it in drinking water pipelines due to migration of organic compounds without any hygienic standards established for their levels in drinking water as well as due to elevated turbidity and inadequate color of the examined water extracts (the latter indicators were not analyzed in this study).

Basic uncertainties in the present study are as follows. First, extracts from polymer pipes can be considered similar to drinking water only conditionally. Second, we relied on using standard exposure factors for a general population without considering the most sensitive population groups. Third, we used maximum levels of the analyzed chemicals in our calculations and this might result in risk overestimation. On the other hand, we did not consider summated exposure to all the analyzed chemicals in this study; due to this fact, a health risk caused by combined exposure to all the analyzed chemicals is considered negligible.

Therefore, the TTC approach is a quite simple practical tool that allows assessing health risks caused by exposure to unregulated and understudied chemicals compounds with unknown toxicological properties occurring in drinking water. It also draws attention to chemicals with expected high toxicity and allows more precise evaluation of materials, reagents and equipment for water treatment, which considers likely health risks caused by their use.

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Competing interests. The authors declare no competing interests.

[8] The Guide 2.1.10.1920-04. Human Health Risk Assessment from Environmental Chemicals, approved and put into force by G.G. Onishchenko, the First deputy to the RF Minister of Health, the RF Chief Sanitary Inspector on March 5, 2004. *KODEKS: electronic fund for legal and reference documentation.* Available at: https://docs.cntd.ru/document/1200037399 (April 12, 2023) (in Russian).

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Research article

ASSESSING RISKS OF HEPATOBILIARY DISORDERS IN CHILDREN UNDER COMBINED EXPOSURE TO PERSISTING HERPES AND TECHNOGENIC CHEMICALS

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Chronic persistent viral infection leads to developing immune deficiency and may induce lesions in many organs, the hepatobiliary system included. This, in its turn, may facilitate the onset of diseases of the digestive system under exposure to technogenic chemicals, especially those able to produce hepatotoxic effects.

In this study, our aim was to examine risks of developing hepatobiliary disorders in children under combined exposure to persisting herpes infection and technogenic chemicals.

We conducted a clinical examination of 324 children aged between 6 and 17 years living either in a large industrial city or on a territory where the sanitary-hygienic situation was favorable. The examination included a clinical checkup, laboratory diagnostic tests identifying herpes markers, chemical analyses aimed at establishing levels of technogenic chemicals in blood, and ultrasound scanning of hepatobiliary organs.

We established that exposure to airborne technogenic chemicals created elevated levels of aromatic hydrocarbons and formaldehyde in 64.9–97.6 % of the exposed children; elevated manganese and chromium levels, in 20.8–34.6 % of them. Markers of cytomegalovirus (CMV) and Epstein Barr virus (EBV) were detected in 75 % of the exposed children; each second child had HSV-1 or HSV-2; each third child had human herpesvirus 6. Hepatobiliary disorders occurring under combined exposure to persistent herpes and technogenic chemicals were represented by structural liver changes in 30.8 % of the examined children; abnormally shaped gallbladder or reactive changes in its walls and dyscholia, in 15.7–48.8 %;. These disorders entail elevated levels of direct bilirubin and greater ALT against imbalance of oxidant and antioxidant systems and manifest themselves as biliary pathology in 69.5 % of cases. Exposed children with persistent herpes infection have 1.2–2.3 times higher likelihood of developing structural changes in the liver and gallbladder pathology and up to 4.3 times higher risks of biliary dysfunction and chronic gastroduodenitis.

Keywords: *children, hepatobiliary disorders, relative risk, persistent herpes, technogenic chemicals, HSV (herpes simplex virus), cytomegalovirus, Epstein Barr virus, hepatotoxicity.*

At present, prevalence of gastrointestinal disorders among children remains high, both in Russia and worldwide [1–7]. Functional disorders of the gastrointestinal tract usually occur in preschoolers and tend to have continuous recurrent clinical course. In adolescence, this may lead to chronic gastroduodenal and hepatobiliary pathology, which, in its turn, results in much poorer quality of life for children and adolescents [1, 8–11].

Nowadays, well-developed transport infrastructure and growing production volumes create substantial chemical pollution of the environment [12, 13]. According to the WHO, ambient (outdoor) air pollution is the second significant factor able to cause non-communicable diseases

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[14]. Multiple epidemiological studies report that population morbidity, that of gastrointestinal disorders included, tends to be higher in RF regions with highly developed industry [15–17].

Anthropogenic environmental pollutants are mostly introduced into the body orally and / or by inhalation. They are removed from the body by detoxification that takes place predominantly in the liver. Damage to the latter can be associated not only with hepatotoxic effects of xenobiotics but also products of their biotransformation [15, 16, 18, 19]. Technogenic chemicals, apart from their ability to affect target organs directly, can also disrupt the endocrine regulation, induce depletion of energy and plastic resources of various organs and systems in the body and, consequently, facilitate development of various pathologies [19–21].

At present, herpes infection is widely spread among all population groups due to its persistence and long-term symptomless circulation of herpes viruses in the human body starting from childhood [22–25]. Herpes viruses are known to be able to induce functional immunodeficiency thereby facilitating chronic inflammation; they are also able to affect lymphoid tissue cells and liver cells inducing dystrophic changes of hepatocytes and cholestasis in the latter [24–29].

According to some researchers, infectious epidemic processes are changing under the contemporary conditions. Infectious pathologies have been shown to be more prevalent on territories with high levels of technogenic environmental pollution and they tend to be chronic there more frequently [30, 31]. However, little attention has been paid to examining peculiarities of herpes infection under exposure to anthropogenic environmental factors.

Therefore, it seems relevant to examine how hepatobiliary disorders develop in children with herpes infection under exposure to airborne technogenic chemicals.

The aim of this study was to examine risks of developing hepatobiliary disorders in children under combined exposure to persistent herpes infection and technogenic chemicals.

Materials and methods. To examine peculiarities of hepatobiliary disorders, we performed clinical examination of 213 children who were selected by random sampling (46.9 % boys and 53.1 % girls, the mean age being 9.84 ± 0.21 years). The children lived on a territory with developed industry in the Perm Krai where ambient air was polluted with aromatic hydrocarbons (benzene and xylenes), average daily levels of formaldehyde were 1.7 times higher and average manganese levels were 4.8 times higher than the established reference levels under chronic inhalation exposure (RfC_{chr}) ($p < 0.05$); average daily chromium levels were 2.6 times higher than on the reference territory ($p < 0.05$). The reference group was made of 111 children (54.1 % boys and 45.9 % girls, the mean age being 9.49 ± 0.29 years) living on a territory where the sanitary situation was relatively favorable. Both groups were comparable in terms of social indicators and sex ($p = 0.219–0.339$). An acute respiratory infection, any exacerbation of a chronic somatic pathology or an organic pathology of the nervous system detected during the clinical examination was used as an exclusion criterion.

The performed clinical examination conformed to the ethical principles stated in the Declaration of Helsinki (with 2008 alterations and addenda) and the RF National Standard GOST R 52379-2005 Good Clinical Practice (ICH E6 GCP)[1]. It was approved by the Ethics Committee of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies (The Meeting Report no. 8, 2021). Prior to the study, legal representatives of the examined children gave their informed voluntary consent to medical interventions.

The clinical examination of the children included medical and social questioning, checkups by a pediatrician and gastroenterologist, analysis of child's medical records (the Form no. 112/u and no. 026/y-2000), laboratory diag-

[1] GOST R 52379-2005. Good Clinical Practice (GCP): the RF National Standard; approved by the Order of the Federal Agency on Technical Regulation and Metrology on September 27, 2005 no. 232-st. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200041147 (June 10, 2023) (in Russian).

nostics (complete blood count, biochemical blood tests, ELISA tests to identify IgG titers to herpes simplex virus 1 and 2 (HSV1,2), cytomegalovirus (CMV), NA-antigens of Epstein – Barr virus (EBV-NA), PCR of buccal epithelium swabs to identify DNA of human herpesvirus 6 (HHV6), cytomegalovirus (CMV), and Epstein – Barr virus (EBV)) and chemical blood analyses. Laboratory diagnostics was accomplished according to conventional procedures; changes in the analyzed indicators were evaluated in comparison with their age-specific physiological norms.

Chemical analyses of technogenic chemicals levels in biological media (blood) were accomplished in accordance with the Methodical Guidelines MUK 4.1.765-99 Quantification of aromatic hydrocarbons (benzene, toluene, ethyl benzene, o-,m-,p-xylene) in biological media (blood) by using gas chromatography, MUK 4.1.2108-06 Determination of phenol mass concentration in biological media (blood) by using gas chromatography, MUK 4.1.2111-06 Identification of mass concentrations of formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde, and acetone in blood samples by using high performance liquid chromatography, MUK 4.1.3230-14 Identification of mass concentrations of chemicals in biological media (blood and urine) by using inductively coupled plasma mass spectrometry[2]. Levels of chemicals in the examined children's biological media were compared with the regional background levels of the same chemicals identified in blood of the children from the reference group who lived on an ecologically clean territory in the Perm Krai.

The study involved evaluating sizes, state and functional peculiarities of hepatobiliary organs. To do that, we performed ultrasound scanning of the liver, gallbladder, extrahepatic biliary tree, and visceral lymph nodes in the abdominal cavity according to conventional procedures on Vividq premium ultrasound system (GE Vingmed Ultrasound AS, Norway) using both convex (1.8–6.0 MHz) and linear transducer (4.0–13.0 MHz). Linear sizes of the examined organs were evaluated as per the standards suggested by I.V. Dvoryakovskiy with colleagues[3].

The obtained data were analyzed using conventional methods of descriptive statistics. We calculated odds ratio (*OR*) and relative risk (*RR*) of hepatobiliary pathology and their 95 % confidence intervals (CI), authenticity of their bottom limit being above 1.0. Cause-effect relations were established by mathematical modeling that relied on univariate dispersion analysis. We used the Fisher's test (*F*), determination co-

[2] MUK 4.1.765-99. Gazokhromatograficheskii metod kolichestvennogo opredeleniya aromaticheskikh uglevodorodov (benzol, toluol, etilbenzol, o-,m-,p-ksilol) v biosredakh (krov') [Quantification of aromatic hydrocarbons (benzene, toluene, ethyl benzene, o-,m-,p-xylene) in biological media (blood) by using gas chromatography]: Methodical Guidelines, approved by G.G. Onishchenko, the RF Chief Sanitary Inspector on July 6, 1999. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200039012 (May 06, 2023) (in Russian); MUK 4.1.2108-06. Opredelenie massovoi kontsentratsii fenola v biosredakh (krov') gazokhromatograficheskim metodom [Determination of phenol mass concentration in biological media (blood) by using gas chromatography], 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 August 9, 2006. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200065240 (May 06, 2023) (in Russian); MUK 4.1.2111-06. Izmerenie massovoi kontsentratsii formal'degida, atsetal'degida, propionovogo al'degida, maslyanogo al'degida i atsetona v probakh krovi metodom vysokoeffektivnoi zhidkostnoi khromatografii [Identification of mass concentrations of formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde, and acetone in blood samples by using high performance liquid chromatography], 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 August 9, 2006. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200065243 (May 06, 2023) (in Russian); MUK 4.1.3230-14. Izmerenie massovykh kontsentratsii khimicheskikh elementov v biosredakh (krov', mocha) metodom mass-spektrometrii s induktivno-svyazannoi plazmoi [Identification of mass concentrations of chemicals in biological media (blood and urine) by using inductively coupled plasma mass spectrometry], approved by A.Yu. Popova, the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing and the RF Chief Sanitary Inspector on December 19, 2014. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/495856222 (May 06, 2023) (in Russian).

[3] Ul'trazvukovaya anatomiya zdorovogo rebenka: prakticheskoe rukovodstvo [The ultrasound anatomy of a healthy child: practical guide], the 1st ed. In: I.V. Dvoryakovskii ed. Moscow, Firma-STROM LLC Publ., 2009, 384 p. (in Russian).

efficient (R^2), and the Student's t-test with the statistical significance level taken at $p \leq 0.05$[4].

Results and discussion. The results obtained by chemical analyses of the examined children's biological media revealed aromatic hydrocarbons in their blood ($p < 0.05$). Mean levels of benzene, toluene, and p-, м-xylene were 1.2–4.25 times higher in the children from the test group ($p = 0.013–0.00009$). Two thirds of the children had elevated benzene and p-, m-xylene levels in their blood and elevated toluene levels were detected in 92.1 % of the cases; the same indicators were identified 1.2–1.8 times less frequently in the reference group ($p = 0.004–0.0001$) (Table 1).

Biological media of 19.4–26.3 % of the examined children were contaminated with phenol ($p = 0.157$). Mean formaldehyde levels were statistically significantly higher than the background levels ($p < 0.05$) practically in all the examined children (95.8–97.6 %) and were 1.2 times higher in the test group against the reference one ($p = 0.019$).

Levels of metals were within their background range in the examined children's blood; however, they tended to be 1.2 times higher in the test group against the reference one ($p = 0.033–0.0001$). The children from the test group had elevated manganese levels in blood 2.2 times more frequently than those from the reference group (20.8 % against 9.6 % accordingly, $p = 0.015$); elevated chromium levels were detected in them 1.4 times more frequently (34.6 % against 24.3 %, $p = 0.077$).

Analyses of throat swabs by the polymerase chain reaction revealed human herpesvirus 6 (HHV6) in practically each third examined child; Epstein – Barr virus, in each third examined child; cytomegalovirus, in singleton cases ($p = 0.466–0.804$). The detected viral loads of HHV6, EBV, and CMV DNA did not have any significant differences between the groups ($p = 0.107–0.862$).

Three quarters of the children in the test group and 2/3 of the children in the reference group had IgG antibodies to CMV antigens and EBV-NA ($p = 0.251–0.291$). The number of children with IgG antibodies to HSV1 and HSV2 antigens was 1.2 times higher in the test group ($p = 0.421$) and HSV1 and HSV2 IgG levels were 1.5 times higher in blood serum in the test group against the reference one ($p = 0.00004$) (Table 2).

Table 1

Mean levels of technogenic chemicals in the examined children's blood, mg/dm^3

Chemical	Background level	The test group	The reference group	Validity of intergroup differences (p)
Benzene	0	0.0034 ± 0.00019*	0.0008 ± 0.0001*	0.00009
Toluene	0	0.0023 ± 0.00021*	0.0019 ± 0.00014*	0.0019
O-xylene	0	0.0032 ± 0.0003*	0.0043 ± 0.0005*	0.032
P-, m-xylene	0	0.0036 ± 0.0003*	0.0026 ± 0.0004*	0.013
Phenol	0.0037–0.01	0.0059 ± 0.001	0.0057 ± 0.001	0.703
Formaldehyde	0.005–0.0076	0.041 ± 0.002*	0.033 ± 0.001*	0.019
Manganese	0.009–0.017	0.014 ± 0.0004	0.012 ± 0.0004	0.033
Chromium	0.0007–0.0047	0.0047 ± 0.0003	0.0039 ± 0.0002	0.0001

Note: * means differences from the background level are authentic ($p < 0.05$).

Table 2

Mean levels of IgG antibodies to herpesvirus antigens in blood serum of the examined children, *Me* [25; 75], arbitrary units

Herpesvirus markers	The test group	The reference group	Validity of intergroup differences (p)
HSV1,2 IgG, a.u.	0.68 [0.45; 5.39]	0.45 [0.25; 5.13]	0.00004
CMV IgG, a.u.	2.06 [1.09; 3.00]	2.26 [0.73; 4.37]	0.304
EBV-NA IgG, a.u.	72.21 [16.07; 111.48]	67.74 [0.87; 144.38]	0.771

[4] Chetyrkin E.M. Statisticheskie metody prognozirovaniya [Statistical forecasting procedures]. Moscow, Statistika, 1977, 356 p. (in Russian).

Each second child was established to have markers of several herpesviruses ($p = 0.632$).

The clinical examination revealed gastrointestinal pathology in 84.5–81.1 % of the examined children ($p = 0.436$); within its structure, biliary disorders were identified in 69.5 % of the cases in the test group and this was 1.2 times more frequent than in the reference group (57.7 %, $p = 0.034$). Chronic GIT diseases were 4.3 times more frequent in the test group (15.5 % against 3.6 % in the reference group, $p = 0.001$). Secondary diffuse hepatitis was diagnosed in 17 children from the test group (7.9 % against 3.6 % in the test group, $p = 0.126$). We established an authentic cause-effect relation between developing liver pathology under elevated levels of manganese, chromium, p-m-xylene, toluene, and phenol in blood ($R^2 = 0.127–0.794$; $32.70 \leq F \leq 418.34$; $p = 0.0001$) and HSV1 and HSV2 IgG, CMV IgG, and EBV-NA IgG levels in blood ($R^2 = 0.151–0.709$; $34.66 \leq F \leq 507.29$; $p = 0.0001$). Biliary dysfunction was 1.2 times more likely ($RR = 1.205$; CI: 1.004–1.447) and chronic gastroduodenitis was 4.3 times more likely ($RR = 4.299$; CI: 1.563–11.828) in children under combined exposure to persistent herpesvirus infection and technogenic chemicals.

Dyspeptic symptoms were mentioned 1.5 times more frequently by the children from the test group (83.1 % against 54.5 % in the reference group, $p = 0.0001$); practically half of the children in the test group had stomach pains (54.1 %) and decreased appetite (56.8 %) whereas such symptoms were detected 1.5–3.6 times less frequently in the reference group (14.9 % and 38.6 % of the children accordingly, $p = 0.005–0.0001$). Dyspeptic symptoms in children were established to be 4.1 times more likely under combined exposure to persistent herpesvirus infection and technogenic chemicals ($OR = 4.115$; CI: 2.300–7.361).

Ultrasound scanning of the hepatobiliary organs revealed that 5.7 % of the children in the test group did not have any hepatobiliary pathology and this share was 3.2 times lower than in the reference group ($p = 0.001$) (Table 3). Hepatobiliary disorders in children were established to be 1.15 times more likely under combined exposure to persistent herpesvirus infection and technogenic chemicals ($RR = 1.148$; CI: 1.034–1.275).

Pathological changes in the liver were 1.2 times more frequent in the children from the test group; enlarged liver was identified in 41.3 % of the examined children in both groups. Structural changes in the liver were established to be 1.9 times more frequent in the children from the test group (30.8 % against 16.3 % in the reference group, $p = 0.01$); they were

Table 3

Ultrasound scanning of the liver and gallbladder: the results obtained for two groups of the examined children, %

Indicators	Test group	Reference group	Validity of intergroup differences (p)
Ultrasound scanning did not reveal any deviations from the healthy state of the hepatobiliary organs	5.7	18.5	0.001
Pathological changes in the liver	61.0	51.1	0.121
Enlarged liver	41.3	41.3	1.0
Structural changes in the liver, including:	30.8	16.3	0.01
–reactive	19.2	10.9	0.082
–diffuse	10.5	5.4	0.162
–nidal	1.2	–	–
Pathological changes of the gallbladder, including:	83.7	68.5	0.004
–abnormally shaped gallbladder	48.8	33.7	0.018
–enlarged volume of the gallbladder	45.4	45.7	1.0
–reactive changes of the gallbladder walls	15.7	6.5	0.031
–signs of dyscholia	41.9	30.4	0.066

predominantly reactive (19.2 % of the cases against 10.9 % in the reference group, $p = 0.082$). Likelihood of structural changes in the liver was 2.3 times higher in the test group against the reference one ($OR = 2.286$; CI: 1.204–4.340). We established an authentic cause-effect relation between developing structural changes in the liver under elevated manganese and toluene levels in blood ($R^2 = 0.359–0.743$; $143.55 \le F \le 529.85$; $p = 0.0001$) and HSV1 and HSV2 IgG and CMV IgG levels in blood ($R^2 = 0.743–0.794$; $515.58 \le F \le 780.66$; $p = 0.0001$).

Gallbladder pathologies were 1.2 times more frequent in the children from the test group ($p = 0.004$) (Table 3). Each second child had abnormally shaped gallbladder (the gallbladder bend or contracted gallbladder) and 41.9 % of the children had inadequate viscosity of bile with some sediment (dyscholia); this was detected 1.4 times more frequently than in the reference group (33.7 % and 30.4 % accordingly, $p = 0.018–0.066$). In addition, 15.7 % of the exposed children with persistent herpesvirus infection had some reactive changes of the gallbladder walls (the share was only 6.5 % in the reference group, $p = 0.031$). Likelihood of the gallbladder pathology in children was established to be 1.2 times higher under combined exposure to persistent herpesvirus infection and technogenic chemicals ($RR = 1.223$; CI: 1.049–1.425). We established an authentic cause-effect relation between abnormally shaped gallbladder and dyscholia under elevated manganese, toluene, and p-, m-xylene levels in blood ($R^2 = 0.278–0.729$; $80.16 \le F \le 525.89$; $p = 0.0001$) and reactive changes of the gallbladder walls and levels of HSV1 and HSV2 IgG and CMV IgG in blood ($R^2 = 0.145–0.609$; $28.27 \le F \le 325.78$; $p = 0.0001$).

Reactive hyperplasia of the lymph nodes in the abdominal cavity was detected 1.2 times more frequently in the reference group (67.4 % against 54.1 % in the test group, $p = 0.037$); reactive changes in the lymph nodes located in the hepatobiliary area were the most frequent (in 41.9 % of the cases in the test group and 56.5 % in the reference group, $p = 0.024$). We established an authentic cause-effect relation between developing hyperplasia of the lymph nodes in the hepatobiliary area and HSV1 and HSV2 IgG level in blood as well as the viral load of HHV6 and EBV DNA ($R^2 = 0.519–0.898$; $181.97 \le F \le 1641.69$; $p = 0.0001$).

Laboratory tests revealed the mean values of basic indicators to be within the physiological ranges in the examined children; still, levels of direct bilirubin and C-reactive protein, as well as ALT activity were authentically higher in the children from the test group ($p = 0.032–0.003$). This may indicate a trend towards developing hepatocellular dysfunction (Table 4). Elevated direct bilirubin levels were 1.5 times more frequent in the test group than in the reference one (15.1 % against 10.0 % accordingly, $p = 0.211$). We established an authentic cause-effect relation between elevated direct bilirubin under elevated levels of manganese and phenol in blood ($R^2 = 0.176–0.295$; $54.59 \le F \le 102.65$; $p = 0.0001$).

Imbalance between the oxidant and antioxidant systems was detected in the children from the both groups. Thus, malonic dialdehyde (MDA) levels in blood plasma were higher than the physiological norm in the children from the test group ($p < 0.05$) but also authentically lower than in the reference group ($p = 0.008$). Elevated MDA levels were detected in 53.0–60.9 % of the examined children ($p = 0.180$). We established a relationship between likelihood of elevated MDA levels in blood and elevated formaldehyde levels in blood ($R^2 = 0.388$; $F = 161.45$; $p = 0.0001$) and elevated EBV-NA IgG in blood ($R^2 = 0.446$; $F = 238.72$; $p = 0.0001$). We also identified a decrease in the total antioxidant activity (AOA) of blood plasma in the examined children against the physiological norm ($p = 0.0001$). Decreased AOA levels were identified in 68.9–75.5 % of the analyzed samples ($p = 0.218$). We established an inverse relationship between a decrease in AOA and elevated manganese ($R^2 = 0.209$; $F = 90.91$; $p = 0.0001$) and HSV1 and HSV2 IgG levels in blood ($R^2 = 0.415$; $F = 168.94$; $p = 0.0001$).

Table 4

Results of the laboratory tests obtained for the examined children, *Me* [25; 75]

Indicator	Physiological range	Test group	Reference group	Validity of inter-group differences (p)
Total protein, g/dm^3	60–80	74.0 [71.0; 77.0]	73.0 [70.0; 75.0]	0.013
Albumins, g/dm^3	35–50	44.0 [42.0; 46.0]	43.0 [41.0; 44.0]	0.039
Total bilirubin, μmol/dm^3	0–18.8	10.0 [8.2; 13.4]	9.5 [7.9; 12.1]	0.333
Direct bilirubin, μmol/dm^3	0–4.3	2.8 [1.9; 3.6]	2.3 [1.7; 3.1]	0.032
AST, U/dm^3	6–37	26.0 [22.0; 30.0]	27.0 [23.0; 31.0]	0.410
ALT, U/dm^3	5–42	15.0 [12.0; 18.0]	13.0 [11.0; 16.0]	0.003
Alkaline phosphatase, U/dm^3	71–645	341.0 [249.0; 475.0]	447.5 [356.0; 564.0]	0.0001
Triglycerides, mmol/dm^3	0.3–1.7	0.7 [0.57; 0.97]	0.79 [0.57; 1.01]	0.316
Total cholesterol, mmol/dm^3	3.11–5.44	4.08 [3.58; 4.53]	4.07 [3.67; 4.64]	0.306
CRP, mg/dm^3	0–12	0.45 [0.03; 12.0]	0.3 [0.01; 0.4]	0.024
Malonic dialdehyde, μmol/cm^3	1.8–2.5	2.6 [2.18; 2.96]*	2.81 [2.34; 3.12]*	0.008
Antioxidant activity of blood plasma, %	36.2–38.6	33.82 [29.1; 37.5]*	32.0 [28.7; 36.2]*	0.142

Note: * means authentic differences from the physiological norms ($p < 0.05$).

Conclusions:

1. Under exposure to airborne technogenic chemicals in levels reaching 4.8 $RfC_{chr.}$, 64.9–97.6 % of the examined children had elevated levels of aromatic hydrocarbons and formaldehyde in blood; elevated manganese and chromium levels were identified in 20.8–34.6 % of the cases.

2. Markers of cytomegalovirus and Epstein – Barr virus were identified in 74.5–77.0 % of the exposed children; markers of herpes simplex virus 1 and 2, in 46.5 %; markers of human herpes virus 6, in 31.3 %.

3. Likelihood of structural changes in the liver and gallbladder pathology was established to be 1.2–2.3 times higher for the exposed children with persistent herpesvirus infection. Hepatobiliary disorders manifested themselves in such children as dyspeptic symptoms (stomach pains and decreased appetites) in 83.1 % of the cases; they included structural changes in the liver, abnormally shaped gallbladder, reactive changes of the gallbladder walls, and dyscholia in 48.8 % of the cases and were accompanied with elevated levels of direct bilirubin and ALT activity against the developing imbalance between the oxidant and antioxidant systems.

4. Relative risk of biliary dysfunctions and chronic pathology equals 1.2–4.3 for children under combined exposure to persistent herpesvirus infection and technogenic chemicals.

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Research article

ELECTRONIC DIGITAL DEVICES AND A RISK OF FUNCTIONAL DISORDERS OF THE VISUAL ANALYZER IN STUDENTS OF DIFFERENT AGE

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The aim of our study was to perform hygienic assessment of use of electronic digital devices and its relationship with likely disorders of the visual analyzer in students of different age.

Our research object is represented by students of different age (5^{th} grade (n = 55), 11^{th} grade (n = 67) and the 6^{th} year of HEI (n = 102)). This study focused on examining a relationship between disorders of the visual analyzer and use of electronic digital devices (EDDs) by students of different ages (5^{th} and 11th grades in school, 6^{th} year in HEI). We conducted social research by using a group indirect survey that relied on a specifically designed questionnaire consisting of 13 questions. Answers were collected by using Google Forms online platform.

Students were established to use a smartphone (99.6 % of the respondents) and / or laptop (83 %) in their everyday activities. We analyzed duration of an activity involving use of various devices and established that 95 % of the respondents did not adhere to the existing hygienic standards when using EDDs and spent more than 4 hours a day on using them. The regression analysis revealed an association between myopia development and simultaneous use of various EDDs (R^2 = 0.68; $p < 0.0001$). A contribution made to developing eyesight disorders by working with a laptop equaled 62 % whereas contributions made by watching TV and use of smart-watch equaled 19 % and 10 % respectively. Our assessment of a relative risk established that use of a laptop (PC) for more than 4 hours a day increased likelihood of myopia by 8.6 times (RR = 8.6; 95 % CI = 1.4–54.9, $p < 0.05$). Development of other functional disorders in school students was primarily associated with watching TV (85–89 %).

Therefore, our study findings provide more precise data on the established relationship between improper EDDs use and disorders of the visual analyzer in students of different age. They provide solid grounds for implementation of relevant prevention activities.

Keywords: *HEI students, school students, myopia, computer vision syndrome, electronic digital devices, electronic learning devices, relative risk.*

Protection and promotion of children's health is a priority target in the development of the healthcare and education in the Russian Federation. The modern digital environment produces considerable effects on children, adolescents, and youth as regards their learning activities, spare time, socialization, and lifestyle [1, 2]. Digitalization of education provides wide opportunities for using electronic educational resources, various simulators and emulators in order to master practical skills [3]. Development of digital skills in children facilitates development of the intellectual component in human potential thereby accelerating development of thinking, memory, attention, and imagination [4, 5]. On the one hand, electronic digital devices (EDDs) make education more effective; however, on the other hand, they are able to create unfavorable conditions, which, in their turn, are likely to

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induce various symptoms and health impairment in students [6, 7]. Students often use gadgets not only in learning activities but also in their spare time; they keep a wrong posture while doing it and do not have sufficient lighting. All this leads to such health disorders as accommodative excess, myopia of various degrees, computer vision syndrome, more rapid fatigue and, consequently, weaker resistance to stress [8–10]. Use of electronic devices is associated with such a civilization disease as dry eye syndrome, which is identified in 9–18 % of the population in developed countries. Over the last 30 years, the prevalence of this disease has grown by 4.5 times. Surveys conducted among medical students reveal dry eye syndrome of various intensity in 43.6 % of respondents [11, 12]. Uncontrolled digitalization will promote an annual growth in prevalence of myopia among school children and myopia progression by 0.5–2 diopters in 30 or higher % of them [13]. At present, a new term, 'epidemics of myopia', is being used in Russia [14]. Some British researchers report that a number of children who use smartphones and have their own electronic devices grows every year. Children aged between 8 and 11 years mostly use gaming gadgets whereas older children aged between 12 and 15 years prefer to use tablets and smartphones. Also, use of tablets by children aged between 5 and 15 has tripled by now against 2012 [15, 16].

The aim of our study was to perform hygienic assessment of use of electronic digital devices and its relationship with likely disorders of the visual analyzer in students of different age.

Materials and methods. Students of different age were selected as our research object. The sample included children who attended secondary schools (5^{th} grade (n = 55) and 11^{th} grade (n = 67)) and medical university undergraduates (6^{th} year, n = 102) (Table 1).

Table 1

Respondents of different age distributed as per sex

Age	Total, n = 224	
	male	female
5^{th} grade	16 (29 %)	39 (71 %)
11^{th} grade	9 (13.4 %)	58 (86.6 %)
6^{th} year university undergraduates	12 (11.8 %)	90 (88.2 %)

We conducted social research by using a group indirect survey that relied on a specifically designed questionnaire consisting of 13 questions. They described respondents' relations with electronic digital devices (EDDs): a gadget type, frequency of its use, duration of uninterrupted use; as well as occurring disorders of the visual analyzer: complaints of feeling unwell during and after EDD use and diagnosed myopia. Answers were collected by using Google Forms online platform.

The study was conducted in conformity with the ethical principles stated in the Declaration of Helsinki and the EU Directives (8/609EC). Prior to the study, all the participants were informed of its aims. An access to the online questionnaire was granted only after participants provided their informed voluntary consent.

We evaluated whether EDDs use conformed to the existing hygienic requirements relying on the Sanitary Rules SP 2.4.3648-20[1] and Sanitary Rules and Norms SanPiN 1.2.3685-21[2].

Research data were statistically analyzed by conventional methods of variation statis-

[1] SP 2.4.3648-20. Sanitarno-epidemiologicheskie trebovaniya k organizatsiyam vospitaniya i obucheniya, otdykha i ozdorovleniya detei i molodezhi; utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha RF 28.09.2020 № 28 [Sanitary-epidemiological requirements to organizing education, leisure and health improvement of children and youth; approved by the Order of the RF Chief Sanitary Inspector on September 28, 2020 no. 28]. *Rospotrebnadzor*. Available at: https://www.rospotrebnadzor.ru/files/news/SP2.4.3648-20_deti.pdf (January 20, 2023) (in Russian).

[2] SanPiN 1.2.3685-21. Gigienicheskie normativy i trebovaniya k obespecheniyu bezopasnosti i (ili) bezvrednosti dlya cheloveka faktorov sredy obitaniya; utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha RF 28.01.2021 № 2 [Hygienic standards and requirements to providing safety and (or) harmlessness of environmental factors for people; approved by the Order of the RF Chief Sanitary Inspector on January 28, 2021 no. 2]. *Rospotrebnadzor*. Available at: https://www.rospotrebnadzor.ru/files/news/GN_sreda%20_obitaniya_compressed.pdf (January 20, 2023) (in Russian).

tics in Microsoft Office 2010 and Statistica 6.0 applied software packages. We used the chi-square test to evaluate significance of difference in prevalence of health disorders. Relationships and combined effects of several EDDs were evaluated by using regression analysis with model significance identified as per the Fisher test and the determination coefficient (R^2). We calculated a relative risk (*RR*) and its 95 % confidence interval (95 % CI) to establish influence the priority EDDs had on prevalence of disorders of the visual analyzer. The significance level was taken as $p < 0.05$ for $RR > 1$ and the CI bottom limit > 1.

Results and discussion. The present study involved examining effects of the following EDDs: mobile electronic devices (MEDs) such as a smartphone or a smart watch; electronic learning devices (ELDs) such as a PC, laptop, or a tablet; other technical devices (TDs) such as a TV set or a gaming console [1].

Our study established that all the students used a smartphone in their everyday activity (99.6 % of the respondents). A laptop took the second place as per frequency of its use by the respondents (83 %). The total daily time of EDDs use is a significant indicator that describes its safety. It is noteworthy that duration of MEDs use (smartphone or smart watch) and TDs (gaming console) is not regulated by the existing regulatory documents; ELDs use (PC, laptop, or tablet), however, should not exceed 120 minutes a day for middle school children and 170 minutes a day for senior school children and HEI students. Actual findings that describe how the examined students were distributed depending on duration of using different technical devices, indicate that 95 % of the respondents do not adhere to the established hygienic standard when using ELDs and use them for more than 4 hours a day. The share of the respondents who use a smartphone for longer than 4 hours a day equals 79 %.

TV is watched and a smart watch is used daily by 39 and 25 % of the respondents respectively. Such devices as an e-book or a gaming console are used by the respondents much less frequently (8–9 %). However, if children and adolescents watch TV, use a smart watch or play games on a console, they spend not less than 4 hours a day on these activities.

Failure to adhere to safety rules when using electronic devices may be a risk factor able to cause functional disorders and chronic diseases of the eye [1]. Table 2 provides data on prevalence of some disorders of the visual analyzer in the students of different age included into the analyzed sample.

Myopia is obviously the most frequent disorder. The regression analysis established an association between myopia development and ELDs use (laptop or PC), watching TV, and use of a smart watch ($R^2 = 0.68$; $p < 0.0001$) (Table 3). A contribution made by laptop use to eyesight disorders was the highest and equaled 65 % whereas contributions made by watching TV and use of a smart watch equaled 19 % and 10 % respectively.

Table 2

Prevalence of functional disorders and chronic diseases of the eye in students of different age, %

Functional disorders and chronic diseases of the eye	Total $n = 224$		5th grade $n = 55$		11th grade $n = 67$		6th year $n = 102$	
	abs.	%	abs.	%	abs.	%	abs.	%
Myopia	171	76.3	35	63.6*	53	79.1	83	81.4*
Blurred vision	154	68.8	18	32.7$^{*\Delta}$	37	55.2$^{\bullet\Delta}$	99	97.1$^{*\bullet}$
Lacrimation	59	26.3	17	30.9*	26	38.8$^{\bullet}$	16	15.7$^{\bullet *}$
Photophobia	42	18.8	14	25.5	15	22.4	13	12.7
Excessive blinking	42	18.8	13	23.6	17	25.4	12	11.8

Note: significant differences ($p < 0.05$) between various age groups: $^{\Delta}$ is between the 5th grade and 11th grade; *, 5th grade and 6th year; $^{\bullet}$, 11th grade and 6th year

Table 3

Parameters of regression models describing relationships between prevalence of functional disorders and chronic diseases of the eye and long EDDs use in students of different age

EDD type	Response	b_1	Error	Fisher's test (F)	p	R^2
All age groups						
laptop	Myopia	0.919355	0.044370	429.3	<0.001	0.65
TV		0.386861	0.052450	54.4	<0.001	0.19
smart watch		0.313609	0.062841	24.9	<0.001	0.10
5th grade school students						
laptop	Myopia	0.972222	0.038405	640.8	<0.001	0.92
TV		0.571428	0.112725	25.7	<0.001	0.33
smart watch		0.476190	0.141107	11.4	0.0013	0.18
laptop	Blurred vision	0.5	0.116852	18.3	<0.001	0.26
TV		0.9	0.051657	303.5	<0.001	0.85
smart watch		0.880952	0.091497	92.7	<0.001	0.64
11th grade school students						
laptop	Myopia	0.854839	0.159942	28.6	<0.001	0.31
TV		0.4375	0.085132	26.4	<0.001	0.29
smart watch		0.264151	0.119629	4.9	0.03	0.07
laptop	Blurred vision	0.596774	0.222728	7.2	0.009	0.10
TV		0.9375	0.041540	509.3	<0.001	0.89
smart watch		0.566037	0.134482	17.7	<0.001	0.21
6th year university undergraduates						
laptop	Myopia	0.943181	0.062485	227.8	<0.001	0.69
TV		0.271428	0.079394	11.7	<0.001	0.11
smart watch		0.256756	0.083377	9.5	<0.001	0.09

We assessed a relative risk caused by eyesight disorders associated with unsafe ELDs use; as a result, we established that laptop (PC) use for more than 4 hours a day increased likelihood of myopia by 8.6 times (RR = 8.6; 95 % CI = 1.4–54.9, $p < 0.05$).

Next, we conducted a more profound examination of effects produced by ELDs, MEDs, and other TDs on students' health considering their age. Analysis of myopia prevalence revealed an overall ascending trend in it among HEI graduates against school students (Table 2). Prevalence of such functional disorders as blurred or double visions also grows in older students.

Myopia prevalence was shown to be associated with long laptop use (the 5th grade, $R^2 = 0.92$; $p < 0.0001$; the 11th grade, $R^2 = 0.31$; $p < 0.0001$; the 6th year, $R^2 = 0.69$; $p < 0.0001$) and watching TV (the 5th grade, $R^2 = 0.33$; $p < 0.0001$; the 11th grade, $R^2 = 0.29$; $p < 0.0001$; the 6th year, $R^2 = 0.11$; $p < 0.0001$) for all the examined age groups. A weaker association was established for use of a smart watch (the 5th grade, $R^2 = 0.18$; $p = 0.0014$; the 11th grade, $R^2 = 0.07$; $p = 0.03$; the 6th year, $R^2 = 0.09$; $p = 0.002$) (Table 3). It is noteworthy that long ELDs use involves more frequent myopia development than in the total sample and no significant differences have been identified between the analyzed age groups: 94.4 ± 3.8 % in the 5th grade, 85.5 ± 4.5 % in the 11th grade, 94.3 ± 2.5 % in the 6th year of HEI ($p > 0.05$).

Blurred vision as an eyesight disorder in school students was associated with watching TV (in the 5th grade, $R^2 = 0.85$; $p < 0.0001$; in the 11th grade, $R^2 = 0.89$; $p < 0.0001$), use of a smart watch (in the 5th grade, $R^2 = 0.64$; $p < 0.0001$; in the 11th grade, $R^2 = 0.21$; $p < 0.0001$), and laptop use (in the 5th grade, $R^2 = 0.26$; $p < 0.0001$; in the 11th grade, $R^2 = 0.10$; $p < 0.009$). Combined contributions made by these factors into the analyzed disorder equaled 88 and 89 % in the 5th and 11th

grade accordingly. Meanwhile, we did not establish any similar associations in HEI undergraduates; this may indicate that high prevalence of this disorder is caused by some other factors. Search for other factors established a trend of blurred vision being likely associated with use of smartphone (*RR* = 1.1; 95 % CI: 0.9–1.3).

Myopia prevalence varies between 19 and 42 % in developed countries and reaches 70 % in some eastern countries. According to A.A. Minnikhanova with colleagues, myopia prevalence is 6–8 % in junior school whereas it grows up to 25–30 % in senior school children [17]. A.M. Abdulina provides some evidence of a negative trend in school ontogenesis in her article 'The Impact of Computer on Eyesight'. Thus, only 2.4 % of children have myopia when they first come to school; by the 5th grade, the share reaches 19.7 %; by the 11th grade, myopia prevalence reaches 36.8 % and this level is quite similar to the European one [14]. At the same time, V.R. Kuchma and others [18] report in their research on children's population health that myopia of different severity is diagnosed in 62 % of school students by the end of school education. O.M. Filkina with colleagues established in their study that the number of children with myopia grew by 2.1 times over the period of school education (p = 0.0098) [19]. Myopia prevalence among school students in Perm was analyzed in dynamics; as a result, a growth in it equaled 2.3 times between the 1st and 5th grade when the share of school students with myopia reached 39 % [20]. Myopia development has its peculiarities due to implementation of different educational programs. In particular, myopia develops much earlier in students who attend school with profound studies of some subjects (*RR* = 1.48–2.50; 95 % CI = 1.22–3.75; $p < 0.001$) [21]. A complex medical examination of medical students in Orenburg detected myopia in 29.5 % of them and mild myopia was the most widely spread (53.8 %) [22]. Findings of the present study revealed a rather high prevalence of the disease: 63.6 % in the 5th grade, 79.1 % in the 11th grade and 81.4 % in HEI graduates. On the one hand, this might be due to respondents' tendency to overestimate their health disorders and to be too anxious about their health. On the other hand, we cannot exclude some errors caused by absence of complete official data.

Computer vision syndrome caused by long use of electronic devices combines symptoms of asthenopia and dry eye syndrome [23]. In the present study, the respondents mentioned blurred and double vision (68.8 %) and lacrimation (26.3 %). When conducting a survey among medical students, O.V. Ievleva found that approximately 62 % of the respondents complained of double vision, lacrimation, and lower visual working capacity after or during EDDs use [24]. However, any signs of computer vision syndrome were mentioned solely in 3.6 % of cases in the study by E.I. Shubochkina with colleagues [25]. These differences are likely to be associated with different duration of gadget use by students.

Duration of students' interaction with such devices was analyzed to find evidence of EDDs negative effects as a risk factor able to cause health disorders in them. Review and generalization of findings reported in published articles make it possible to conclude that children who rarely use gadgets have higher values of the health index [5]. Parental control of MEDs use decreases the risk of myopia development by more than 2 times [14]. Other authors report an association between myopia in school students and use of gadgets by them for longer than 6 hours a day (*RR* = 1.8; 95 % CI = 1.21–3.61, $p < 0.05$) [19]. Some studies by foreign authors confirm this association as well: R. Saxena with colleagues provide some data on growing risks of myopia when time spent on PC games exceeds 4 hours a week (*OR* = 8.1; 95 % CI = 4.05–16.2; $p < 0.001$) [26]. Examination of adolescents aged between 10 and 15 years revealed an association between myopia prevalence and EDDs use for more than 1 hour a day (p = 0.011) [27, 28]. An association between visual acuity disorders and failure to use EDDs safely is also well-known and is identified for several parameters of unsafe use (absence of necessary breaks, irrational working posture, insufficient

lighting, failure to do eye gymnastics, etc.) (*RR* = 3.07; 95 % CI = 1.88–5.03, $p < 0.05$) [1]. Our research results provide more precise data on the established relationship between improper EDDs use and disorders of the visual analyzer. In particular, we identified priority EDDs and established the relationship between their use and myopia prevalence in students of different age (5^{th} grades, 11^{th} grades, and 6^{th} year). ELDs (laptop and PC) were established to increase the risk of visual acuity disorders by 8.6 times in case they were used for longer than 4 hours a day. We also determined peculiarities of associations between ELDs and prevalence of functional disorders in schoolchildren and HEI students.

Limitations of the study. Since the sample does not cover cases when some MEDs, ELDs and TDs are used for a shorter period of time than two or four hours, it is not deemed possible to fully evaluate likelihood of functional disorders and chronic diseases of the eye associated with use of such devices. In addition, we should consider the fact that the examined sample was predominantly made of females and we can expect certain bias in the study findings towards overestimation given the well-known and evidenced sex-specific differences in myopia prevalence.

Conclusions:

1. Smartphone (99.6 %) and laptop (83 %) are priority digital devices used by the respondents. Simultaneously, students of the 5^{th} grade also watch TV and those of the 11^{th} grade tend to use gaming consoles.

2. Myopia prevalence equals 76.3 % on the whole among schoolchildren and students in the examined sample; prevalence of functional disorders is 141.1 %.

3. Daily MEDs, ELDs and TDs use causes visual acuity disorders. Contribution to myopia development made by laptop (PC) use equals 65 %; contributions made by watching TV and use of a smart watch equal 19 % and 10 % accordingly. The total contribution made by all the factors amounts to 68 %.

4. Use of ELDs (laptop or PC) that does not conform to the existing hygienic standards for its duration (longer than 4 hours) increases the risk of myopia by 8.6 times (*RR* = 8.6; 95 % CI: 1.4–54.9, $p < 0.05$).

5. Development of functional disorders (blurred or double vision, lacrimation) in schoolchildren is primarily associated with watching TV (85–89 %), use of a smart watch (21–64 %) and laptop (PC) use (10–26 %). Similar disorders are caused in HEI students by some other risk-inducing factors, including those not covered by the present study.

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Research article

RELATIONSHIP OF PARENTAL PERCEPTION OF CHILDREN'S SHAPE WITH NUTRITIONAL STATUS OF CHILDREN: A POPULATION-BASED STUDY IN 24–60-MONTH-OLD VIETNAMESE CHILDREN

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This cross-sectional study aimed to evaluate the nutritional status of 24–60-month-old children in Hanoi, Vietnam, and explore parents' perception of their child's body shape, as well as related factors.

The study found that parents' wishes had a significant impact on their children's nutritional status, as reflected in the high percentage of parents dissatisfied with their child's weight and shape. Malnutrition, overweight, and obesity were defined based on WHO 2006 standards, and children's anthropometric indices were measured. A self-reported questionnaire was used to collect information on parents' perception of their child's health based on body shape and their satisfaction with it.

The results showed highest dissatisfaction with the child's shape in malnourished children (86.8 %), then in the obese group (60.4 %), and lowest in overweight children (28 %). Correct parental perception about the child's nutritional status and the healthiest shape was only 61.1 % and 34.5 %, respectively. Several factors related to parental correct perception about the child's shape were found and it was higher 22.5 % with the parent living in suburban area than those living in urban area, 20 % with the parent of girls than those of boys, it decreased to 54 % in group of malnourished children, and 66 % in group of obese and overweight children.

The findings of this study highlight the importance of parental education on healthy child development and the need for interventions to address the high prevalence of malnutrition, overweight, and obesity in preschool children.

Keywords: *nutritional status, preschool children, parental perception, body shape, parental dissatisfaction, malnutrition, obesity, overweight.*

Childhood obesity is a growing public health concern worldwide, and Vietnam is no exception. According to a recent report using data released by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF), the prevalence of childhood overweight in Vietnam has increased significantly in recent years, from 5.6 % in 2010 to 7.4 % in 2019 in children under 5 years old [1–3]. This alarming trend highlights the need for effective strategies to prevent and manage childhood obesity in Vietnam.

Nutritional status is always a matter of concern to parents with the expectation that the majority of children will have a weight and height that meet or exceed the standard. This is one of the important reasons for the rate of overweight and obese children increased rapidly in Vietnam in recent years. Parents' awareness can influence changes in eating behavior and physical activities of young children, thereby determining the nutritional status of children [4, 5]. One possible factor contributing to childhood obesity is parental perception and/or dissatisfaction with their children's shape and weight [6]. Previous studies have shown that parental dissatisfaction with their children's body shape can lead to negative atti-

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tudes towards food and eating habits, which in turn can increase the risk of childhood obesity [7, 8]. However, little is known about the relationship between parental perception and dissatisfaction with children's shape and the nutritional status of children in Vietnam.

To address this research gap, a population-based study was conducted to investigate the relationship between parental dissatisfaction with children's shape and the nutritional status of preschool children in Vietnam. **Our study aimed to** determine the prevalence of parental perception of children's shape, and to explore the association between this and several related factors as parental dissatisfaction and nutritional status indicators, living areas, and sex of a child. The findings of our study have important implications for the development of effective interventions to prevent childhood obesity in Vietnam. By identifying the role of parental attitudes towards their children's body shape in the development of childhood obesity, our study can give grounds for the development of targeted interventions aimed at promoting healthy eating habits and preventing obesity in Vietnamese children.

Research methodology. This cross-sectional survey was carried out among 15.483 preschool children and their parents in 36 kindergartens in three different districts of Hanoi (Hoan Kiem – urban district and Dong Anh, Hoang Mai – suburban districts). These locations were selected in order to create a sample of families with low incomes that can affect the parental perceptions and desires about children's nutritional status. The information was collected between September and November, 2018. Criteria for inclusion were that children attended selected preschools; were aged between 24 and 60 months; a written consent from their parents to participate in the study was provided; and they did not have any chronic diseases proved by medical records and managed by health care facilities. Exclusion criteria were age younger than 24 months or older than 60 months; established medical records mentioning chronic diseases or long-term medications administration that might cause obesity or malnutrition such as congenital heart disease, HIV, metabolic disorders, genetic diseases, or corticosteroid drugs.

Anthropometric indices including weight and height were measured with subjects in light clothing and without shoes twice for each individual, and the mean was used for the purpose of analysis. BMI was calculated as the weight per square of the height (kg/m^2).

The children's anthropometric indices were measured, and malnutrition, overweight, and obesity were defined as BMI below -2SD, above 2SD, and 3SD, respectively, based on WHO 2006 standards [9]. It is noteworthy that children who were obese due to medical reasons were excluded from the study.

Data collection. Information on parents' perception of their child's health based on body shape (scale containing shapes from 1 – thinnest to 9 – fattest) (Figure 1) and their satisfaction with their child's body shape was collected through a self-reported questionnaire from parents. The questionnaire was developed in Vietnamese and was pre-tested for clarity and validity.

Statistical analysis. Descriptive statistics were used to summarize the demographic characteristics of the participants, parental satisfaction with children's shape, and nutritional status indicators. Chi-square tests and t-tests were used to examine the association between parental satisfaction with children's shape and nutritional status indicators. Multivariable logistic regression was used to assess the independent association between parental satisfaction with children's shape and the risk of wasting/overweight-obesity after adjusting for potential confounders such as age and sex. SPSS software version 16.0 (SPSS, Chicago, USA) and R programming language (version 3.0.2) were used to analyze data.

The study was approved by the Medical Ethics Council of the Institute of Nutrition with Decision no. 343/VDD-QLKH on July 27, 2018. The parents or guardians of all children were clearly explained the purposes of the study and the written informed consent form was signed by them. All data were kept confidential and were used for research purposes only.

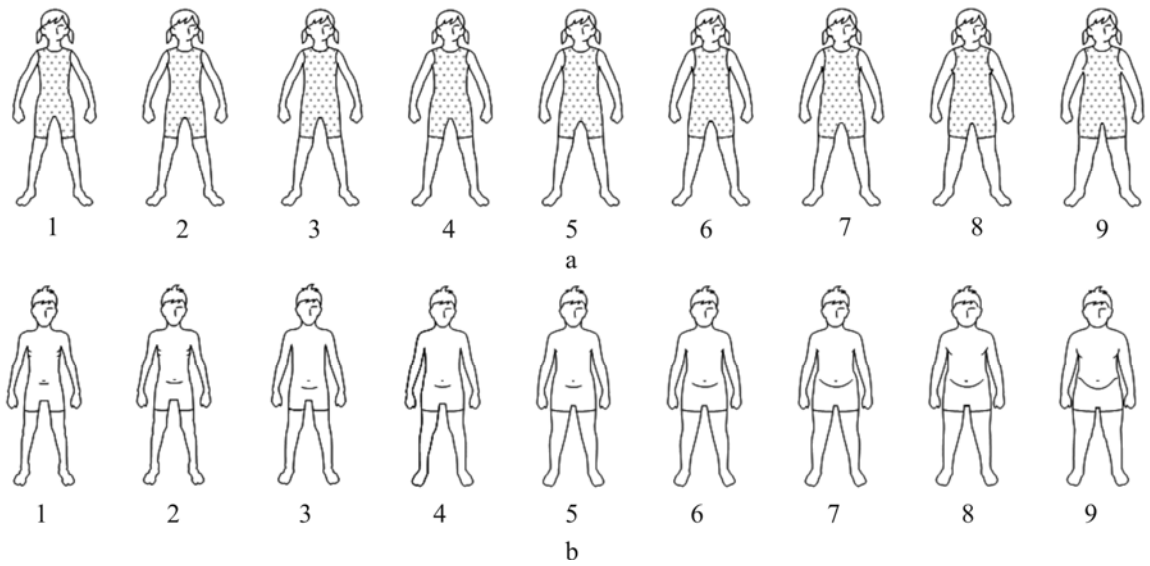

Figure 1. Body image scale from 1–9 for girls (a) and boys (b), according to nutritional status: scale 1 – severe wasting; 2 – wasting; 3, 4, 5, 6 – normal; 7, 8 – overweight; 9 – obesity

Table 1

Characteristics of participants

Characteristics	*N* (%) / Mean ± SD (*N* = 15,486)
Boys (%)	8136 (52.5)
Age (months)	46.9 ± 12.5
Height (cm)	98.5 ± 9.7
Z-score height/age	-0.8 ± 1.1
Weight (kg)	29 ± 15.1
Z-score weight/age	-0.5 ± 1.1
BMI (kg/m^2)	15.5 ± 1.7
Z-score BMI/age	0.0 ± 1.1
Z-score weight/height	-0.1 ± 1.0
Nutrition status: - Severe malnutrition	0.6 %
- Mild / moderate malnutrition	2.5 %
- Normal	85.3 %
- Overweight	7.1 %
- Obesity	4.5 %
Living area: - Urban (Hoankiem District) - Suburban (Donganh and HoangMai Districts)	 34.7 % 65.3 %

Note: BMI, body mass index; data were given by the mean ± SD or %.

Results and discussion. The characteristics of subjects are shown in Table 1.

In the group of preschool children participating in the study, the predominant group of children was boys, which is consistent with the sex disparity in the Vietnamese community. This group of children had Z-scores close to zero, especially the z-score BMI/age and z-score height/weight/age. This could be explained by both a large enough sample size as well as the normal distribution of analyzed variables as the majority (more than 85 %) of children had normal nutritional status. About two-thirds of the children participating in the study lived in suburban areas and one-third of the children lived in the urban district.

Parental dissatisfaction in groups of children with different nutritional status. The prevalence of parental dissatisfaction with the child's weight and shape is shown in Figure 2. Out of a total of 15,483 questionnaire sheets distributed, 89.8 % had answers to the related questions provided by a parents or legal representative. As a result, a difference was revealed in the percentage of parents who were not satisfied with a child's weight and shape depending on the actual nutritional status of children. The percentage of parents who were not satisfied with their child's weight was the highest in the group of malnourished children (90.2 %), followed by the obese group (69.2 %). The shares of parents not satisfied with their child's weight were close in the normal nu-

tritional status group and the overweight group, at 35.2 % and 37.2 %, respectively, and they were approximately 2 times lower than in the obese group. When assessing the dissatisfaction of parents about the child's shape, the results showed that the highest rate of dissatisfaction with the child's appearance was still in the malnourished group (86.8 %), the second was the group of children with obesity (60.4 %), but the lowest rate of dissatisfaction was identified among overweight children (28 %).

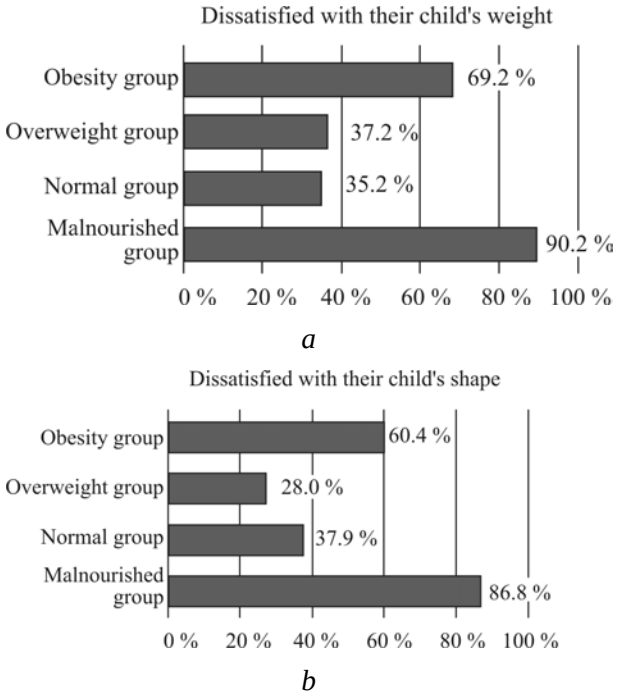

Figure 2. Parental dissatisfaction with the weight (a) and shape (b) of children with different nutritional status

When comparing two groups of malnourished and over-nourished children (including overweight and obese children), the results showed that the prevalence of parental dissatisfaction with the shape and weight of children in the undernourished and over-nourished groups was 45.7, 64.6 % and 25.1, 27.8 %, respectively. The percentage of parents who were not satisfied in the over-nutrition group was 2–2.5 times lower than in the undernourished group, this difference was statistically significant with $p < 0.001$. In particular, the results obtained by comparing the children with severely malnourished group and the obese group showed that the prevalence of parental dissatisfaction with the child's weight and shape in malnourished children group was about 1.5 times higher than in the obese group, and about 3.5 times higher in the group of overweight children, with $p = 0.034$.

Parental perception of children's nutritional status and the shape. Out of the total number of answer sheets collected, 13,039 (84.2 %) filled out by parents or legal representatives provided answers to questions related to the parental perception of nutritional status and shape of children. The results showed that 14.7 % of parents believed that only being overweight or obese was not good for health (group 1); 24.2 % of parents believed that only malnutrition was not good for health (group 2), and only 61.1 % of parents perceived that both malnutrition and overweight/obesity were not good for children's health (group 3). Univariate regression analysis found a relationship between parental knowledge and the nutritional status of children. In detail, if parents were in group 1, their child was 1.8 times more likely to be malnourished and if parents were in group 2, their child was 2.7 times more likely to be overweight or obese compared to children with parents in group 3.

A survey of parents' perception based on the shape that represented the healthiest child was carried out relying on the provided scale and the results are given in Figure 3. They show what shape was believed the healthiest according to parents' opinion. Scale 5 was selected by only about one-third of participated parents, while about one-third of parents believed that scale 6 and 7 were the healthiest shapes – although these shapes illustrated a slightly excessive weight.

Related factors and parental perception about children's shape. Of the total questionnaire sheet received, 22.2 % without full related necessary information filled out by parents or legal representatives were excluded from the analysis. Analysis of the relationship

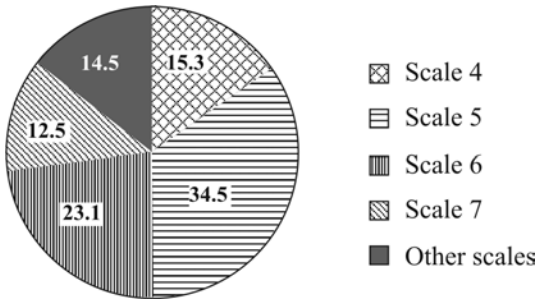

Figure 3. Parents' perception of the healthiest child's shape based on the provided scale (Figure 1)

between the correct perception of the healthiest body shape of the child and the parents' dissatisfaction with the child's weight showed that there was no relationship between the factors ($p > 0.05$). However, a relationship with parental dissatisfaction with the child's body shape was found ($p = 0.016$). Therefore, our next task was to find out the association between some factors and parents' correct perception of children's healthiest shape. Parental perception of the scale 5 as healthiest shape was accounted as the right opinion (case group) while other scales chosen were estimated as misperception about the shape of children (control group). Several related factors were studied and the results are illustrated in Table 2.

If a child lived in suburban areas, the parental perception about the healthiest shape was 22.5 % higher compared with a child living in urban areas. Child's sex was also related to parents' correct perception of a child's shape. Parents of girls were 1.2 times more frequently correct about the healthiest shape than parents of boys. The nutritional status of children was an important factor related to parents' judgments about the healthiest body shape of a child. Specifically, for malnourished children, the rate of correct parental perception was 54 % lower and 66 % lower for overweight and obese children than in the group of children with the normal nutritional status. Parents' dissatisfaction with the child's weight was not related to parents' correct perception of the healthiest body shape of children but parental satisfaction with the child's body shape decreased the correct perception of the healthy body shape children by 12.3 % compared to the group of unsatisfied parents. This difference was statistically significant with $p = 0.016$.

The total number of children and parents participating in the study was large, that is, our sample can be considered large as well. The research subjects were chosen from different living areas in Hanoi and the sampling relied on selecting each kindergarten randomly to ensure the accuracy of this population-based study. The results also showed that the proportion of boys and girls was relatively uniform and the nutritional status of children had a relatively standard distribution since the

Table 2

The relationship between some factors and parents' correct perception of the child's healthiest shape

Related factors		*OR*	95 % CI		*p*
			Higher	Lower	
Living area	Urban	1			**< 0.001**
	Suburban	1.225	1.140	1.316	
Child's sex	Male	1			**0.001**
	Female	1.224	1.048	1.205	
Child's nutritional status	Normal	1			
	Malnutrition	0.540	0.449	0.649	**< 0.001**
	Over-nutrition	0.660	0.559	0.732	**< 0.001**
Parental dissatisfaction with the child's weight	yes	1			0.547
	no	1.031	0.933	1.141	
Parental dissatisfaction with the child's shape	yes	1			**0.016**
	no	0.877	0.789	0.976	

Note: *p*-value were calculated by using logistic regression.

majority children had the normal nutritional status (85.3 %). However, the percentage of children with overweight and obesity tended to be higher than the rate of children with severe malnutrition and moderate malnutrition, this prevalence was respectively 7.1 and 4.5 % in compared with 0.6 and 2.5 %. The trend of double nutritional burden is being observed in low- and middle-income countries such as Indonesia, Asian and sub-Saharan Countries [10, 11].

Parents' dissatisfaction with children's weight and shape was the highest in the group of malnourished children with specific frequencies of 90.2 and 86.8 %. This rate was 69.2 and 60.4 % lower in obese children. The majority of Brazilian mothers who brought their children to the primary health care facility participating in the study by L.S. Duarte et al. also expressed dissatisfaction with their toddler's body size [12]. Even in the group of children with the normal nutritional status, about a third of their parents were dissatisfied with their shape and weight. The rate of dissatisfaction with the shape and weight of children in the undernourished group was 2 to 2.5 times higher than the rate of dissatisfaction in the over-nutrition group ($p < 0.001$). Thus, it is clear that parents were most concerned if their child was in malnourished group, which is understandable given that parents were educated about the short-term consequences such as increased morbidity and mortality, growth retardation and likely cognitive impairment as well as long-term consequences of stunting, poorer immunity and disability [13].

Study of parental perception about the healthiest scale of body shape yielded some variable results. The rate of correct perception only accounted for about one-third of the parents participating in the study. The findings also revealed that parental perception of a healthy body shape varied across different weight categories. Interestingly, parents perceived a slightly overweight shape as the healthiest, whereas a normal shape was associated with a lower perception of health. More than one third of the group of parents participating in the study (35.1 %) think that the strongest shape of the child belongs to the shape 6–7, although this is a body of a child who is slightly overweight. Thus, the problem of parental misperception tends to increase the rate of overweight right from the age of children under 5 years old. This is similar to the comment of Ashraf et al. [6]. When examining 305 children and their parents, it also revealed a significant difference between the actual weight of children and the problem of parents' perceptions, the case of overweight and obese children was associated with increased rate of parents' incorrect perception.

When examining the issues related to parental incorrect perception about the child's body shape, we found a relationship between the living area as well as the child's sex. The percentage of parents correctly assessing the child's body shape was lower among children living in the urban area than among children living in the suburbs; also, the correct perception of parents about the child’s body shape was about 1.2 times higher among girls than among boys. This difference may help partly explain the reason why the proportion of overweight and obese children in urban areas is always higher than in suburban areas, as well as a higher proportion of overweight and obese boys than girls [14]. This situation is not only encountered in Vietnam but also in China, where, as it was revealed in a national survey, the difference in the perception of overweight and obesity was related to sex thereby promoting the difference in the nutritional behavior of children. According to the survey, there were differences associated with consuming fried food and sugar-sweetened drinks by two sexes, the consumption being much higher among boys both in urban and in rural living areas [15]. Another study on Hispanic mothers with overweight children showed that they might not realize their children were overweight, and as a result the nursing intervention was ineffective. So, intervention programs should primarily stimu-

late changes in cultural and social beliefs and provide health education for mothers in order to reduce the prevalence of overweight and obesity in children [16].

Misperception about the healthiest body shape of children might be closely related to the actual nutritional status of children. If a child was in the malnourished group, the rate of parents' correct perception decreased to 54 % and it was 66 % for a child in the over-nutrition group. This difference is statistically significant with $p < 0.001$. Similar to our study, a systematic review by Francescatto et al. also showed a correlation between mothers' assessment of their child's overweight status; the share of mothers who underestimated their child's actual nutritional status and inadequately perceived it was still relatively high and in the group of overweight or obesity children [17].

Next, when analyzing the relationship between the correct perception of the child's healthiest body shape and the parents' dissatisfaction with the child's weight and shape, we did not reveal any relationship between the child's weight dissatisfaction and the parental perception about the child's weight ($p > 0.05$) but there was a relationship with dissatisfaction with the child's body shape ($p = 0.016$). It could be argued that coding the nutritional status of children by body shape scale helps parents' perception become closer to the factual nutritional status. It makes the instrument more effective and can be used in intervention programs to improve children's nutritional status reducing the prevalence of overweight and obesity in them. Many charts on the shape of children have been developed so far, for example, body shape scale developed by Gardner et al. or toddler silhouette scale of Hager et al. Both scales are used effectively in assessing the nutritional status of children [18, 19], for example they were applied with success in several studies of Pallan et al. [20].

Finally, the study found a significant association between parental knowledge and their child's nutritional status. Children born in families with parents in group 2 who judged only malnutrition as bad health status were 2.7 times more likely to be overweight or obese, while those born in families with parents in group 1 judging only over-nutrition as bad health status were 1.8 times more likely to be malnourished in comparison to children in families with correct judgment both malnutrition and over-nutrition as bad health status (group 3). This indicates that parental perception might influence their child's nutritional status, and highlights the importance of providing parents with accurate information about the health risks associated with different weight categories.

The present study aimed to investigate the relationship between parental dissatisfaction with their child's shape and the nutritional status of Vietnamese preschool children. The results showed that the majority of parents in the malnourished group were dissatisfied with their child's weight and shape, followed by the obese group. In contrast, parents of normal weight and overweight children as a rule showed relatively lower levels of dissatisfaction.

Conclusions. In conclusion, we'd like to point out that the present study provides valuable insights into the relationship between parental perception and their child's nutritional status. The findings suggest that efforts are needed to educate parents about the health risks associated with different weight categories and promote more comprehensive understanding of the factors that contribute to their child's nutritional status.

This population-based study in Vietnamese preschool children highlights the relationship between parental dissatisfaction with their child's weight and shape and the child's nutritional status. The study found that parents in the malnourished and obese groups were more likely to be dissatisfied with their child's weight and shape than parents in the normal and overweight groups. Additionally, incorrect judgment of parents about a healthy weight might increase the risk of being malnourished or overweight/obesity for their children.

Our findings have important implications for public health interventions aimed at im-

proving the nutritional status of children. It is assumed that addressing parental perception and satisfaction with their child's weight and shape may be an important component of such interventions. Furthermore, public health messages should emphasize the importance of a balanced and healthy diet and promote awareness of the risks associated with both malnutrition and overweight/obesity. Finally, our study highlights the need for continued monitoring and research on the nutritional status of children in Vietnam to ensure the development and implementation of effective interventions.

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Research article

METHODICAL APPROACHES TO PERSONIFIED ASSESSMENT OF HEALTH RISKS CAUSED BY WORK INTENSITY AND ITS SPECIFIC COMPONENTS

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High work intensity (HWI) can occur in various occupational groups and induce health disorders, which means occupational health risk (OHR) assessment is necessary.

This article describes methodical approaches to assessing OHR caused by HWI with a possibility to examine contributions made by its specific components and transition to personified risk assessment.

The suggested approaches to assessing OHR caused by HWI include subjective assessment of the factor and health self-assessment. They allow identifying additional likelihood of health disorders and performing further risk assessment when exposure to HWI grows by one unit as per separate HWI indicators describing its specific components. Personified risk assessment involves using a template created for specific HWI components (intellectual, sensory, or emotional loads; work monotony; work regime).

The approaches were tested on workers with mostly mental work (n = 137, respondents' mean age was 43.9 ± 8.01 years; mean work records were 14.5 ± 3.7 years). Calculated data of personified levels of the integral health risk were used to rank likely health outcomes as per their priority. Mental disorders and diseases involving elevated blood pressure were established to correspond to 'high' health risk. Myopia, strained headache, atherosclerosis of peripheral vessels, and chronic laryngitis corresponded to 'medium' risk. Certain disorders involving the immune mechanism, tinnitus, ischemic heart disease, and atherosclerosis of coronary vessels as well as stomach and duodenum ulcer corresponded to 'moderate' risk.

Detailed HWI assessment made it possible to identify its leading components; the shares of sensory and emotional loads in the integral health risk reached 29.0 ± 2.4 and 25.9 ± 3.9 % accordingly (p = 0.37). It is advisable to use these findings for creating personified activities aimed at OHR mitigation.

Keywords: *risk assessment, health risk, occupational risk, work-related factors, work intensity, health disorder, personified assessment, methodical approaches.*

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High work intensity (HWI) is a factor that describes working conditions for employed population. According to official statistics, the share of workers exposed to HWI in their workplaces amounted to 3.7 % in 2022; this level declined by 5.6 times over 10 years[1]. At the same time, various occupational groups now tend to face growing informational loads that make for the development of adverse health outcomes [1]. Furthermore, experts have revealed that HWI assessment can pose certain challenges in the study where aircraft pilots were used as an example of an occupation ranked among priority ones as per work intensity both according to official statistics and research data [2]. These challenges can influence results of assessment of working conditions making them less informative [3, 4]. Physiological costs of workloads can lead to health disorders in a situation when available functional reserves have come to an end [5]. High work intensity primarily induces development of cardiovascular diseases and mental disorders (burnout syndrome and anxiety and depression disorders) [6–8].

In accordance with the sanitary legislation, an employer is obliged to perform prophylaxis activities to prevent occupational and work-related diseases in workers[2]. To make implemented activities the most effective, it is advisable to provide them with solid substantiation relying on health risk assessment. The methodology for assessing occupational risk (OR) caused by occupational diseases (ODs) and work-related diseases (WRDs), its acceptable level taken into account, is the most interesting tool for health harm assessment and subsequent development of recommendations on management decisions aimed at OR mitigation [9].

Previously, we suggested some methodical approaches that allow actual quantification of health risks caused by HWI including identification of roles (contributions) made by specific types of workloads (intellectual, sensory, emotional, monotony, or work regime) [10]. However, they rely on epidemiological criteria and are limited by group risk identification.

In this study, our aim was to develop methodical approaches to assessing occupational risks associated with high work intensity; this would make it possible to perform personified health risk assessment considering all the components of work intensity.

Materials and methods. Approaches to OR assessment were substantiated by analyzing and generalizing published articles and regulatory and methodical documents with data on HWI assessment practices, OR assessment, as well as HWI effects on health.

To assess OR for health, we relied on using data that described both HWI, the factor itself, and workers' health (both being the integral parts of posterior (quantitative) OR assessment). A social survey was considered an acceptable research tool and therefore we developed a questionnaire that provided information about objective facts and workers' subjective evaluations of various aspects of work intensity in their workplaces, on the one hand, and workers' health, on the other hand. When developing this questionnaire about HWI, we relied on indicators included into the Guide R 2.2.2006-05[3]. The HWI assessment methodology involves using matrices that combine interrelated indicators as per specific intensity components and are adapted to peculiarities of assessing these components. The suggested levels have six categories: 'optimal', 'permissible', 'harmful, hazard category 1', 'harmful,

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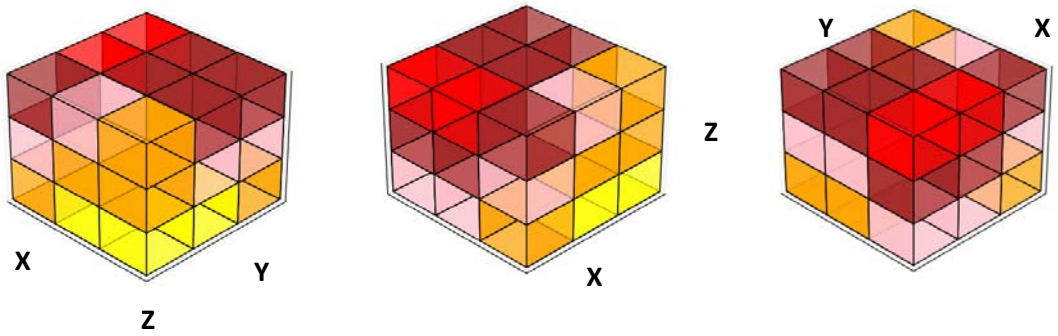

Figure 1. The matrix for assessing intensity levels (exemplified by sensory loads as a specific intensity component): yellow is 'optimal' level; orange, 'permissible'; pink, 'harmful, hazard category 1'; brown, 'harmful, hazard category 2'; red, 'harmful, hazard category 3'

hazard category 2', 'harmful, hazard category 3', and 'harmful, hazard category 4'. Integral assessment of working conditions is performed for the limiting type of intensity. Figure 1 provides an example of an illustrated matrix for qualitative assessment of sensory loads. The relevant categories are identified depending on a combination of duration of loads on the vocal apparatus (X), visual (Y), and auditory systems (Z).

When developing the questionnaire about health, we used a list of likely diseases caused by HWI that was created based on relevant literature sources and published in a study by V.B. Alekseev and others [10]. Likely diseases were established as per workers' complaints and their correspondence with diagnoses enlisted in the ICD-10. To achieve that, a team of expert physicians supervised by O.Yu. Ustinova, Deputy Director for Healthcare Services, created a matrix that was applied to identify a disease likely caused by HWI. The methodology, which was used to create the disease identification matrix, had the following stages:

• stage 1 at which expert evaluations were collected. First, we created a list of medical specialties that would be necessary to make a list of symptoms (complaints) describing likely health disorders caused by HWI. Totally, 11 healthcare workers took part in expert evaluation including neurologists (2 experts), ENT specialists (2 experts), gastroenterologists (2 experts), therapists (2 experts), oculist (1 expert), cardiologist (1 expert), and allergologist (1 expert). Each expert made a list of symptoms (complaints), which, in their opinion, described suggested likely diseases caused by HWI.

• stage 2 involved analysis of expert evaluations. The whole set of suggested symptoms was analyzed and systematized at this stage.

• stage 3 involved ranking symptoms (complaints). All the symptoms (complaints) were ranked considering their frequency under relevant suggested likely diseases: 1 meant a symptom belonged to basic manifestations of a certain pathological process and always occurred under it; 2 meant additional symptoms of a disease that would occur in a half of cases when a disease manifested itself clinically; 3 meant a symptom was rare and occurred in 1/3 or a lower share of cases when a disease manifested itself clinically.

The questions in the survey were based on the developed matrix (61 question overall). Each question involved respondents' evaluation of occurrence / presence of a specific symptom as well as its frequency. The following categories of symptom frequency (intensity) were suggested: rarely or once per 6 months; frequently, once every 2–3 months; constantly, each month or even more frequently. A likely negative outcome would be fixed in case a half of symptoms describing a specific disease were present (that is, a disease is established with 50 % likelihood).

The very determination whether negative health outcomes caused by HWI (or by its specific components) were likely was performed by using a template for data analysis created in

MS Excel. The template for data analysis considered the following events: A meant a respondent mentioned presence of a given symptom and HWI was not higher than a certain threshold level as per each category; B, a respondent did not mention presence of a given symptom and HWI was not higher than a certain threshold level as per each category; C, a respondent mentioned presence of a given symptom and HWI was higher than a certain threshold level as per each category (work intensity); D, a respondent did not mention presence of a given symptom and HWI was higher than a certain threshold level as per each category. The events A and B may happen with certain likelihood p; the events C and D, with likelihood $q = 1 - p$. Likelihood of an event p belongs within 0 to 1: $P \in [0, 1]$.The number of favorable outcomes is $M \in [0, N]$ where N is the number of respondents.

If x = the number of positive answers, n = the number of tests and p = is likelihood of positive answers, then the integral binomial distribution is given as follows (formula 1):

$$P(x) = \sum_{i=1} x_i p(x_i). \quad (1)$$

Quantitative risk assessment should consider additional likelihood of a negative response (disease) and its severity. The principle formula (2) is applied to calculate the risk level:

$$R = P_{add.\,ij} \cdot G_i, \quad (2)$$

where $P_{add\,ij}$ is additional likelihood of the i-th negative response caused by the j-th intensity component (intellectual, emotional or sensory load, work monotony, work regime), G_i is severity of the i-th negative response. Severity of specific health outcomes (diseases) is determined considering the coefficient values recommended by the WHO [11, 12].

The resulting values are used to calculate the integral risk associated with different HWI components (formula 3):

$$R_{int} = 1 - (1 - R_{IL})\cdot(1 - R_{SL})\cdot(1 - R_{EL})\cdot \cdot (1 - R_{WM})\cdot(1 - R_{WR}), \quad (3)$$

where

R_{IL} is the level of risk associated with intellectual loads;

R_{SL} is the level of risk associated with sensory loads;

R_{EL} is the level of risk associated with emotional loads;

R_{WM} is the level of risk associated with work monotony;

R_{WR} is the level of risk associated with work regime.

Risk levels are described considering the criteria suggested in the work by N.V. Zaitseva [13]. Negligible and low ORs are considered acceptable (permissible).

The suggested approaches were tested on the example of workers with predominantly mental work (healthcare workers, researchers, teachers, and office clerks). The ultimate sample included 137 people considering completeness and correctness of their answers to the questionnaire, 77 % of them were females. The respondents' mean age was 43.9 ± 8.01 years; work records, 14.5 ± 3.7 years. The survey was anonymous and implemented by using Questionstar[4], expert online survey and test constructor. The research was accomplished between August 2022 and April 2023.

The results were statistically analyzed in Microsoft Office 2010 and Statistica 10.0 applied licensed software packages. We used Kruskal – Wallis non-parametric H-test to evaluate significance of differences between several independent groups and the Newman – Keuls (NK) procedure for subsequent pairwise comparison. The statistical significance was taken at $p \leq 0.05$.

Results and discussion. The suggested methodical approaches to personified assessment of risks caused by HWI are provided in Figure 2.

[4] QUESTIONSTAR: expert online survey and test constructor. Available at: https://www.questionstar.com/ (April 10, 2023).

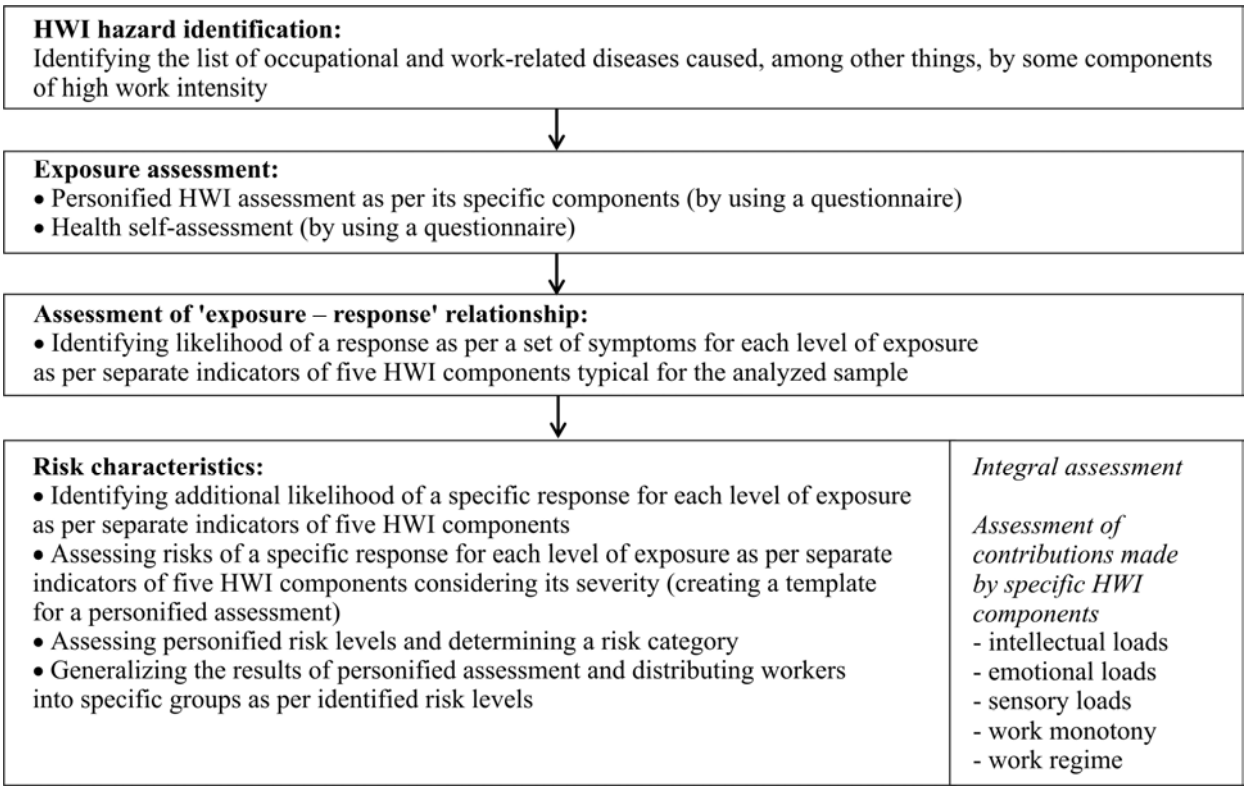

Figure 2. Personified assessment of health risks caused by HWI

The list of identified likely adverse health outcomes, manifested both as ODs and WRDs, was created based on research literature and published in the work by V.B. Alekseev [10]. At the exposure stage, use of the developed questionnaire when answering an online survey makes it possible to accumulate a database with data on an analyzed sample and feed in new data into it upon their occurrence.

At the stage when 'exposure – response' relationships are analyzed, it is advisable to use probabilistic methods to identify likely health outcomes (prevalence of diseases symptoms). This allows calculating additional likelihood of responses when an exposure to HWI as per specific indicators describing its specific components grows by one. Overall, we considered 19 indicators: 5 described the intellectual component; 5, the sensory component; 5, the emotional component; 1, work monotony, 3, work regime. Such an approach is preferable since the known threshold values established by the Guide R 2.2.2006-05[5] have not changed since their first publication in the first version of the Guide (R 2.2.013-94) [2] and their use can fail to reveal the already existing health disorders caused by an analyzed factor.

At the stage involving risk characterization, the basic task is to establish risk levels associated with levels of exposure to specific HWI components for a specific health outcome and to integrate them. These data are then used as a template when a personified risk level is calculated.

When testing the suggested approaches, we identified personified risk levels for workers with predominantly mental work. Likely negative health outcomes included myopia

[5] The Guide R 2.2.2006-05. 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, came into force on November 01, 2005. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200040973 (August 01, 2023) (in Russian).

(H52.1) (ranked as OD[6]); certain disorders involving the immune mechanism (D80–D89); neurotic, stress-related and somatoform disorders: reaction to severe stress, and adjustment disorders (F43); other neurotic disorders (neurasthenia) (F48); tension-type headache (G44.2); noise effects on inner ear (H83.3); hypertensive diseases (I10–I15); ischaemic heart diseases (I20–I25); atherosclerotic heart diseases (coronary) (I25.1); diseases of arteries, arterioles and capillaries (atherosclerosis) (I70–I79); chronic laryngitis (J37.0); gastric and duodenal ulcer (K25–K26). Distribution of the respondents as per the integral risk levels is given in Table 1.

Next, we calculated the averaged risk level in the analyzed group (the group risk). This made it possible to rank likely health outcomes as per their priority. Thus, risks caused by neurotic, stress-related and somatoform disorders: reaction to severe stress, and adjustment disorders (F43), other neurotic disorders (neurasthenia) (F48) (0.068 ± 0.0031), and hypertensive diseases (I10–I15) (0.035 ± 0.0021) were ranked as 'high'. Risks caused by myopia (H52.1) (0.011 ± 0.0005), tension-type headache (G44.2) (0.010 ± 0.0005), diseases of arteries, arterioles and capillaries (atherosclerosis) (I70–I79) (0.011 ± 0.0007), and chronic laryngitis (J37.0) (0.0102 ± 0.0005) were ranked as medium. Risks caused by certain disorders involving the immune mechanism (D80–D89) (0.0016 ± 0.0002), noise effects on inner ear (H83.3) (0.004 ± 0.0002), ischaemic heart diseases (I20–I25) (0.002 ± 0.0004), atherosclerotic heart disease (coronary) (I25.1) (0.0015 ± 0.0002), and gastric and duodenal ulcer (K25–K26) (0.009 ± 0.0005) were ranked as 'moderate'.

Sensory and emotional loads make the greatest contribution to the integral risk of negative health outcomes; their shares are 29.0 ± 2.4 and 25.9 ± 3.9 % accordingly (p = 0.37). We revealed certain peculiarities for various health outcomes when examining the structure of contributions made by specific HWI components (Table 2).

In particular, likely coronary artery disease is primarily caused by sensory loads (44.8 ± 4.0 %, $p \leq 0.05$) as well as work monotony (25.1 ± 3.6 %), and work regime (24.0 ± 3.4 %); ischaemic heart disease, by sensory loads (42.4 ± 4.1 %) and work regime (32.8 ± 3.9 %); certain disorders involving the immune mechanism, by sensory loads (35.7 ± 3.7 %), work regime (26.2 ± 3.2 %), and work monotony (20.6 ± 3.2 %, $p \leq 0.05$).

These findings that determine the leading HWI components are consistent with the well-known regularities. Prevalence of nervous and cardiovascular diseases among workers dealing with different types of mental work has been analyzed in research literature in detail. These analyses give evidence of intense mental work being unable to produce adverse effects on the body unless it involves another stressor factor associated with negative emotional loads [14]. Therefore, it is advisable to consider a substantial contribution made by the emotional component primarily in assessment of working conditions as well as when developing activities aimed at prevention of work-related diseases.

Likely development of various health disorders can be directly induced by HWI influence (its priority components) or mediated by development of other unrelated disorders. Literature also provides some data on higher risks of mental disorders, a priority negative health outcome for the analyzed sample, under exposure to HWI. Correlations between psychoemotional factors in the occupational environment and emotional burnout and anxiety and depression disorders have also been reported in research articles [8]. In their turn, such states can be a trigger of developing cardiovascular diseases (CVDs) including essential hypertension, atherosclerosis, ischaemic

[6] Ob utverzhdenii perechnya professional'nykh zabolevanii: Prikaz Minzdravsotsrazvitiya Rossii ot 27.04.2012 № 417n [On approval of the list of occupational diseases: The Order by the RF Ministry of Health 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 (August 01, 2023) (in Russian).

Table 1

Distribution of workers with predominantly mental work as per the levels of their personified integral health risks, abs. (%)

Likely health outcome	Risk level and category						
	0–0.001 Negligible	0.0001–0.001 Low	0.001–0.01 Moderate	0.01–0.03 Medium	0.03–0.1 High	0.1–0.3 Very high	0.3–1 Extremely high
Hypertensive diseases (I10–I15)	0	0	14 (10.2)	57 (41.6)	63 (46.0)	3 (2.2)	0
Tension-type headache (G44.2)	0	0	74 (54.0)	62 (45.3)	1 (0.7)	0	0
Myopia (H52.1)	0	0	71 (51.8)	65 (47.4)	1 (0.7)	0	0
Noise effects on inner ear (H83.3)	0	3 (2.2)	129 (94.2)	5 (3.6)	0	0	0
Chronic laryngitis (J37.0)	0	1 (0.7)	75 (54.7)	60 (43.8)	1 (0.7)	0	0
Neurotic, stress-related and somatoform disorders: reaction to severe stress, and adjustment disorders (F43); other neurotic disorders (neurasthenia) (F48)	0	0	1 (0.7)	15 (10.9)	100 (73)	21 (15.3)	0
Gastric and duodenal ulcer (K25–K26).	0	0	79 (57.7)	57 (41.6)	1 (0.7)	0	0
Diseases of arteries, arterioles and capillaries (atherosclerosis) (I70–I79)	0	2 (1.5)	73 (53.5)	58 (42.3)	4 (2.9)	0	0
Atherosclerotic heart disease (coronary) (I25.1)	87 (63.5)	11 (8.0)	37 (27.0)	2 (1.5)	0	0	0
Ischaemic heart diseases (I20–I25)	98 (71.5)	7 (5.1)	21 (15.3)	10 (7.3)	1 (0.7)	0	0
Certain disorders involving the immune mechanism (D80–D89)	51 (37.2)	36 (26.3)	48 (35.0)	2 (1.5)	0	0	0

Table 2

The structure of contributions made by specific HWI components into the integral risk level, %

Likely health outcome	HWI components				
	Intellectual loads	Sensory loads	Emotional loads	Work monotony	Work regime
Hypertensive diseases (I10–I15)	11.8 ± 1.2	25.0 ± 1.9	34.4 ± 2.1	11.5 ± 1.7	17.3 ± 1.9
Tension-type headache (G44.2)	16.1 ± 0.9	24.6 ± 1.6	32.4 ± 1.4	11.2 ± 1.3	15.7 ± 1.5
Myopia (H52.1)	16.9 ± 0.9	24.3 ± 1.5	32.0 ± 1.4	11.3 ± 1.3	15.5 ± 1.4
Noise effects on inner ear (H83.3)	20.1 ± 1.2	24.0 ± 1.7	35.8 ± 1.7	4.2 ± 0.8	15.9 ± 1.4
Chronic laryngitis (J37.0)	14.1 ± 1.0	24.7 ± 1.7	33.2 ± 1.6	11.7 ± 1.5	16.4 ± 1.6
Neurotic, stress-related and somatoform disorders: reaction to severe stress, and adjustment disorders (F43); other neurotic disorders (neurasthenia) (F48)	16.4 ± 0.9	24.5 ± 1.5	32.2 ± 1.4	11.3 ± 1.3	15.6 ± 1.4
Gastric and duodenal ulcer (K25–K26)	15.2 ± 1.0	24.5 ± 1.6	32.8 ± 1.5	11.5 ± 1.4	16.0 ± 1.5
Diseases of arteries, arterioles and capillaries (atherosclerosis) (I70–I79)	12.3 ± 1.1	24.9 ± 1.9	34.3 ± 1.9	11.7 ± 1.6	16.7 ± 1.8
Atherosclerotic heart disease (coronary) (I25.1)	0.0	44.8 ± 4.0	6.2 ± 1.9	25.1 ± 3.6	24.0 ± 3.4
Ischaemic heart diseases (I20–I25)	0.0	42.4 ± 4.1	8.3 ± 2.2	16.5 ± 3.1	32.8 ± 3.9
Certain disorders involving the immune mechanism (D80–D89)	14.1 ± 2.6	35.7 ± 3.7	3.4 ± 1.4	20.6 ± 3.2	26.2 ± 3.2
On average	12.5 ± 2.0$^{*\times}$	29.0 ± 2.4*	25.9 ± 3.9$^{\times\circ}$	13.3 ± 1.7$^{*\circ}$	19.3 ± 1.7*

Note: * × ○ is the significance level $p \leq 0.05$ between the relevant HWI components.

heart disease, and arrhythmia; they create elevated risks of sudden cardiac death. It is still unclear, though, how negative cardiovascular events are related to adverse mental exposures. Experts assume some changes in the functioning of the hypothalamic-pituitary-adrenal axis (HPA) as a key element of the neuroendocrine regulation involving growing levels of cortisol and catecholamines (adrenalin and noradrenalin). In addition, there might be disrupted ratios of lipids circulating in blood; thrombocytes dysfunction; vascular walls inflammation [15–18]. Hypokinesia also plays an important role in CVD development [19]; it can be evidenced by such HWI components as work monotony as well as sensory loads and work regime. Since indicators that describe these HWI components involved assessing time periods when relevant mental work was being done, they consequently were eligible to assess how well workers were able to maintain their working state under limited motor activity.

Mental disorders can cause negative outcomes for physical health, developing headaches, diseases of the gastrointestinal attract, and respiratory diseases [19, 20].

It is noteworthy that the suggested approaches to risk assessment have some uncertainties. To be more exact, they rely on using a survey for assessing exposure to identify a likely disease as per a set of symptoms describing a certain health disorder; this may yield some overestimated results. However, the methodology is quite acceptable since it allows identifying certain existing peculiarities of ODs onset even prior to using objective clinical diagnostic procedures.

Conclusions. The suggested methodical approaches to assessing OHR caused by HWI include subjective factor assessment and health self-assessment. They allow identifying additional likelihood of health disorders and performing subsequent risk assessment when exposure to HWI grows by one as per a specific indicator describing a specific HWI component. This makes it possible to create a template for personified health risk assessment.

The approaches were tested on a group of workers with predominantly mental work. As a result, we established personified levels of the integral health risk, which were then used to rank likely negative health outcomes as per their priority (mental disorders, diseases of the circulatory system, as well as diseases of the eye and ear, diseases of the gastrointestinal tract, and weaker resistance). Sensory and emotional loads were revealed as priority HWI components with their contributions to the integral health risk equaling 29.0 ± 2.4 и 25.9 ± 3.9 % ($p = 0.37$) accordingly.

It is advisable to use these findings for creating personified activities aimed at mitigating risks caused by occupational and work-related diseases.

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Research article

SUBJECTIVE ASSESSMENT OF OCCUPATIONAL RISK FACTORS FOR HEALTH AND PSYCHOEMOTIONAL STATE OF HEALTH CARE WORKERS UNDER CHANGED WORKING CONDITIONS DURING THE COVID-19 PANDEMIC

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We accomplished a cross-sectional study using a specifically designed questionnaire. The aim of our study was to examine subjective assessment of influence exerted on healthcare workers' health and psychoemotional state by changed working conditions and use of personal protective equipment during the COVID-19 pandemic. The examined healthcare workers were employed at a multi-field re-profiled in-patient hospital. We established a considerable change in the workplace setting of healthcare workers in an unfavorable epidemic situation. It involved longer contacts with hazardous biological and chemical factors, elevated work hardness and intensity as well as the necessity to use personal protective equipment for a long time.

Longer use of personal protective equipment when tending COVID-19 patients was associated with higher frequency of several variable complaints made by the questioned healthcare workers. Respondents were more likely to report difficulty in breathing ($p < 0.001$) and some discomfort around the face and/or behind the ears ($p = 0.035$) when wearing a medical face mask / respirator; wearing goggles was likely to involve itching, redness and/or maceration in the area where goggles contacted the head ($p = 0.009$), headache ($p = 0.002$) and discomfort in the area where goggles contacted the head ($p < 0.001$); healthcare workers who wore medical gloves reported itching ($p = 0.004$) and skin peeling ($p < 0.001$); use of protective overalls led to elevated sweating ($p < 0.001$), feeling overheated ($p < 0.001$), thirst ($p < 0.001$), and palpitation ($p = 0.012$). A significant proportion of respondents experienced some difficulties in using personal protective equipment related to visual and auditory perception of information, physical discomfort, putting on and taking off personal protective equipment, performance of work requiring precise movements, and decreased work capacity. The frequency of such complaints grew statistically significantly during a period when a healthcare worker had to treat COVID-19 patients.

Keywords: *cross-sectional study, survey, COVID-19, pandemic, healthcare workers, occupational health risks, working conditions, biological factor, personal protective equipment.*

During the COVID-19 pandemic, healthcare workers and their family members had to face considerable health risks. Although healthcare workers account for less than 3 % of the population in the overwhelming majority of countries worldwide (less than 2 % in almost every low- and middle-income country), approximately 14 % of all COVID-19 cases are registered in healthcare workers. This share can reach 35 % in some countries [1, 2]. Investigations accomplished in the Russian Federation, European countries and East-Southern Asia also give some evidence that in 2020 the COVID-19 infection turned out to be the most widely spread occupational disease in healthcare workers due to biological factors [3–6].

In Belarus, the existing system for managing occupational health risks, including those for healthcare workers, relies on the development of complex preventive activities. They

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are based on assessment of working conditions within evaluation of workplaces as per working conditions and complex hygienic assessment of working conditions that takes place every 5 years in accordance with the current legislation. This system fails to consider possible substantial temporary changes in working conditions and only involves hygienic assessment of occupational factors under a permanent technological process. When a considerable epidemic rise in incidence occurs, the COVID-19 being a good example, in-hospital bed reserves are re-profiled into isolation wards and healthcare workers have to work in completely different workplace settings during this period.

The pandemic not only created risks for healthcare workers' physical health but also put them under a tremendous mental stress associated with overwork, abnormal work schedules, huge workloads, infection hazards, and social stigmatization. Healthcare workers all over the world had already had elevated risks of suicide even before the pandemic started [7, 8].

Healthcare provided for patients with respiratory diseases able to cause a pandemic always involves direct health risks associated with a biological factor, growing physical loads and loads on the nervous system. But in addition to them, we should also consider risks associated with the necessity to use personal protective equipment (PPE) for a long time [9–13].

Long-term use of a face mask or respirator can induce adverse skin reactions (itching, redness and/or maceration on the face or behind the ears) as well as subjective signs of hypoxia (labored breath, shortness of breath, and dizziness) [14–16]. It is noteworthy that wearing a face mask for longer than 4 hours a day or reusing it creates even higher risks of adverse skin reactions [14]. Protective goggles and face shields can also stimulate occupational dermatoses, especially in people with more sensitive skin and such diseases as seborrheic dermatitis and acne in their case history [17].

Hand hygiene plays the key role in preventing COVID-19 among healthcare workers. However, active use of detergents and disinfectants results in longer contacts with chemicals in their composition; these chemicals can produce both general toxic effects and local irritating ones on hand skin. Long-term use of latex gloves can also cause occupational contact dermatitis and eczema [18–20].

Therefore, growing burdens on a healthcare system caused by a pandemic spread of respiratory infections highlight the relevance of preserving healthcare workers' health and working capacity. Under a pandemic, occupational health risks for healthcare workers grow substantially; they are associated with not only a possibility to get infected at a workplace but also considerable physical, intellectual, sensory and emotional loads as well as the necessity to use PPE for a long time. All the above stated makes it necessary to develop targeted activities aimed at preserving both physical and mental health of healthcare workers in addition to using the existing system for managing occupational health risks in workplace settings.

In this study, our aim was to examine subjective assessment of influence exerted on healthcare workers' health and psychoemotional state by changed working conditions and use of personal protective equipment during the COVID-19 pandemic. The examined healthcare workers were employed at a multifield re-profiled in-patient hospital.

Materials and methods. To achieve our aim, we conducted a cross-sectional study using a specifically designed questionnaire made of 40 questions. The questionnaire was filled in by 95 healthcare workers employed at a multi-field in-patient hospital in Minsk, which was re-profiled to treat COVID-19 patients during the pandemic. The hospital has some therapeutic divisions (pulmonology, cardiology, gastroenterology and rheumatology), injury and orthopedic division and surgical division; gynecology and obstetrics division, diagnostic divisions (clinical laboratories; x-ray, endoscopic, and functional examinations) as well as a municipal transfusion center. Prior to filling in the questionnaire, the respondents gave their consent to personal data analysis and were informed of their personal data being used only for research purposes and with proper adherence to anonymity and confidentiality.

The questionnaire covered social and demographic characteristics of the respondents (age, sex, position, and work records); it included questions about any chronic diseases; questions about PPE use and any complains associated with its long use under usual (regular) functioning of the in-patient hospital and when it was re-profiled to treat COVID-19 patients under an adverse epidemic situation; questions about physical loads and work intensity, duration of contacts with hazardous biological factors, antiseptics and disinfectants when providing healthcare for patients under regular conditions and under extreme ones during the pandemic; questions about COVID-19 in a case history and any possible associations between the disease and a respondent's occupation.

The respondents were offered multiple choice questions with respect to any complaints about PPE use, physical loads, work intensity, use of antiseptics and disinfectants.

In the questionnaire, 'usual (regular) functioning' of the in-patient hospital implied usual shift work in accordance with a schedule stipulated in a given division without any specific anti-epidemic measures associated with treating COVID-19 patients.

The obtained data were statistically analyzed in Excel and Statistica 13 statistical software packages.

The data analysis involved calculating absolute and relative frequencies. The standard error and 95 % confidence interval $P \pm m$ (95 % CI) were calculated for intensive indicators. Confidence intervals for intensive indicators were calculated by using the Wilson CI. Qualitative ordinal signs in dependent groups were compared by using the Wilcoxon test. Frequencies of binary signs in dependent groups were compared by using the McNemar test.

The respondents who mentioned relevant chronic diseases were excluded from the analysis for more precise investigation of differences in the number of complaints associated, in the respondents' opinion, with PPE wearing (face mask / respirator, goggles, gloves, or overalls) under usual (regular) functioning of the in-patient hospital and in an adverse epidemic situation.

The results were considered authentic and differences between the indicators were considered significant under likelihood of error-free prognosis being not lower than 95.5 % ($p < 0.05$).

Results and discussion. Twelve men or 12.6 % (7.4–20.8) of the respondents and 83 women, or 87.4 % (79.2–92.6) took part in the study. The respondents who filled in the questionnaire were of the following ages: 20 years and younger, 1.1 % (0.2–5.7); between 21 and 30 years, 30.5 % (22.2–40.4); between 31 and 40 years, 26.3 % (18.5–36.0); between 41 and 50 years, 25.3 % (17.6–34.8); and 51 years and older, 16.8 %.

About a half of the respondents (49.5 % (39.6–59.4)) were nurses / paramedics; 21.1 % (14.1–30.3) were heads of various divisions; 14.6 % (9.0–23.2) were doctors; 13.7 % (8.2–22.0) were middle- and lower-level supervisors such as senior staff nurses; 1.1 % (0.2–5.7) were hospital orderlies.

The respondents' answers about their work records established that most had rather long work records in healthcare: 53.7 % (43.7–63.4), 15 years and longer; 13.7 % (8.2–22.0), between 10 and 14 years; 13.7 % (8.2–22.0), between 5 and 9 years; 18.9 % (12.3–28.0), between 1 and 4 years.

We included a relevant question to exclude any association with chronic diseases in the respondents and subjective symptoms of irritation in the upper airways, face and hand skin, hypoxia, overstrain of the central nervous system and cardiovascular system that might be caused by PPE use. The respondents' answers established that 29.5 % (21.2–39.3) of them had chronic ENT diseases or respiratory diseases; 11.6 % (6.6–19.6), chronic cardiovascular diseases; 7.4 % (3.6–14.4), chronic skin diseases on the face, hair part of the head, and hands. Most respondents, 57.9 % (47.8–67.3), did not have any of the aforementioned chronic diseases in their case history.

The questioning revealed that the number of respondents who wore a face mask / respirator grew significantly in an adverse epidemic situation; 91.6 % (84.3–95.7) wore respiratory PPE under usual (regular) functioning of the

hospital whereas the share reached 100 % (96.1–100.0) under adverse epidemic conditions ($p = 0.005$). Time of wearing a face mask / respirator by healthcare workers grew considerably when the in-patient hospital was re-profiled to treat COVID-19 patients against working under usual (regular) functioning: 52.6 % (41.6–63.5) of the respondents mentioned longer wearing of respiratory PPE during a working day ($p < 0.001$). Longer face mask / respirator wearing was mentioned by 54.6 % (38.0–70.2) of supervisors ($p < 0.001$), 71.4 % (45.4–88.3) of doctors ($p = 0.012$) and 35.4 % (23.4–49.6) of middle and junior healthcare workers ($p < 0.001$).

In general, only 7 out of 55 (12.7 % (6.3–24.0)) respondents without any chronic diseases did not have complaints associated with respiratory PPE wearing under usual (regular) functioning of the in-patient hospital. The share went down to 10.9 % (5.1–21.8) under adverse epidemic conditions. The identified differences were not statistically significant. Discomfort on the face and / or behind the ears was the most frequent complaint occurring both under usual (regular) functioning (mentioned by 56.4 % (43.3–68.6) of the respondents) and when treating COVID-19 patients (mentioned by 69.1 % (56.0–79.7) of the respondents). Shortness of breath associated with PPE wearing was mentioned both under regular functioning and adverse epidemic conditions by 34.6 % (23.4–47.8) and 43.6 % (31.4–56.7) of the respondents respectively. Thirty-eight point two percent (26.5–51.4) and 49.1 % (36.4–61.9) of the respondents believed there was a relation between wearing a face mask under different functioning of the in-patient hospital and such symptoms as redness and / or maceration on the face and behind the ears. Labored breath was mentioned both under regular functioning and adverse epidemic conditions by 16.4 % (8.9–28.3) and 36.4 % (24.9–49.6) of the respondents respectively. Shortness of breath was believed to be associated with respiratory PPE by 34.6 % (23.4–47.8) of the respondents under regular functioning and by 43.6 % (31.4–56.7) when treating COVID-19 patients. Analysis of frequency of specific complaints established that the respondents mentioned labored breath ($p < 0.001$) and discomfort on the face and / or behind the ears ($p = 0.035$) statistically significantly more frequently when wearing a face mask / respirator under adverse epidemic conditions (Figure 1).

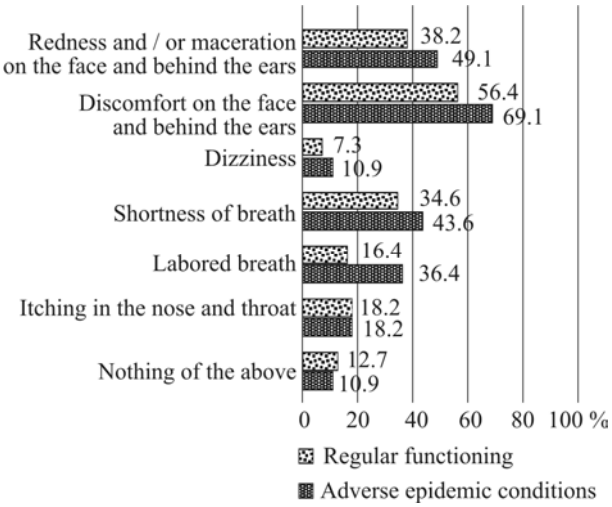

Figure 1. The respondents' answers to the question about any complaints associated with wearing a face mask / respirator

Long use of protective goggles can also be a risk factor able to induce several pathological symptoms. The share of the respondents who used goggles in their everyday work grew statistically significantly under adverse epidemic conditions, from 50.5 % (40.7–60.4) under regular functioning to 86.3 % (78.0–91.8) respectively ($p < 0.001$). The questioning results also indicate that most respondents mentioned longer use of goggles during a work shift when treating COVID-19 patients in the re-profiled in-patient hospital, namely, 52.6 % (42.7–62.4) ($p < 0.001$), including 63.6 % (46.6–77.8) supervisors ($p < 0.001$), 57.1 % (32.6–78.6) doctors ($p = 0.012$) and 43.8 % (30.7–57.7) junior and middle healthcare workers ($p < 0.001$).

Twenty percent (11.6–32.4) of the respondents who used goggles as PPE had no complaints when wearing them under regular functioning of the hospital. When healthcare was provided for COVID-19 patients under adverse epidemic conditions, 23.6 % (14.4–36.4)

of the respondents had no complaints associated with wearing goggles. These differences were not statistically significant. The highest share of the respondents, both under regular functioning (27.3 % (17.3–40.2)) and adverse epidemic conditions 52.7 % (39.8–65.3)) mentioned some discomfort in the area where goggles contacted the head. Twelve point seven percent (6.3–24.0) and 30.9 % (20.3–44.0) of the respondents believed their headaches to be associated with wearing goggles under regular functioning and adverse epidemic conditions respectively. Itching, redness and / or maceration in the area where goggles contacted the head was believed to be associated with wearing goggles by 5.5 % (1.9–14.9) of the respondents under regular functioning and by 18.2 % (10.2–30.3) of those who treated COVID-19 patients. Complaints about itching, redness and / or maceration in the area where goggles contacted the head were established to be statistically significantly more frequent under adverse epidemic conditions ($p = 0.009$). Similar dependence was established for such symptoms as 'headache' ($p = 0.002$) and 'discomfort in the area where goggles contact the head' ($p < 0.001$) (Figure 2).

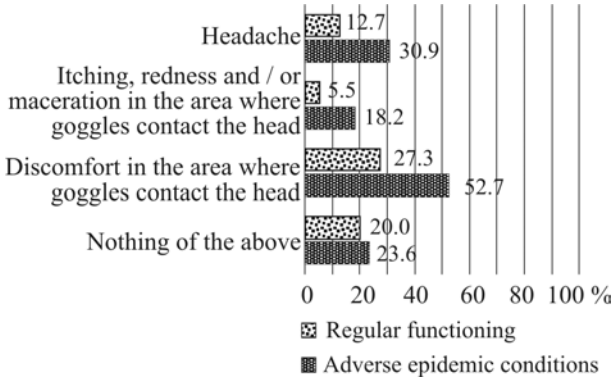

Figure 2. The respondents' answers to the question about any complaints associated with wearing goggles

Analysis of the respondents' answers to the question about time of wearing gloves established a statistically significant growth in the number of the respondents who used gloves in their everyday work under adverse epidemic conditions, from 83.2 % (74.4–89.4) to 99.0 % (94.3–99.8) ($p < 0.001$). Gloves were also used for longer periods by all the categories of healthcare workers when they were treating COVID-19 patients. Longer time of wearing gloves was mentioned by 75.8 % (59.0–87.2) supervisors ($p < 0.001$), 64.3 % (38.8–83.7) doctors ($p = 0.008$) and 43.8 % (30.7–57.7) middle and junior healthcare workers ($p < 0.001$). Overall, 57.9 % (47.8–67.3) of the respondents mentioned longer tine of wearing gloves during a work shift ($p < 0.001$).

The respondents believed that wearing gloves both under regular functioning and when treating COVID-19 patients was associated with such symptoms as skin peeling (37.5 % (28.1–47.9) and 53.4 % (43.1–63.5) respectively), redness, maceration, chaps, including the interdigital space (30.7 % (22.0–41.0) and 36.4 % (27.1–46.8) respectively) and itching (22.7 % (15.2–32.5) and 34.1 % (25.0–44.5) respectively). Out of these symptoms, itching ($p = 0.004$) and skin peeling ($p < 0.001$) were mentioned by the respondents under adverse epidemic conditions statistically significantly more frequently (Figure 3).

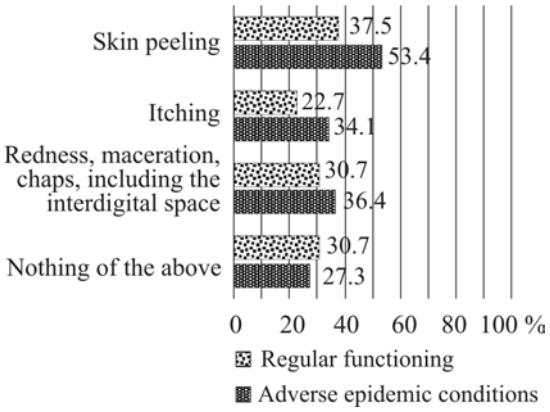

Figure 3. The respondents' answers to the question about any complaints associated with wearing gloves

The number of the respondents who wore protective overalls grew statistically significantly under adverse epidemic conditions: only 30.5 % (22.2–40.4) of the respondents used overall in their everyday work under regular functioning whereas the share grew to 92.6 % (85.6–96.4) under adverse epidemic conditions ($p < 0.001$). Overalls were also used for a statistically significantly longer pe-

riod of time under adverse epidemic conditions as it was mentioned by 69.5 % (59.6–77.8) of the respondents ($p < 0.001$), including 90.9 % (76.4–96.9) supervisors ($p < 0.001$), 64.3 % (38.8–83.7) doctors ($p = 0.008$) and 56.3 % (42.3–69.3) junior and middle healthcare workers ($p < 0.001$). The highest share of healthcare workers, both under regular functioning (20.7 % (12.3–32.8)) and under adverse epidemic conditions (63.8 % (50.9–74.9)) mentioned elevated sweating when wearing overalls. Thirteen point eight percent (7.2–24.9) and 50.0 % (37.5–62.5) of the respondents believed that feeling overheated was associated with wearing protective overalls under different functioning modes of the hospital; 12.1 % (6.0–22.9) and 41.4 % (29.6–54.2) were thirsty; 3.5 % (1.0–11.7) and 19.0 % (10.9–30.9) had palpitation; 3.5 % (1.0–11.7) and 10.3 % (4.8–20.8) mentioned such a symptom as 'dizziness'. Statistical analysis established that frequency of such symptoms as 'elevated sweating' ($p < 0.001$), 'feeling overheated' ($p < 0.001$), 'thirst' ($p < 0.001$), and 'palpitation' ($p = 0.012$) was higher under adverse epidemic conditions than under usual (regular) functioning of the hospital (Figure 4).

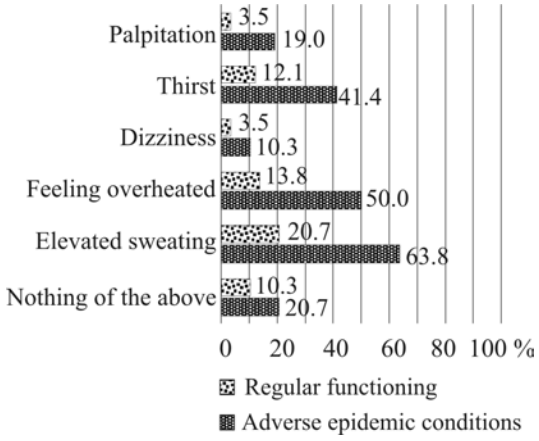

Figure 4. The respondents' answers to the question about any complaints associated with wearing protective overalls

Apart from some specific symptoms that are associated with PPE, some non-specific complaints may occur due to their long use. Such complaints can still create certain difficulties in performing work functions and produce considerable effects on work hardness and work intensity of healthcare workers. The questioning results revealed that a lot of the respondents had certain difficulties associated with PPE use; some statistically significant differences were identified between PP use under regular functioning of the hospital and when treating COVID-19 patients: 20.0 % (13.2–29.1) and 53.7 % (43.7–63.4) of the respondents mentioned some difficulties in visual perception of information (limited vision, difficulty in object discrimination) ($p < 0.001$); 22.1 % (14.9–31.5) and 45.3 % (35.6–55.3) complained about difficulties in auditory perception of information (ability to understand speech and percept audio signals) ($p < 0.001$); 28.4 % (20.3–38.2) and 63.2 % (53.1–72.2) felt physical discomfort when using PPE ($p < 0.001$); 6.3 % (2.9–13.1) and 14.7 % (9.0–23.2) mentioned difficulties in putting PPE on and off ($p = 0.005$); 17.9 % (11.5–26.8) and 37.9 % (28.8–47.9) found it difficult to perform work tasks that required precise movements (injections, surgical manipulation and the like) ($p < 0.001$); 12.6 % (7.4–20.8) and 27.4 % (19.4–37.1) mentioned decreased work capacity that was associated with PPE use ($p < 0.001$) (Figure 5).

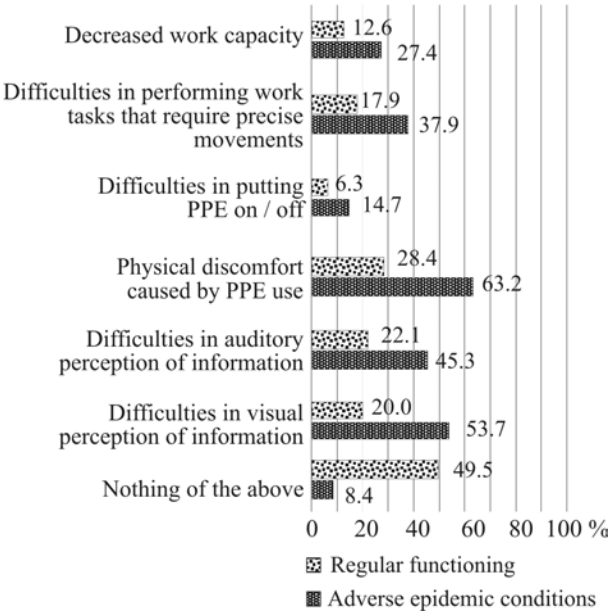

Figure 5. The respondents' answers to the question about any difficulties associated with PPE use

Work hardness and work intensity also changed considerably in workplace settings of

healthcare workers depending on how the hospital functioned. Greater physical loads in everyday work under adverse epidemic conditions were mentioned by 79 out of 95 respondents (83.2 % (74.4–89.4)); 51.9 % (41.1–62.6) of them believed it was due to longer time spent standing during a work shift; 46.8 % (36.2–57.7), due to a greater number of cargos that had to be moved by hand during a work shift (lifting and moving patients, medical devices, medications, cleaning equipment, etc.); 41.8 % (31.5–52.8), due to longer distances covered on foot during a work shift; both with and without moving up or down; 29.1 % (20.3–39.9), due to changes in a work posture (doing work in an uncomfortable posture with body bends, uncomfortable poses of extremities, a forced work posture and the like) and / or greater quantity of body bendovers during a work shift. Only 12 out of 79 (15.2 % (8.9–24.7)) of the respondents did not have any complaints as regards the musculoskeletal system, which they believed were associated with greater physical loads whereas 68.4 % (57.5–77.6) of the respondents had lower back pain; 40.5 % (30.4–51.5), leg weakness or pain; 36.7 % (26.9–47.7), arm and shoulder weakness and pain; 26.6 % (18.1–7.2), joint pain.

Greater work intensity was also mentioned by 83.2 % (74.4–89.4) of the respondents; this was associated with greater intellectual, sensory, and emotional loads as well as changes in working conditions (Figure 6).

Growing work intensity was believed to be associated with several pathological symptoms by 75 out of 79 respondents (94.9 % (87.7–98.0)); among them, 82.3 % (72.4–89.1) mentioned feeling overstrain and accumulated fatigue, 39.2 % (29.2–50.3) complained of feeling depressed and devastated, 20.3 % (12.9–30.4) did not feel satisfied with work they were doing, 24.1 % (16.0–34.5) had problems with attention focusing, 34.2 % (24.7–45.2) complained about poorer memory, 5.1 % (2.0–12.3) mentioned longer time of reacting to external stimuli, 40.5 % (30.4–51.5) had sleepiness, 44.3 % (33.9–55.3) suffered from headaches, 5.1 % (2.0–12.3) felt some discomfort in the area near the eyes.

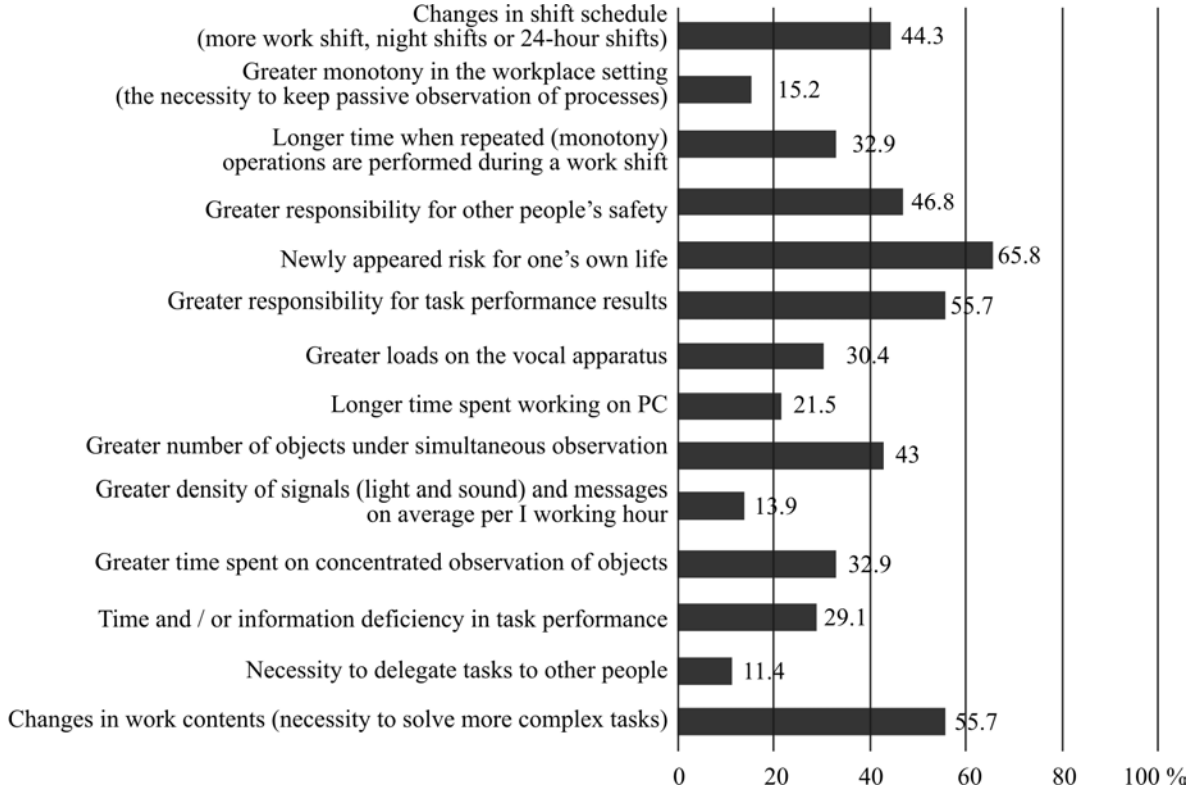

Figure 6. The respondents' answers to the question about the reasons for growing work intensity

Biological factors are usually evaluated in most workplace settings of healthcare workers, both when workplaces are assessed as per working conditions and during complex hygienic assessment of working conditions. The latter involves evaluating duration of direct contacts with patients (examination, questioning, medical manipulations, and transportation) and indirect ones (collection, sorting and disinfection of bed linen, medical devices, laboratory and dining dishes, ward cleaning, contacts with patients' biological materials). Given that, it seems interesting to analyze within occupational health risk analysis how duration of such contacts was influenced after the hospital had been re-profiled to treat COVID-19 patients. Our questioning established that 63.2 % (53.1–72.2) and 51.6 % (41.7–61.4) of the respondents believed duration of their everyday contacts with patients, both direct and indirect ones, grew under adverse epidemic conditions.

The study established that 83.2 % (74.4–89.4) of the respondents had COVID-19 confirmed with laboratory tests; an association between the disease and an occupation was found in 20.3 % (12.9–30.4) (16 people) of them and these disease cases were considered occupational infection. Still, 42.9 % (31.4–55.1) of those respondents with the disease not considered an occupational case believe that COVID-19 infection in them was also related to performing their occupational tasks. Ninety-three point seven percent (86.7–97.1) of the respondents were vaccinated against COVID-19.

Longer contacts with a biological factor do not only require longer PPE use by healthcare workers, but also lead to longer contacts with chemicals such as antiseptics and disinfectants. Ninety-nine percent (94.3–99.8) of the respondents mentioned longer contacts with antiseptics or disinfectants during a work shift (hand treatment, disinfection of surfaces and medical devices, cleaning) when performing their work tasks under adverse epidemic conditions. Out of them, 89.4 % (81.5–94.1) believed these contacts to be associated with several pathological symptoms: 21.3 % (14.2–30.6) mentioned dry or irritated eye mucosa; 58.5 % (48.4–67.9), irritation of the upper airways (nasal mucosa irritation, a tickle in the throat, dry cough); 70.2 % (60.3–78.5), skin irritation (redness, skin peeling or itching on the hands or face).

Conclusions. The study results give evidence of considerable changes in working conditions and PPE use during an epidemic rise in incidence and effects produced by them on health and psychoemotional state of healthcare workers employed at the multi-field re-profiled in-patient hospital. The number of the respondents who mentioned mandatory PPE use in everyday work grew considerably under adverse epidemic conditions. Respiratory PPE was used by 91.6 % (84.3–95.7) of the respondents under usual (regular) functioning of the hospital whereas the share reached 100 % (96.1–100.0) under adverse epidemic conditions ($p = 0.005$); goggles were worn by 50.5 % (40.7–60.4) and 86.3 % (78.0–91.8) of the questioned healthcare workers respectively ($p < 0.001$); gloves, 83.2 % (74.4–89.4) and 99.0 % (94.3–99.8) ($p < 0.001$); protective overalls, 30.5 % (22.2–40.4) and 92.6 % (85.6–96.4) ($p < 0.001$). There was a substantial growth in PPE wearing time when the hospital was re-profiled to treat COVID-19 patients against its regular functioning: 52.6 % (41.6–63.5) of the respondents mentioned longer respiratory PPE use during a working day ($p < 0.001$); 52.6 % (42.7–62.4), longer goggles wearing ($p < 0.001$); 57.9 % (47.8–67.3), longer gloves wearing ($p < 0.001$); and 69.5 % (59.6–77.8), longer wearing of protective overalls ($p < 0.001$). This dependence is the most apparent for supervisors (heads of divisions and senior staff nurses) and doctors.

Longer PPE use under adverse epidemic conditions is associated with more frequent complaints made by the questioned healthcare workers. When wearing a face mask, the respondents statistically significantly more often mentioned labored breath ($p < 0.001$) and discomfort on the face and / or behind the ears ($p = 0.035$); when wearing goggles, itching, redness and / or maceration in the area where they contact the head ($p = 0.009$), headaches

($p = 0.002$) and discomfort in the area where goggles contact the head ($p < 0.001$); when wearing gloves, itching ($p = 0.004$) and skin peeling ($p < 0.001$); when wearing overalls, elevated sweating ($p < 0.001$), feeling overheated ($p < 0.001$), thirst ($p < 0.001$), and palpitation ($p = 0.012$).

A considerable part of the respondents had certain difficulties associated with PPE use; complaints about them were statistically significantly more frequent when treating COVID-19 patients: 20.0 % (13.2–29.1) and 53.7 % (43.7–63.4) of the respondents mentioned difficulties in visual perception of information ($p < 0.001$); 22.1 % (14.9–31.5) and 45.3 % (35.6–55.3), difficulties in auditory perception of information ($p < 0.001$); 28.4 % (20.3–38.2) and 63.2 % (53.1–72.2) had physical discomfort when wearing PPE ($p < 0.001$); 6.3 % (2.9–13.1) and 14.7 % (9.0–23.2) had difficulties in putting PPE on / off ($p = 0.005$); 17.9 % (11.5–26.8) and 37.9 % (28.8–47.9) had difficulties in performing work tasks that require precise movements ($p < 0.001$); 12.6 % (7.4–20.8) and 27.4 % (19.4–37.1) complained about decreased working capacity due to PPE use ($p < 0.001$).

Greater physical loads in everyday work under adverse epidemic conditions were mentioned by 83.2 % (74.4–89.4) of the respondents and only 15.2 % (8.9–24.7) of them did not have any complaints as regards functioning of the musculoskeletal system. Greater work intensity was mentioned by 83.2 % (74.4–89.4) of the respondents and 94.9 % (87.7–98.0) of them believed it was associated with several pathological symptoms.

The questioning results also established that 63.2 % (53.1–72.2) and 51.6 % (41.7–61.4) of the respondents believed their everyday direct and indirect contacts with patients became longer under adverse epidemic conditions. COVID-19 confirmed with laboratory tests was diagnosed in 83.2 % (74.4–89.4) of the respondents; an association between the disease and an occupation was established for 20.3 % (12.9–30.4) of them and their disease cases were considered occupational infection. Still, 42.9 % (31.4–55.1) of those respondents with the disease not considered an occupational case believe that COVID-19 infection in them was also related to performing their occupational tasks. Ninety-three point seven percent (86.7–97.1) of the respondents were vaccinated against COVID-19.

Ninety-nine percent (94.3–99.8) of the respondents mentioned longer contacts with antiseptics or disinfectants during a work shift when performing their work tasks under adverse epidemic conditions. Out of them, 89.4 % (81.5–94.1) believed these contacts to be associated with several pathological symptoms including dry or irritated eye mucosa, irritation of the upper airways, skin irritation.

Therefore, this study established considerable changes in working conditions of healthcare workers under adverse epidemic conditions. These changes included longer contacts with biological and chemical health risk factors, greater work hardness and intensity, as well as the necessity to use PPE for a longer time. All this creates elevated occupational health risks for healthcare workers and stimulates development of occupational diseases and several various pathological states.

The study has a certain limitation. We did not have any objective data on the respondents' health prior to the pandemic and during it and this does not allow us to make unambiguous conclusions about an authentic association between specific subjective complaints and changed working conditions. However, our study results make a valuable contribution to investigating occupational health risks associated with treating patients during an epidemic rise in incidence of respiratory infections; they allow subjective assessment of changes in healthcare workers' health due to changes in their working conditions and can therefore provide substantiation for further profound study of the issue with relevant objective methods.

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Competing interests. The authors declare no competing interests.

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Research article

RISK OF PERINATAL MORTALITY AMONG THE OFFSPRING OF WORKERS EMPLOYED AT PRODUCTION WITH RADIATION HAZARDS

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Studies that address risks of perinatal mortality among the offspring of people exposed to ionizing radiation in the workplace are significant for developing hygienic standards at production facilities with radiation hazards.

The purpose was to analyze perinatal mortality (stillbirths and early neonatal deaths) among the offspring of workers employed by Mayak Production Association (Mayak PA), the first atomic production facility in Russia.

A retrospective analysis was performed among 25,007 children born in 1949–1973; parents of 14,580 of these children were exposed to long-term occupational radiation at Mayak PA. The study provides frequency and dynamics of perinatal mortality and comparative analysis of perinatal mortality by sex, year of birth, parental age at childbirth, and dose categories of radiation exposure. Research data were analyzed by methods of non-parametric statistics. We calculated a relative risk (RR) of perinatal mortality among the offspring of exposed and unexposed parents with 95 % CI.

The rate of perinatal mortality was generally the same in both groups, 19.9 for 10^3 in the test group and 17.9 for 10^3 in the control, $p > 0.05$. Stillbirths among male offspring were statistically significantly more often observed in the test group due to contribution of the children with only mothers exposed to occupational radiation exposure at Mayak PA prior to conception and offspring exposed in utero. Intrauterine fetal death was observed statistically significantly more often among boys of the test group compared to controls: 2.9 against 0.9 for 10^3. Rates of stillbirths and perinatal mortality in the main group statistically significantly exceeded the values in the comparison group in 1949–1953: RR = 2.69 (CI: 1.46–4.95) and 2.12 (1.38–3.28) respectively. Significant statistical differences in the perinatal mortality risk were established in certain categories of preconception and intrauterine gamma-exposure.

The identified peculiarities of unfavorable outcomes in the perinatal period that were detected among the offspring of Mayak PA workers could be eligible for further epidemiological monitoring. Poly-etiology character of perinatal mortality requires further follow up of the cohort of the offspring born to atomic production workers.

Keywords: *perinatal mortality, stillbirths, early neonatal deaths, Mayak PA, production with radiation hazards, offspring of exposed workers, preconception exposure, in utero exposure, dose to the gonads.*

Infants' mortality is singled out of the overall sphere of population mortality due to its special social and demographic significance since it is one of key indicators of population health [1]. It was reasonably demonstrated that well-being of postnatal development depends a lot on specific characteristics of early stages of ontogenesis[1].

Defining the contribution of radiation exposure to the risk of unfavorable reproduction outcomes is a topical aspect of scientific research in many experimental [2, 3] and epidemiological studies [4–6]. According to modern estimates of perinatal mortality in the cohort of the offspring of atomic bomb survivors in Japan [7] radiation exposure of parents was associated with increased risk of severe congenital malformations and perinatal death. However, the estimates of direct radiation exposure were imprecise and most of them weren't statistically significant. L. Parker et al. [8] in their analysis of stillbirths among the offspring of men exposed to radiation at the nuclear materials processing plant in Sellafield describe a statistically

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significant correlation between the risk of stillbirth and the total exposure to external ionizing radiation of the father prior to conception: adjusted odds ratio for 100 mSv 1.24 (95 % CI: 1.04–1.45). At the same time P. Doyle et al. [9] in their study of reproduction outcomes in the cohort of atomic production workers in the UK (11,697 men and 1903 women) found no evidence of relationship between exposure to low-rate ionizing radiation prior to conception and increased risk of an unfavorable reproduction outcome in men involved in atomic production. However, the authors indicate that the conclusions regarding maternal exposure prior to conception and increased risk of fetal death are ambiguous and require further research. The increase of perinatal mortality in Fukushima and four neighboring prefectures after the accident at Fukushima Nuclear Power Plant was described by A. Körblein and H. Küchenhoff [10]. The authors point out that the results obtained are consistent with similar observations in Germany [11], Ukraine and Belarus following the Chernobyl accident [12, 13].

Mayak Production Association (PA) is the first atomic production facility in Russia that has been in operation since 1948. Due to extremely tight deadlines for obtaining ionizing radiation sources for industrial and military purposes, due to lack of experience and imperfect technologies as well as due to radiation safety standards that were in effect at that time Mayak PA personnel comprising a large proportion of people in reproductive age could undergo significant occupational exposure in the period of production development.

The cohort of Mayak PA workers' offspring could be used as a valuable source for assessing late effects of radiation due to occupational exposure of parents. This research is performed in order to obtain an up-to-date mortality estimate in an extended cohort of the offspring of atomic production personnel taking into account the updated dosimetry data.

The purpose was to analyze perinatal mortality (stillbirths and early neonatal deaths) among the offspring of Mayak PA workers.

Material and methods. A retrospective epidemiological study was performed based on the registries developed and maintained in the Laboratory of Radiation Epidemiology in Southern Urals Biophysics Institute:

– The Medical-dosimetry Registry of personnel of Mayak PA [14];

– The Children Registry of a closed administrative territorial unit (CATU) Ozyorsk population exposed in childhood to anthropogenic radiation due to operation of Mayak PA [15];

– The Causes of Death Registry of CATU Ozyorsk population [16];

– The Ozyorsk Children's Health Registry of CATU population comprising medical and social information from archival pediatric outpatient records [17].

Information on individual doses of occupational radiation exposure to the parents was obtained from the "Mayak Worker Dosimetry System – 2013" [18]. The analysis takes into account absorbed doses of external gamma-exposure of the gonads prior to conception and gamma-exposure doses to the uterus.

Composing of the studied groups was performed as follows:

The cohort of Mayak PA workers employed in the period from 1948 to 1982 at the main (reactor, radiochemical and plutonium production) and auxiliary (water treatment and mechanical repairs) facilities comprises 25,757 individuals (19,395 men – 75.3 %; 6362 women – 24.7 %). The number of their offspring born after employment of the parents at Mayak PA makes 14,580 children (7543 boys – 51.7 %; 7037 girls – 48.3 %). The study includes children of Mayak PA workers born in CATU Ozyorsk. The period of childbirth is 1949–1973.

The comparison group was based on the Children Registry comprising information on children population of CATU Ozyorsk. The comparison group was composed of children of unexposed parents born in CATU Ozyorsk in 1949–1973 (their parent weren't exposed to occupational radiation prior to conception, didn't take part in liquidation of the consequences of radiation accidents, weren't relocated from radioactively contaminated areas). The comparison group finally comprised 10,427 individuals: 5301 (50.8 %) men; 5126 (49.2 %) women.

The analyzed groups are comparable in terms of year of birth, sex, and being born in the CATU. Those born outside the city and migrating into it at a young age were excluded from the study to ensure that the observed groups were characterized by the same climatic and geographic living conditions, as well as the same level and quality of healthcare.

The main causes of death were classified according to the 'International Statistical Classification of Diseases and Related Health Problems' (ICD) of the IX and X revisions.

The stillbirth rate was calculated as the number of stillbirth cases per 1000 live and stillborn births:

$$\text{Stillbirth rate} = \frac{\text{Number of stillborn}}{\text{Total live and stillborn births}} \cdot 1000.$$

In the studied period of children's births (1949–1973), in the USSR, stillbirth was understood as a birth that took place after 28 weeks of gestation, with fetal length of at least 35 cm and weight of at least 1000 g, in case the newborn did not take any breath after birth. Stillbirth was divided into the following types: antenatal – the fetus dies in utero before delivery; intranatal – the fetus dies directly in the course of delivery; and postnatal – the fetus is born with a heartbeat but dies because it fails to start extrauterine respiration. The criteria for stillbirth were significantly changed later [19].

Early neonatal mortality was calculated as the ratio of the number of children who died within 7 days after birth to the number of children born alive. Perinatal mortality rate included stillbirths and those who died in their first week (within the first 168 hours or 7 days) per 1000 live and stillborn births.

Statistical analysis was carried out using the STATISTICA Version 10 software package (StatSoft, USA). Comparison of rates was performed using the Pearson's chi-squared test and the two-tailed Fisher's exact test; the differences were considered significant at $p < 0.05$. The relative risk (*RR*) of perinatal losses among the offspring of exposed and unexposed parents was calculated with a 95 % confidence interval (CI).

RR was calculated by the formula:

$$RR = (a/a + b) / (c/c + d),$$

where

a – number of offspring in the main group with perinatal losses as an outcome;

b – number of offspring in the main group with no perinatal losses as an outcome;

c – number of offspring in the comparison group with perinatal losses as an outcome;

d – number of offspring in the comparison group with no perinatal losses as an outcome with the standard square error of the logarithmic relative risk:

$$\mathrm{SE}\{\ln(RR)\} = \sqrt{\frac{1}{a} + \frac{1}{c} + \frac{1}{a+b} + \frac{1}{c+d}},$$

and a 95 % confidence interval:

$$95\,\%\ \mathrm{CI} = \exp\left(\ln(RR) - 1.96 \cdot \mathrm{SE}\{\ln(RR)\}\right)$$

$$\text{to } \exp\left(\ln(RR) + 1.96 \cdot \mathrm{SE}\{\ln(RR)\}\right).$$

We carried out the analysis of the rates and relative risk of stillbirth, of early neonatal mortality, and perinatal losses by sex, year of birth, and age of parents at the time of the child's birth.

The calendar period of children's births was divided into 5-year intervals: 1949–1953, 1954–1958, 1959–1963, 1964–1968 and 1969–1973. The age of parents at the time of the child's birth was divided into the following categories: 20 years and younger, 21–25, 26–30, 31–35, 36 years and older. Analysis of the rates was performed for each interval.

The risk assessment of perinatal losses in different dose categories among the offspring of Mayak PA workers was performed in comparison with the offspring of the corresponding sex in the comparison group. The following dose categories were defined for preconception external gamma-exposure of the gonads: 0.1–20, 20.1–50, 50.1–100, 100.1–500, 500.1–1000, 1000.1 and more mGy; for in utero external gamma-exposure – 0.1–20, 20.1–50, 50.1–100, 100.1–500, 500.1 and more mGy.

RR estimates taking into account dose categories of radiation exposure were performed with separate analysis of each component.

Results and discussion. The rates of perinatal losses and its structural components in the groups for the whole period of follow up are presented in Table 1.

During the period from 1949 to 1973, a total of 291 cases of perinatal mortality were registered in the main group, with no statistically significant differences compared to the comparison group (187 cases), $\chi^2 = 1.32$, $p > 0.05$. Comparative analysis of perinatal losses by sex demonstrated no statistically significant differences: in the main group, 58.1 % (169 cases) of the offspring were male, and 41.9 % (122 cases) were female, while in the comparison group, these percentages made 56.2 % (105 cases) and 43.8 % (82 cases), respectively, $p > 0.05$.

Overall perinatal mortality rates did not differ significantly between the groups: 9.95 per 10^3 in the main group and 7.9 per 10^3 in the comparison group, $\chi^2 = 2.93$, $p > 0.05$. However, the rate of stillbirths among male offspring in the main group significantly exceeded the corresponding rate in the comparison group (11.4 vs 7.7 per 10^3, $\chi^2 = 4.27$, $p = 0.038$). Stillbirth rates among female offspring in both groups were comparable: 8.4 per 10^3 in the main group and 8.0 per 10^3 in the control group, $\chi^2 = 0.05$, $p > 0.05$.

No statistically significant differences were found in the incidence of early neonatal mortality between the groups: the contribution of offspring of both sexes to early neonatal mortality in the groups was almost identical – 10.1 and 10.2 per 10^3, $\chi^2 = 0.0008$, $p > 0.05$.

According to official statistics, perinatal mortality rates in various countries around the world during the study period ranged from 12 to 50 ‰, and early neonatal mortality ranged from 5.4 to 16.4 ‰ [20, 21]. In the USSR, based on selective data, perinatal mortality rates ranged from 12 to 25 ‰, varying by regions[2] [22]. Subsequently, perinatal mortality rates in Russia showed a consistent decrease, from 17.9 ‰ in 1990 to 10.2 ‰ in 2005 [23].

For a correct comparison of perinatal mortality among the offspring of Mayak PA workers with the national data, a further analysis of standardized mortality ratio (SMR) is necessary.

Given the statistically significant differences in stillbirth rates among male offspring, this category was studied in more detail. The distribution of male offspring in the main group demonstrated that in 15 % (1131/7543) of male offspring in the main group mothers only were exposed to preconception occupational radiation at Mayak PA, fathers only – in 66.2 % (4991/7543), and both parents in 18.8 % (1421/7543). In utero external gamma-exposure was registered in every third male offspring making 34 % (2567/7543).

Table 1

Rates of perinatal losses

Main group						Comparison group					
Boys (n = 7543)		Girls (n = 7037)		Both (n = 14,580)		Boys (n = 5301)		Girls (n = 5126)		Both (n = 10,427)	
abs.	per 10^3	abs.	per 10^3	abs.	per 10^3	abs.	per 10^3	abs.	per 10^3	abs.	per 10^3
Stillbirth rates											
86*	11.4	59	8.4	145	9.95	41	7.7	41	8.0	82	7.9
Early neonatal mortality**											
83	11.1	63	9.0	146	10.1	64	12.2	41	8.1	105	10.2
Perinatal mortality											
169	22.4	122	17.3	291	19.9	105	19.8	82	16.0	187	17.9

Note: * – statistically significant differences with the comparison group; ** – from the total number of children born alive.

[2] Petrov-Maslakov M.A., Klimets I.I. Perinatal'naya smertnost' [Perinatal mortality]. Leningrad, Meditsina Publ., 1965, 218 p. (in Russian).

Table 2

Comparative analysis of stillbirths among male offspring

Main group			Comparison group			χ^2	p
Number of stillbirths	Total number of offspring*	per 10^3	Number of stillbirths	Total number of offspring*	per 10^3		
Exposed mother only							
22**	1131	19.5	41	5301	7.7	13.19	0.0003
Exposed father only							
49	4991	9.8	41	5301	7.7	1.28	> 0.05
Both parents exposed							
15	1421	10.6	41	5301	7.7	1.08	> 0.05
In utero exposure							
37**	2567	14.4	41	5301	7.7	7.86	0.005

Note: * – number of male offspring in this category, ** – statistically significant differences with the comparison group.

Significant statistical differences in stillbirth rates among male offspring compared to male offspring in the comparison group (Table 2) were observed for children with only mothers exposed to preconception occupational radiation ($\chi^2 = 13.19$, $p = 0.0003$) and for in utero exposed offspring ($\chi^2 = 7.86$, $p = 0.005$). In these categories, the stillbirth rates were the highest (19.5 and 14.4 per 10^3), exceeding the level of stillbirths among male offspring in the comparison group (7.7 per 10^3) by 2.5 and 1.9 times, respectively.

Dynamics of perinatal mortality by calendar periods is presented in Figure 1.

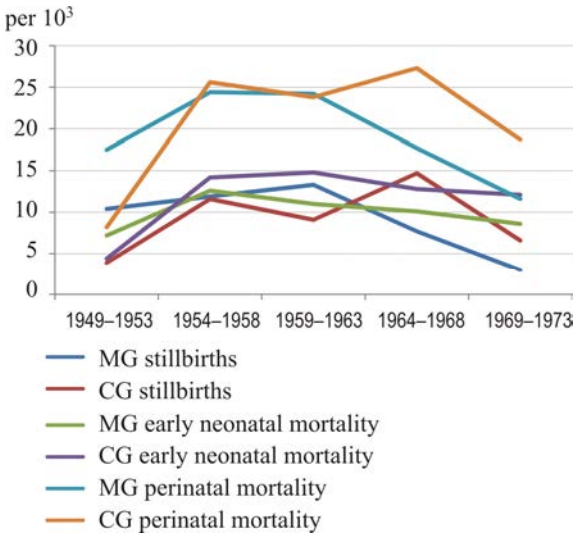

Figure 1. Dynamics of perinatal mortality for the period 1949–1973: MG – main group, CG – comparison group

The maximum rate of stillbirth in the main group was observed in 1959–1963 (13.3 per 10^3), followed by a steady decrease, while in the comparison group, the peak of stillbirth rate was observed in 1964–1968 (14.7 per 10^3). Comparison of stillbirth rates by calendar periods demonstrated statistically significant differences between the groups only for 1949–1953 when stillbirth rate in the main group (10.4 per 10^3) significantly exceeded the rate in the control group (3.9 per 10^3), $\chi^2 = 10.9$, $p < 0.001$.

The dynamics of early neonatal mortality in both groups was rather proportional: the minimum values were registered at the beginning of the follow up period (in 1949–1953 – 7.2 per 10^3 in the main group, 4.4 per 10^3 in the comparison group) with a gradual decrease reaching the plateau in 1954-1963 and moderate decrease by 1969–1973 (8.6 and 12.1 per 10^3, respectively). There were no significant statistical differences in early neonatal mortality between the groups when considering each calendar period.

The dynamics of perinatal mortality, in general, mirrored the stillbirth trends in the groups. Statistically significant differences were only observed for the period 1949–1953 when the perinatal loss rate in the main group (17.5 per 10^3) significantly exceeded that of the comparison group (8.2 per 10^3), $\chi^2 = 12.1$, $p < 0.001$.There was a stabilization of perinatal mortality rates in the periods 1954–1958 and 1959–1963, with little difference between the

groups, reaching 24.4 and 24.2 per 10^3 in the main group and 25.6 and 23.8 per 10^3 in the comparison group, respectively. Subsequently, there was a decrease in perinatal loss rates, starting from 1963 in the main group (from 24.2 to 11.6 per 10^3) and from 1968 in the comparison group (from 27.3 to 18.7 per 10^3).

Analysis of the relative risk of perinatal loss by calendar period (Table 3) proved significant statistical differences only for the period 1949–1953, when stillbirth and perinatal mortality in the main group significantly exceeded those in the comparison group: *RR* = 2.69 (1.46–4.95) and 2.12 (1.38–3.28), respectively. Risk assessment of early neonatal mortality, both overall and regarding gender, demonstrated no statistically significant differences.

The majority of perinatal losses in both groups (Figure 2) were 'Certain conditions originating in the perinatal period' (ICD-10 codes P00–P96): 78.3 % (228/291) in the main group and 80.2 % (150/187) in the comparison group, $\chi^2 = 0.64$, $p > 0.05$. Intrauterine fetal deaths made 11 % (32/291) in the main group and 7.5 % (14/187) in the comparison group, $\chi^2 = 2.4$, $p > 0.05$. According to archival statistical data[3], the proportion of antenatal fetal deaths in the overall stillbirth rate was very high during the study period, ranging from 17 to 61 %.

There were no significant statistical differences in perinatal losses due to congenital malformations, perinatal-specific infections, respiratory diseases, and other disorders occurring in the perinatal period.

Thus, the structure of perinatal losses did not differ between the groups. However, the analysis of the structure of perinatal mortality by offspring sex demonstrated that intrauterine fetal death was statistically significantly more common among boys in the main group compared to the control group: 2.9 vs 0.9 per 10^3, *F*-test = 0.018. Y.M. Wong et al. [24] in their review of the effects of radiation therapy on the fetus pointed out that a fetus exposed to radiation has a higher probability of side effects, such as congenital abnormalities and even fetal death, especially when the threshold of 0.1 Gy is exceeded.

Table 3

Perinatal losses by calendar periods of birth of the offspring

		Main group (*n* = 14,580)		Comparison group (*n* = 10,427)		*RR*	95 % CI
		abs.	per 10^3	abs.	per 10^3		
1949–1953	Stillbirth rate	32/3085	10.4	15/3884	3.9	2.69*	1.46–4.95
	Early neonatal mortality**	22/3053	7.2	17/3869	4.4	1.64	0.87–3.1
	Perinatal mortality	54/3085	17.5	32/3884	8.2	2.12*	1.38–3.28
1954–1958	Stillbirth	43/3608	11.9	29/2500	11.6	1.03	0.64–1.64
	Early neonatal mortality	45/3565	12.6	35/2471	14.2	0.89	0.57–1.38
	Perinatal mortality	88/3608	24.4	64/2500	25.6	0.95	0.7–1.31
1959–1963	Stillbirth	44/3308	13.3	13/1429	9.1	1.46	0.79–2.71
	Early neonatal mortality	36/3264	11.0	21/1416	14.8	0.74	0.44–1.27
	Perinatal mortality	80/3308	24.2	34/1429	23.8	1.02	0.68–1.5
1964–1968	Stillbirth	20/2591	7.7	14/953	14.7	0.53	0.27–1.04
	Early neonatal mortality	26/2571	10.1	12/939	12.8	0.79	0.4–1.6
	Perinatal mortality	46/2591	17.7	26/953	27.3	0.65	0.4–1.05
1969–1973	Stillbirth	6/1988	3.0	11/1661	6.6	0.46	0.17–1.23
	Early neonatal mortality	17/1982	8.6	20/1650	12.1	0.71	0.37–1.35
	Perinatal mortality	23/1988	11.6	31/1661	18.7	0.62	0.36–1.06

Note: * – statistically significant differences with the comparison group; ** – from the number of children born alive.

[3] Petrov-Maslakov M.A., Klimets I.I. Perinatal'naya smertnost' [Perinatal mortality]. Leningrad, Meditsina Publ., 1965, 218 p. (in Russian).

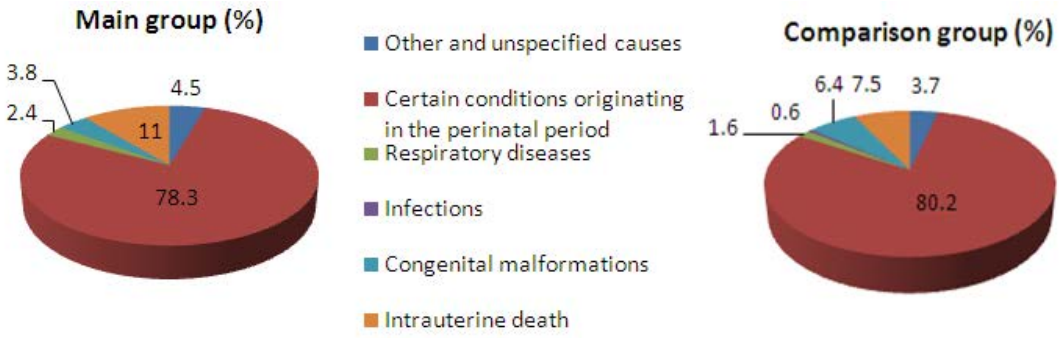

Figure 2. Perinatal mortality structure

The frequency of 'Certain conditions originating in the perinatal period' among offspring of different sexes did not differ: in the main group, it was 17.1 per 10^3 among boys and 14.1 per 10^3 among girls; in the comparison group, it was 16.0 and 12.7 per 10^3, respectively, $p > 0.05$. An analysis of nosological forms included in 'Certain conditions originating in the perinatal period' (Figure 3) demonstrated that various respiratory disorders were the most common cause of perinatal losses in both groups (8.8 per 10^3 in the main group and 7.7 per 10^3 in the comparison group, $\chi^2 = 0.9$, $p > 0.05$). Among stillborn infants, respiratory pathology was primarily represented by intrauterine hypoxia and intranatal asphyxia ($\chi^2 = 0.08$, $p > 0.05$). Among live-born infants who died in the early neonatal period respiratory distress syndrome and atelectasis were the most frequent causes of death ($\chi^2 = 0.02$, $p > 0.05$).

Statistically significant differences in the incidence of nosological forms in the structure of 'Certain conditions originating in the perinatal period' were only observed for birth traumas, which were more frequently registered in the main group (1.65 vs 0.67 per 10^3 in the control group, $\chi^2 = 4.66$, $p = 0.03$), and early neonatal mortality due to prematurity, which was more common among the offspring of unexposed parents (1.2 per 10^3 in the main group and 2.2 per 10^3 in the comparison group, $\chi^2 = 4.12$, $p = 0.042$).

It should be noted that the groups did not differ in the level of medical care provided in the closed administrative-territorial unit (CATU) and, in particular, in availability of obstetric and gynecological services. Medical care for the population of CATU, along with employees of the city-forming enterprise, was provided by the Federal Medical and Biological

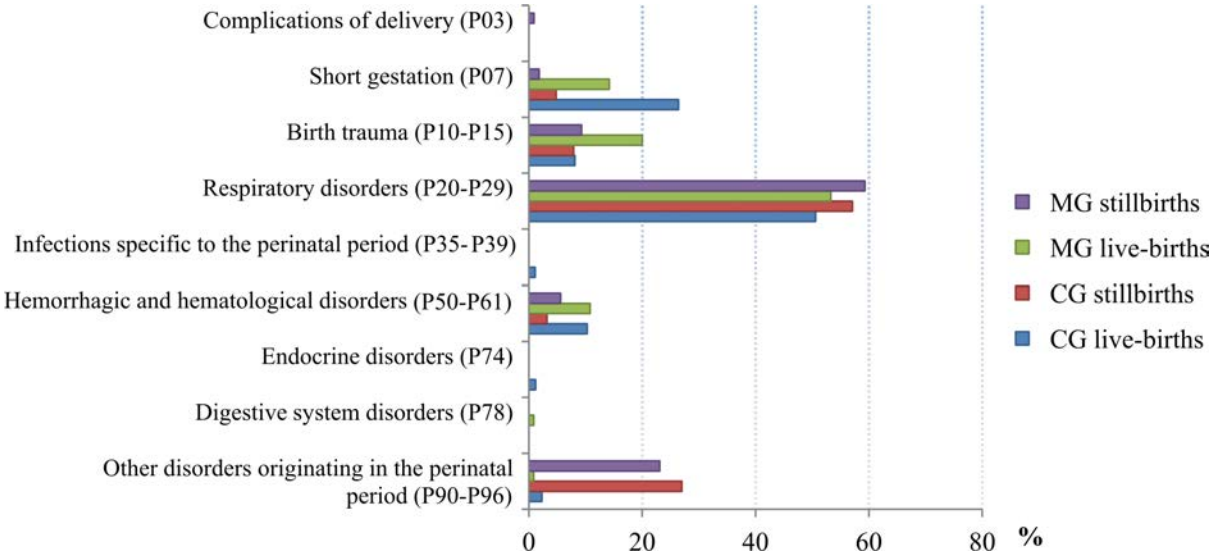

Figure 3. Certain conditions originating in the perinatal period (P00–P96): MG – main group, CG – comparison group

Table 4

Perinatal losses by age of parents at childbirth

		Main group (n = 14,580)		Comparison group (n = 10,427)		*RR*	95 % CI
		abs.	per 10^3	abs.	per 10^3		
Number of offspring	Boys	169/7543	22.4	105/5301	19.8	1.13	(0.89–1.44)
	Girls	122/7037	17.3	82/5126	16.0	1.08	(0.82–1.43)
	Both	291/14580	19.9	187/10427	17.9	1.11	(0.93–1.34)
Mothers							
20 years and younger	Boys	18/831	21.7	17/750	22.7	0.96	0.5–1.84
	Girls	16/764	20.9	7/655	10.7	1.96	0.8–4.73
	Both	34/1595	21.3	24/1405	17.1	1.25	0.7–2.1
21–25	Boys	65/2968	21.9	39/2093	18.6	1.17	0.8–1.74
	Girls	42/2818	14.9	29/2074	14.0	1.1	0.67–1.71
	Both	107/5786	18.5	68/4167	16.3	1.13	0.84–1.53
26–30	Boys	51/2453	20.8	25/1495	16.7	1.24	0.77–1.99
	Girls	41/2273	18.0	25/1510	16.6	1.1	0.67–1.78
	Both	92/4726	19.5	50/3005	16.6	1.17	0.83–1.65
31–35	Boys	28/998	28.1	14/649	21.6	1.3	0.7–2.5
	Girls	16/901	17.8	15/603	24.9	0.71	0.36–1.43
	Both	44/1899	23.2	29/1252	23.2	1.0	0.63–1.6
36 years and older	Boys	7/293	23.9	10/314	31.8	0.75	0.29–1.95
	Girls	7/281	24.9	6/284	21.1	1.18	0.4–3.47
	Both	14/574	24.4	16/598	26.8	0.91	0.45–1.85
Fathers*							
20 years and younger	Boys	5/234	21.4	2/142	14.1	1.52	0.3–7.72
	Girls	4/206	19.4	3/131	22.9	0.85	0.2–3.73
	Both	9/440	20.5	5/273	18.3	1.12	0.38–3.3
21–25	Boys	51/2532	20.1	39/1776	22.0	0.92	0.61–1.39
	Girls	40/2411	16.6	22/1683	13.1	1.27	0.76–2.13
	Both	91/4943	18.4	61/3459	17.6	1.04	0.76–1.44
26–30	Boys	60/2887	20.8	35/1802	19.4	1.1	0.71–1.62
	Girls	45/2282	16.8	31/1873	16.5	1.0	0.6–1.6
	Both	105/5569	18.8	66/3675	18.0	1.05	0.77–1.4
31–35	Boys	28/1241	22.6	16/938	17.1	1.32	0.72–2.4
	Girls	16/1153	13.9	22/869	25.3	0.55	0.29–1.04
	Both	44/2394	18.4	38/1807	21.0	0.87	0.57–1.34
36 years and older	Boys	4/479	8.4	13/641	20.3	0.41	0.14–1.25
	Girls	8/457	17.5	4/557	7.2	2.44	0.74–8.0
	Both	12/936	12.8	17/1198	14.2	0.9	0.43–1.9

Note: * there's no data on father's age for 298 children in the main group and 15 children in the comparison group.

Agency of Russia in the form of medical-sanitary units and clinics [25]. It is also important to indicate that the study groups comprised only children born and residing in the CATU Ozyorsk, that excludes the possibility of including cases of perinatal death registered in other territories.

Distribution of the offspring by age of parents at childbirth (Table 4) demonstrated that among children who died in the perinatal period, more than one third of the mothers in both groups belonged to the age category of 21–25 years: 36.8 % (107/291) in the main group and 36.4 % (68/187) in the comparison group (χ^2 = 0.01, p > 0.05). Meanwhile, the category of 26–30 years was more frequently observed among the fathers: 36.1 % (105/291) in the main group and 35.3 % (66/187) in the comparison group (χ^2 = 0.03, p > 0.05).

The average age of mothers of stillborn children in the main group was 26.8 ± 5 years (27.2 ± 5.3 years in the comparison group), and the average age of fathers was 27.6 ± 4.6 (29.2 ± 5.9 in the comparison group). Regard-

ing live-born children who died in the early neonatal period, the average age of mothers reached 25.9 ± 5.1 years in the main group and 26.3 ± 5.8 in the comparison group, and fathers' ages were 27.0 ± 4.7 and 27.8 ± 5.1, respectively. There was no information about fathers' dates of birth for 2 % (298/14,580) of children in the main group, 30 of these offspring died in the perinatal period. In the comparison group, the father's age at the date of the child's birth was unknown for 0.14 % (15/10,427) of the children, and no cases of perinatal death were observed among them.

The perinatal mortality rate in the main group was the highest among male offspring born to parents aged 31–35 years (28.1 per 10^3 in the given maternal age category and 22.6 per 10^3 in the paternal age category); in the comparison group this rate was the highest among boys born to mothers aged 36 and older (31.8 per 10^3) and among girls whose fathers were aged 31–35 years (25.3 per 10^3). However, no statistically significant differences in perinatal losses were found based on parental age, both when considering genders separately and overall in the groups.

Given the previously noted statistically significant difference in the incidence of stillbirths among male offspring, additional analysis of relative risk was performed in this category, taking into account parental age as well (Table 5).

In general, the relative risk of stillbirths was higher among male offspring in the main group by almost 1.5 times: *RR* = 1.47 (1.02–2.14). Statistically significant risk estimates for stillbirths were obtained for male offspring with only mothers employed at Mayak PA: *RR* = 2.51 (1.5–4.21) and for offspring of the mothers exposed to occupational radiation during pregnancy: *RR* = 1.86 (1.2–2.9).

Assessment of the risk of stillbirths in different age categories of parents demonstrated significant statistical differences only in the category of paternal age of 31–35 years: stillbirths among male offspring in the main group were observed three times more often than in the control group – *RR* = 3.2 (CI: 1.08–9.51). However, the results of this analysis should be interpreted carefully, since there was no information on paternal age for 2.3 % (170/7543) of the boys in the main group.

Distribution of the offspring in the main group by the year of employment of their parents at Mayak PA demonstrated that 71.7 % of mothers and 55.4 % of fathers of stillborn children, and 68.5 % of mothers and 39.8 % of fathers of live-born offspring started their work in the early period of development of this atomic production facility (1948–1953). Most of the parents in the main group were employees of the radiochemical facility: 42.6 % of mothers and 39.9 % of fathers. Maximum doses of preconception external gamma-radiation to the gonads reached 4075.6 mGy for mothers and 5653.1 mGy for fathers, and in utero exposure

Table 5

Stillbirth rate by parental age at childbirth (male offspring)

	Main group		Comparison group		*RR*	95 % CI
	abs.	per 10^3	abs.	per 10^3		
Number of male offspring	86 / 7543	11.4	41/ 5301	7.7	1.47**	(1.02–2.14)
Mothers						
20 years and younger	6/831	7.2	6/750	8.0	0.9	0.29–2.79
21–25	30/2968	10.1	13/2093	6.2	1.63	0.85–3.11
26–30	33/2453	13.5	13/1495	8.7	1.54	0.82–2.93
31–35	15/998	15.0	6/649	9.2	1.63	0.63–4.17
36 years and older	2/293	6.8	3/314	9.6	0.71	0.12–4.25
Fathers*						
20 years and younger	1/234	4.3	1/142	7.0	0.61	0.04–9.63
21–25	24/2532	9.5	15/1776	8.5	1.12	0.6–2.13
26–30	32/2887	11.1	13/1802	7.2	1.54	0.81–2.92
31–35	17/1241	13.7	4/938	4.3	3.2**	1.08–9.51
36 years and older	2/479	4.2	8/641	12.5	0.33	0.07–1.6

Note: * there's no data on father's age for 170 children in the main group and 2 children in the comparison group; ** – statistically significant differences with the comparison group.

doses made up to 916.1 mGy. 'Zero dose' meant that a worker was included into Mayak PA workers' cohort, but no individual doses of occupational radiation were recorded during the study period.

Distribution of the offspring who died in the perinatal period by the doses of radiation exposure of their parents at workplaces (Figure 4) demonstrated that parents working at Mayak PA were exposed to prolonged occupational radiation over a wide range of doses.

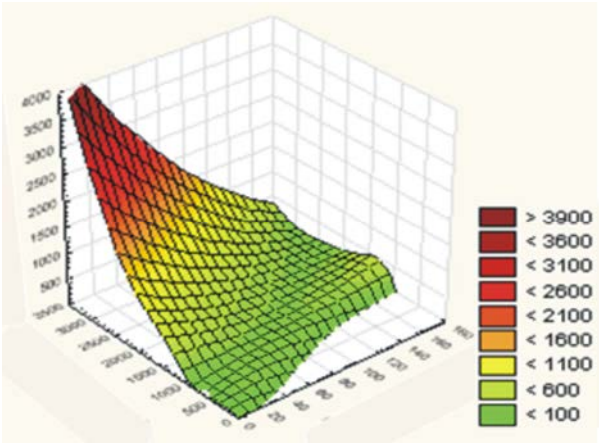

Figure 4. Distribution of offspring by parental doses of occupational exposure, mGy: X-axis – in utero exposure; Y-axis – preconception exposure of the ovaries; Z-axis – preconception exposure of the testicles

Thus, regarding stillborn children the median dose of preconception radiation exposure of the mothers made 192.8 mGy (interquartile range 46.7–626.4 mGy), and 225.5 (102.3–790.7) mGy – of the fathers; in utero radiation exposure was 25.0 (9.5–87.2) mGy.

Distribution of the offspring who died in the perinatal period by categories of preconception external gamma-radiation doses to the ovaries demonstrated that the highest incidence of perinatal mortality was observed for doses above 1 Gy: among boys – 44.6 per 10^3, among girls – 25.6 per 10^3, for the offspring of both sexes – 35.8 per 10^3. Distribution of the offspring by dose categories of preconception exposure of the testicles prior to conception revealed the highest incidence of perinatal losses in the dose range of 500.1–1000 mGy for girls – 27.5 per 10^3 and for offspring of both sexes – 25.6 per 10^3; and in the dose category of 100.1–500 mGy for boys – 26.0 per 10^3. Regarding in utero gamma-radiation exposure, the highest perinatal mortality rate was observed in the dose category of 50.1–100 mGy for girls – 17.9 per 10^3 and for offspring of both genders – 24.8 per 10^3; and in the dose category of 20.1–50 mGy for boys – 34.2 per 10^3.

Calculation of the relative risk of perinatal losses in relation to dose categories of radiation exposure of parents in their workplaces demonstrated significant differences in the preconception radiation exposure to ovaries in the dose category of over 1 Gy (compared to the control group): among boys – 2.25 (1.19–4.25) and for both genders – 2.0 (1.19–3.35); and among male offspring of the fathers who were exposed to preconception radiation in a cumulative dose to the gonads from 500.1 to 1000 mGy – 1.72 (1.05–2.81). The analysis of the risk of perinatal mortality among offspring of the mothers exposed to radiation during pregnancy did not reveal any significant differences from the comparison group in all the dose intervals.

Maximum differences were found in the course of a comparative analysis of stillbirths (Table 6). Thus, a significant increase of stillbirth risk was registered for male offspring in the following dose categories of preconception external gamma-exposure of the ovaries: 0.1–20 mGy – *RR* = 2.9 (95 % CI: 1.3–6.5), 100.1–500 mGy – 2.15 (1.1–4.2) and for overall observation among boys – 1.87 (1.21–2.92). Statistically significant differences against control group were obtained in dose category over 1 Gy: 3.21 (1.28–8.0) for girls and 2.4 (1.18–4.98) for the whole group.

The risk of stillbirths in relation to preconception exposure of the testicles generally did not differ from the comparison group. The only exceptions were observed among male offspring in the main group, the risk of stillbirths in the dose categories of 100.1–500 mGy and more than 1 Gy significantly exceeded the control group values: 1.8 (1.1–2.9) and 1.98 (1.05–3.75), respectively.

Analysis of stillbirths regarding in utero external gamma-exposure demonstrated that in the dose category of 20.1–50 mGy, risk for male offspring of the main group was almost three times higher than in the control group: 2.8 (1.3–6.2). Additionally, statistically significant

Table 6

Risk of stillbirth by dose categories of radiation exposure
(against the offspring of the corresponding gender in the comparison group)

Dose categories, mGy	Offspring sex	Main group		Comparison group		*RR*	95 % CI
		abs.	per 10^3	abs.	per 10^3		
Preconception external gamma-exposure of the ovaries:							
= 0	Boys	7/597	11.7	41/5301	7.7	1.50	0.7–3.4
	Girls	5/597	8.4	41/5126	8.0	1.05	0.42–2.64
	Both	12/1194	10.1	82/10427	7.9	1.28	0.7–2.3
0.1–20	Boys	7/309	22.6	41/5301	7.7	2.9*	1.3–6.5
	Girls	2/283	7.1	41/5126	8.0	0.88	0.22–3.6
	Both	9/592	15.2	82/10427	7.9	1.93	0.98–3.8
20.1–50	Boys	2/235	8.5	41/5301	7.7	1.1	0.3–4.5
	Girls	1/184	5.4	41/5126	8.0	0.7	0.1–4.9
	Both	3/419	7.2	82/10427	7.9	0.9	0.3–2.9
50.1–100	Boys	4/258	15.5	41/5301	7.7	2.0	0.7–5.6
	Girls	2/198	10.1	41/5126	8.0	1.3	0.31–5.2
	Both	6/456	13.2	82/10427	7.9	1.7	0.7–3.8
100.1–500	Boys	11/663	16.6	41/5301	7.7	2.15*	1.1–4.2
	Girls	5/607	8.2	41/5126	8.0	1.03	0.41–2.6
	Both	16/1270	12.6	82/10427	7.9	1.6	0.94–2.7
500.1–1000	Boys	3/266	11.3	41/5301	7.7	1.46	0.45–4.7
	Girls	2/264	7.6	41/5126	8.0	0.95	0.23–3.9
	Both	5/530	9.4	82/10427	7.9	1.2	0.5–2.9
1000.1 and more	Boys	3/224	13.4	41/5301	7.7	1.7	0.5–5.5
	Girls	5/195	25.6	41/5126	8.0	3.21*	1.28–8.0
	Both	8/419	19.1	82/10427	7.9	2.4*	1.18–4.98
Total	Boys	37/2552	14.5	41/5301	7.7	1.87*	1.21–2.92
	Girls	22/2328	9.5	41/5126	8.0	1.18	0.71–1.98
	Both	59/4880	12.1	82/10427	7.9	1.54*	1.1–2.15
Preconception external gamma-exposure of the testicles:							
= 0	Boys	6/1016	5.9	41/5301	7.7	0.76	0.33–1.8
	Girls	6/952	6.3	41/5126	8.0	0.8	0.34–1.85
	Both	12/1968	6.1	82/10427	7.9	0.77	0.42–1.4
0.1–20	Boys	7/649	10.8	41/5301	7.7	1.4	0.63–3.1
	Girls	5/662	7.6	41/5126	8.0	0.94	0.37–2.4
	Both	12/1311	9.2	82/10427	7.9	1.16	0.64–2.1
20.1–50	Boys	4/595	6.7	41/5301	7.7	0.87	0.3–2.4
	Girls	4/564	7.1	41/5126	8.0	0.89	0.32–2.5
	Both	8/1159	6.9	82/10427	7.9	0.88	0.43–1.8
50.1–100	Boys	1/652	1.5	41/5301	7.7	0.2	0.03–1.4
	Girls	3/641	4.7	41/5126	8.0	0.6	0.18–1.9
	Both	4/1293	3.1	82/10427	7.9	0.4	0.14–1.1
100.1–500	Boys	27/1962	13.8	41/5301	7.7	1.8*	1.1–2.9
	Girls	15/1821	8.2	41/5126	8.0	1.03	0.6–1.86
	Both	42/3783	11.1	82/10427	7.9	1.4	0.98–2.0
500.1–1000	Boys	7/755	9.3	41/5301	7.7	1.2	0.54–2.7
	Girls	10/692	14.5	41/5126	8.0	1.81	0.91–3.6
	Both	17/1447	11.7	82/10427	7.9	1.5	0.9–2.5
1000.1 and more	Boys	12/783	15.3	41/5301	7.7	1.98*	1.05–3.75
	Girls	5/724	6.9	41/5126	8.0	0.86	0.34–2.2
	Both	17/1507	11.3	82/10427	7.9	1.4	0.85–2.4
Total	Boys	64/6412	10.0	41/5301	7.7	1.29	0.87–1.91
	Girls	48/6056	7.9	41/5126	8.0	0.99	0.65–1.5
	Both	112/12468	9.0	82/10427	7.9	1.14	0.86–1.52

The end of Table 6

In utero external gamma-exposure:							
= 0	Boys	15/906	16.6	41/5301	7.7	2.14*	1.2–3.85
	Girls	11/898	12.3	41/5126	8.0	1.5	0.8–2.97
	Both	26/1804	14.4	82/10427	7.9	1.83*	1.18–2.8
0.1–20	Boys	6/770	7.8	41/5301	7.7	1.0	0.43–2.4
	Girls	8/649	12.3	41/5126	8.0	1.54	0.73–3.3
	Both	14/1419	9.9	82/10427	7.9	1.25	0.71–2.21
20.1–50	Boys	7/322	21.7	41/5301	7.7	2.8*	1.3–6.2
	Girls	2/276	7.2	41/5126	8.0	0.91	0.22–3.73
	Both	9/598	15.1	82/10427	7.9	1.91	0.97–3.8
50.1–100	Boys	4/220	18.2	41/5301	7,7	2.35	0.85–6.5
	Girls	1/223	4.5	41/5126	8.0	0.56	0.1–4.1
	Both	5/443	11.3	82/10427	7.9	1.4	0.6–3.5
100.1–500	Boys	5/337	14.8	41/5301	7.7	1.9	0.76–4.82
	Girls	1/286	3.5	41/5126	8.0	0.44	0.1–3.2
	Both	6/623	9.6	82/10427	7.9	1.22	0.54–2.8
500.1 and more	Boys	-/12	-	41/5301	7.7	-	–
	Girls	-/14	-	41/5126	8.0	-	–
	Both	-/26	-	82/10427	7.9	-	–
Total	Boys	37/2567	14.4	41/5301	7.7	1.86*	1.2–2.9
	Girls	23/2346	9.8	41/5126	8.0	1.23	0.74–2.04
	Both	60/4913	12.2	82/10427	7.9	1.55*	1.12–2.16

Note: * – statistically significant differences from the comparison group.

differences were observed in the overall group, in boys – 1.86 (1.2–2.9), and in both sexes – 1.55 (1.12–2.16), as well as in the category of "zero" doses: in boys – 2.14 (1.2–3.85), and in both genders – 1.83 (1.18–2.8).

Analysis of the relative risk of early neonatal mortality demonstrated significant differences from the control only for male offspring of the mothers exposed to preconception external gamma-radiation with cumulative doses exceeding 1 Gy: 2.6 (1.21–5.6).

Direct comparison of the obtained risk estimates in relation to dose categories with literary data is challenging since the cohort of Mayak PA workers is characterized by high doses of prolonged occupational radiation exposure, as opposed to other research groups. Cumulative preconception doses of external gamma-exposure to the gonads exceeding 1 Gy was registered in 419 (2.9 %) mothers and 1507 (10.3 %) fathers of the offspring in the main group.

Most research works describe the risks of perinatal losses in the category of low doses. For example, a study of the reproductive health of employees at four nuclear power plants (Smolensk, Kursk, Kalinin, and Novovoronezh) did not show any effect of occupational radiation exposure on health of newborn children in families of male personnel with calculated accumulated individual preconception radiation doses under 30 mSv [26]. The authors plan to follow up the reproductive health of a small group of male personnel at nuclear power plants whose accumulated effective doses may exceed 100 mSv. According to S. Yasuda et al. [27], an analysis of perinatal outcomes among women survivors of the nuclear accident at the Fukushima Daiichi nuclear power plant, with an average external radiation dose of 0.5 mSv (maximum 5.2 mSv), did not show any interrelation with congenital anomalies, low birth weight, immaturity at gestational age, or preterm births.

However, regarding the categories of prolonged radiation exposure in the course of radiotherapy, in a cohort analysis among children of patients who had cancer in childhood L.B. Signorello et al. [28] note that exposure of ovaries and uterus significantly increased the risk of stillbirths and of neonatal death at doses exceeding 10 Gy (9.1 [3.4–24.6]). The authors point out that if girls had received treatment before menarche, radiation exposure of ovaries and uterus at doses of 1.00–2.49 Gy significantly increased the risk of stillbirth or neonatal death (4.7 [1.2–19.0]). Practical radiation protection system recommended by the

International Commission on Radiological Protection (ICRP) supports embryonic predisposition to lethal radiation effects during the preimplantation period of embryonic development but notes that such lethal effects are very rare at doses below 100 mGy [29].

Beyond all doubt, the multi-factor nature of perinatal losses significantly complicates risk assessment and expands the list of possible parameters for studying this issue. Scientific literature presents a wide range of adverse risk factors for children health, including such medical and biological factors as abortion anamnesis, birth order, the course of pregnancy, and the mother's health status [30, 31]. Obstetric and extragenital pathologies complicate the course of antenatal period and lead to development of various pathologies in the fetus, as well as increase the risk of pathology during the neonatal period and at older age [32, 33].

The polyetiological nature of deviations in the perinatal period emphasizes the importance of studying the health of offspring of Mayak PA workers, taking into account the medical and social aspects in closed administrative-territorial units (CATU) [34, 35]. Issues of preconception exposure of parents not related to their occupation, such as effects of low doses of diagnostic radiation exposure, is also an object of scientific interest [36]. The Ozyorsk Children's Health Registry of CATU population is being actively expanded at the moment that will allow performing a multi-factor analysis of perinatal mortality in the nearest future.

Further analyses of perinatal losses in this sample are planned in the following directions: factor analysis in a cohort of offspring, taking into account non-radiation factors, comparison of perinatal mortality incidence and its structural components among the offspring of Mayak PA workers with regional and national statistics, and a dose-response analysis defining risk coefficients for perinatal losses in the offspring of Mayak PA workers based on accumulation rates of cumulative doses of occupational radiation exposure of their parents.

Conclusions. This retrospective epidemiological study was performed in a cohort of 25,007 children, 14,580 of them were the offspring of Mayak PA workers exposed to prolonged occupational radiation. An analysis of perinatal losses and their structural components (stillbirths and early neonatal mortality) was performed in comparison to a group of offspring of the parents who were not exposed to radiation at work (n = 10,427).

The study resulted in the following conclusions:

– during the period from 1949 to 1973, a total of 291 cases of perinatal mortality were registered in the main group, with no statistically significant differences compared to the control group (187 cases), $\chi^2 = 1.32$, $p > 0.05$;

– there was a significant increase of stillbirth rate among male offspring in the main group (11.4 per 10^3 compared to 7.7 per 10^3 in the comparison group, $\chi^2 = 4.27$, $p = 0.038$), owing to the children with only mothers exposed to preconception occupation radiation ($\chi^2 = 13.19$, $p = 0.0003$) and to the offspring exposed in utero ($\chi^2 = 7.86$, $p = 0.005$);

– analysis of the relative risk of perinatal losses by calendar periods showed significant statistical differences only for the period of 1949–1953 when stillbirth rates and perinatal mortality in the main group substantially exceeded those in the comparison group: RR = 2.69 (1.46–4.95) and 2.12 (1.38–3.28), respectively;

– in the structure of perinatal mortality, intrauterine fetal death among the boys of the main group was statistically significantly more frequent than in the comparison group: 2.9 per 10^3 vs 0.9 per 10^3, F-test = 0.018;

– relative risk of stillbirths among male offspring in the main group was 1.5 times higher than that in the comparison group: RR = 1.47 (1.02–2.14);

– a high risk of stillbirths was observed among male offspring, where only mother was a Mayak PA worker: RR = 2.51 (1.5–4.21), and among the offspring of the mothers exposed to occupational radiation in the course of their pregnancy: RR = 1.86 (1.2–2.9);

– statistically significant risk estimates of stillbirths in different parental age categories were obtained for male offspring of the main group in paternal age category of 31–35 years: RR = 3.2 (CI: 1.08–9.51), but this conclusion is based on the number of offspring with known dates of birth of their fathers;

– assessment of the risk of perinatal losses in the categories of preconception and in utero

gamma-exposure demonstrated significant statistical differences in certain dose intervals with the offspring of unexposed parents.

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Review

WEST NILE FEVER AS A RELEVANT HEALTH HAZARD: THE HISTORY OF STUDYING AND MEASURES OF ITS PREVENTION IN RUSSIA

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The review generalizes data on West Nile fever manifestations in Russian between 1963 and 2022. Researchers have determined peculiarities of the endemic process typical for this arboviral infection: cyclic rises in incidence with an interval of 1 to 8 years; the disease cases being predominantly registered in the south of the European part of the country; elevated risks of the disease for people aged 60 years and older; most West Nile fever cases without affecting the central nervous system with a continuous steady increase in the share of neuroinvasive forms. There are ongoing discussions of a considerable growth in an area where West Nile fever spreads as the incidence of the disease has been registered in Central Russia and this calls for assessment studies aimed at determining the northern borders of the infection area. The reviewed studies also systematize data on the WNV carriers and vectors and highlight the necessity to conduct large-scale experimental studies with their focus on examining susceptibility of various species of vertebrates and arthropods to the West Nile virus and assessing the efficiency of its transmission. The West Nile virus population that circulates in Russia has been shown to be heterogeneous and represented by the genotypes 1, 2, and 4, of which the genotype 2 is prevailing at present. The review also provides the findings of our own research with its focus on the genomes of the West Nile virus isolates indicating circulation of various genetic variants of the pathogen belonging to the genotype 2. The reviewed studies consider issues related to establishing epidemiological surveillance and sanitary-anti-epidemic (preventive) measures regarding West Nile fever in Russia and the principles of their organization at the present stage.

Keywords: *West Nile fever, epidemic process, epidemiological situation, carriers and vectors, West Nile virus, epidemiological surveillance, preventive measures.*

West Nile fever (WNF) was discovered in 1937 and at first manifested itself as some isolated outbreaks of an acute feverish (influenza-like) disease in African countries. But in the second half of the 20th century, the disease spread beyond its historical area and occurred in the Middle East, Southern Asia, and then Europe [1–3]. In the middle 1990s, the WNF epidemiological situation changed considerably involving both extensive and intensive manifestations of the disease worldwide. Relatively large WNF outbreaks involving severe neurological symptoms and deaths were detected in Northern and Eastern Africa (Algeria in 1994 and 1997, Morocco and Tunis in 1996, Sudan in 2002), Middle East (Israel, 2000), and some European countries (Romania in 1996 and Russia in 1999) [2, 4–6]. In 1999, the West Nile virus (WNV) reached the Western Hemisphere for the first time where it caused a meningoencephalitis outbreak in the USA. It took WNF only three years to spread rapidly throughout the USA and then border areas of Canada and Mexico as well as Central and Southern America countries [1, 7].

This rapid growth in the WNF area, occurring outbreaks with severe cases and high case fatality rate (reaching 14 %) as well as absence of any specific treatment or prevention [8] were major arguments for assigning

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the infection to a group of potential threats to the global healthcare and this was fixed in the International Health Regulations (2005) [9].

In Russia, WNF is considered a significant concern for the national epidemiological surveillance given its all-round prevalence and annually registered incidence, outbreaks included.

The aim of this study was to generalize data on WNF epizootic and epidemiological aspects in Russia and organization of the system for epidemiologic surveillance and control over it.

The history of WNF studies in Russia and peculiarities of epidemic process manifestations. The first direct evidence of WNF occurrence was obtained in Russia in 1963. Back then, experts from the Institute of Poliomyelitis and Viral Encephalitis of the USSR Academy of Medical Sciences headed by the Academician M.P. Chumakov and personnel of the Astrakhan Regional Sanitary-Epidemiological Station isolated WNV strains from larvae and nymphs of *Hyalomma plumbeum plumbeum* Panz (*H. marginatum*) ticks when investigating foci of Crimean-Congo hemorrhagic fever in the Astrakhan oblast [10]. We have reason to believe that WNV had been circulating in Russia even prior to that year; however, its presence could only be evidenced due to development of virologic and serological identification techniques. In 1965, A.M. Butenko with colleagues established the identity of three WNV strains isolated in 1963 and Egypt 101 prototype strain; given that, the 'Astrakhan' virus was assigned into the African-Middle East group [10, 11]. Further research in the Astrakhan oblast gave evidence of human and animal contacts with the WNV vectors as well as of existing natural foci of the disease. This indicated the necessity to investigate WNF prevalence in Russia.

In the following years, the Center for Virus Ecology of the Ivanovskiy Institute of Virology in cooperation with relevant support stations performed extensive monitoring investigations covering 35 administrative territories and approximately 14 thousand people. This wide-scale research was performed largely due to efforts by D.K. Lvov, an outstanding Soviet and Russian virologist. As a result, WNF was proven to be circulating in southern and central regions of the European part of Russia, south of Western Siberia and the Far East [11–13]. Out of all the examined territories, WNV infection was the most active in the Volga Delta where the share of people with the immunity to the disease reached 50 % of local population [12].

Despite convincing evidence of WNV being widely spread in Russia, only isolated diseases cases were registered in the country over many years. First WNF cases were confirmed by laboratory tests in 1967 in the Astrakhan oblast. Six out of 12 infected patients had signs of the central nervous system (CNS) involvement and one patient died. This death drew a lot of attention by experts since WNF was considered a relatively mild infection [11, 14]. Prior to those events, neuroinvasive WNF cases were described only once during the 1957 Israel outbreak (49 cases overall, 16 of them involved the CNS, and the case fatality rate was 8.2 %) [2].

Later on, some singleton WNF cases were detected only in the Astrakhan oblast (one in 1989, 10 in 1990–1996, 8 in 1997, and 9 in 1998) [11, 15] since there was ongoing scientific research in the region with its aim to investigate the infection; starting from 1997, the State Sanitary Service included laboratory tests to identify WNF markers in patients with acute fevers into its routine practices.

The first serious WNF outbreaks were detected in 1999 in southern regions of the country when 475 cases were officially registered in the Volgograd oblast (380) and Astrakhan oblast (95). In the same year, 85 WNF cases were retrospectively confirmed in the Krasnodar Krai, although they were not included into the official statistical reports [12, 15].

When analyzing WNF manifestations in the Volgograd and Astrakhan oblast, we should note some considerable differences between them. Thus, 87 % of hospitalized patients in the Volgograd oblast had CNS involvement and the case fatality rate reached 10 % among them. Attention should also be paid to a high specific share of children younger than 14 years among the infected (16 %) [16], which was higher than in all the following rises in WNF incidence in Russia. In the Astrakhan oblast, while moderate and severe cases prevailed in the clinical picture, the share of neuroinvasive cases equaled 36.8 % and the case fatality rate was 5.3 %.

Experts believed this relatively low incidence and milder disease cases could be explained by considerable part of the Astrakhan oblast population being immune to WNV due to long-term WNF circulation in the region [14].

However, it is noteworthy that results of earlier serological tests in the Volgograd oblast indicated some contacts between the local population and the WNV. There was also evidence that the WNV caused disease cases in the Volgograd oblast with CNS involvement in July – August 1997 and August – early September 1998, that is, prior to official registration of the WNF incidence in 1999 [16]. Since in 1999 laboratory tests were conducted only among hospitalized patients in the region, we have reason to assume that there were a lot of non-diagnosed influenza-like WNF cases; the latter could influence the case fatality rate and the share of neuroinvasive cases. In 1999, the disease in southern Russia was caused by WNV strains of different origins (the homology between them was 96.2–96.4 %). A strain from the Astrakhan oblast was the closest to strains from the same cluster that were isolated in Tunis (1997) and Hungary (2003); a strain from the Volgograd oblast was the closest to that isolated in Romania (1996) [17]. Differences in the genome structures of WNV isolates responsible for the pathogenic properties of the virus could also be a reason for the disease manifesting itself with different severity.

In 2000–2009, the WNF incidence was annually registered in the Astrakhan oblast and almost every year in the Volgograd and Rostov (starting from 2000) oblasts; in 2006 it was also first confirmed in the Ulyanovsk oblast. During this period, incidence higher than the average long-term levels was detected in 2005 in the Astrakhan oblast (73 cases, 4 deaths) and in 2007 in the Volgograd oblast (63 cases, 2 deaths); in the latter oblast, an etiological relation was established between the disease cases and the WNV of genotype 2, which was identified in the region for the first time.

The second rise in the WNF incidence occurred in Russia in 2010; the total number of disease cases was 524 identified in six regions: the Volgograd oblast (413, 5 deaths), Rostov oblast (59, 1 death), the Astrakhan oblast (12) and for the first time the Voronezh oblast (27), Chelyabinsk oblast (1) and Kalmykia (1). By that time, 19 RF regions had officially notified of the WNV circulation [15].

The aforementioned outbreak in the Volgograd oblast became the largest WNF outbreak in Russia over the whole observation period. In contrast to the events of 1999, the specific share of neuroinvasive cases went down (5.1 %) as well as the share of children younger than 14 among the infected patients (2 %); the case fatality rate was also relatively low (1.2 %). The disease was caused by the WNV of genotype 2 with the 99.6 % homology to the isolate circulating in 2007.

The incidence and clinical course had similar structure in the Rostov and Astrakhan oblasts. Predominantly young people were involved into the epidemic process in those oblasts where WNF cases were detected for the first time; also, the share of neuroinvasive cases tended to be high there but outcomes were favorable [15].

The next rise in the WNF incidence occurred in 2012 with 453 registered cases in 21 RF regions and markers of the infectious agent identified already in 53 regions in the country. The analysis of territorial distribution of WNF cases in 2012 revealed that most infected people (73 %) lived in southern Russia, namely the Volgograd (211 cases), Astrakhan (72), and Rostov (48) oblasts. In 2012, neuroinvasive WNF forms were identified in 17.2 % of the cases and this was higher than in 2010. The growth in this indicator was caused by high frequency of neuroinvasive cases in ‘new’ foci. Influenza-like WNF prevailed on those territories where WNV had been circulating earlier. The case fatality rate was 1.0 % in 2012 and this level was comparable with 2010. Urban residents prevailed among infected patients (68.8 %) but still the share of rural residents grew from 19 % in 2010 to 31.2 % in 2012. This might indicate that the WNF diagnostics improved in healthcare organizations in rural areas.

The last known rise in the WNF incidence was detected in Russia in 2019 (352 cases in 14 RF regions). The greatest number of cases was established in the Krasnodar Krai (120),

Rostov oblast (93), and Astrakhan oblast (81). The WNF epidemic process had certain peculiarities in 2019, in particular, higher shares of clinical forms with the CNS involvement (29 %) and cases when people got infected by mosquitos that had survived a winter season and basement mosquitos (in early April and late November). In total, 67 % of the WNF cases in Russia were identified in urban residents. Children and adolescents younger than 14 years accounted for 1.7 % of all the infected people. The WNF case fatality rate was 1 % in 2019 in Russia.

In 2020–2022, the recorded WNF incidence was not higher than its average long-term levels; this was mostly due to a drastic decrease in volumes of diagnostic WNF tests performed among patients treated at out- and in-patient healthcare organizations.

Overall, 3072 WNF cases were officially established in Russia between 1997 and 2022, including 83 deaths. The intensity of the WNF epidemic process in its long-term dynamics tends to grow slightly (Figure 1) and the WNF incidence tends to rise within a range between 1 and 8 years.

The cyclicity of the WNF epidemic process established in Russia is rather different from other WNF-endemic countries. The fluctuations in the WNF incidence tend to be within 4–6 years in Canada, 3–5 years in the USA, and 3–4 years in Italy as a European country where the situation with WNF is the most unfavorable. Given these data, we can assume that in Russia the detected WNF incidence is influenced by social factors, namely, volumes and quality of medical examinations provided for patients with symptoms similar to WNF.

Territorial analysis of the WNF incidence shows that the disease cases tend to be distributed heterogeneously. Out of all the infected patients, 84 % live in southern Russia; the epidemic process tends to be the most active in the Volgograd oblast (43.1 % of the cases), Astrakhan oblast (22.6 %), and Rostov oblast (10.8 %). However, the WNF cases have been registered more frequently in central Russia in recent years (75 % in 2021 and 51 % in 2022). Local WNF cases were established in 31 RF regions, including 7 new ones in 2021–2022 located both in central and northern Russia, such as the Tula, Tver, Vladimir, and Tambov oblasts, Moscow (capital), and the Khanty-Mansi Autonomous Area. Major reasons underlying all the aforementioned peculiarities include climate change (global warming) that creates favorable conditions for growing numbers of WNF vectors, more intense virus accumulation in them and more effective transmission, and social interventions, namely, more intensive monitoring over the WNV conducted by the Reference center on some of the aforementioned territories.

The WNF incidence indicates that the infection is distinctively seasonal active between June and October with its peaks in August (45.6 %, 95 % CI: 43.42–47.78; $p < 0.001$) and September (38.1 %, 95 % CI: 35.98–40.22; $p < 0.001$). An average epidemic season lasts for 21.08 ± 3.75 weeks.

People aged 60 years and older tend to prevail among WNF-infected patients; the share of this age group is 31.9 % of all the detected cases. High specific weight of this age group is associated with more severe clinical course of the disease in it, which makes elderly

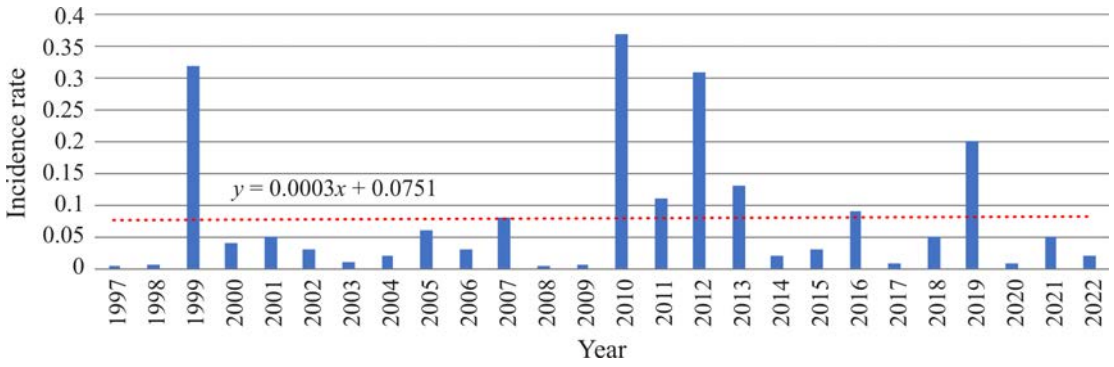

Figure 1. The WNF incidence in dynamics in Russia in 1997–2022

patients apply for medical aid. The lowest contribution to the WNF incidence belongs to children (6 % on average with its maximum value of 19 % established in 2014). Men get infected 1.3 times more frequently than women (men account for 56.7 % among the infected patients, 95 % CI: 41.36–45.23). WNF infected people are mostly urban residents (76.1 %, 95 % CI: 74.39–77.81).

The analysis of clinical manifestations revealed prevalence of the influenza-like WNF form (76.7 %). However, the number of cases with the CNS involvement has been growing steadily over the last decade ($y = 1.5049x + 15.012$). Moderate WNF forms are established most frequently (72.8 %); mild forms account for 16.3 % of all the detected cases; severe, 10.9 %. The average case fatality rate is 2.7 %; it varies between 1 and 11 % in some years (its maximum was established in 2009).

Monitoring of the WNF agent revealed its circulation in 77 RF regions over 1997–2022 (Figure 2). Still, it should be noted that the WNF area does not have any well-established borders in Russia since any data on people with the immunity to the WNV or identification of WNV markers (antigens) in vectors and carriers are not reliable enough on territories that are endemic as per tick-borne viral encephalitis. No diagnostics tests to differentiate the WNV from other flaviviruses are conducted when such positive results are established in serological reactions. It is still relevant to try to identify the northern borders of the infection area where local (permanent or temporary) WNF foci would appear in case the WNV virus was brought there.

Basic reservoirs and vectors. Birds are known to be the basic component in the WNV circulation. Birds do not only serve as natural reservoirs of the infection but also, considering their ability to migrate, facilitate the WNV spread onto new (previously non-endemic) territories as well as bring new (changed) genetic variants of the virus into Russia.

According to the results obtained by monitoring of the WNF agent in Russia, the WNV markers have been identified in more than 60 bird species from such orders as passerines (*Passeriformes*), charadriiforms (*Charadriiformes*), waterfowls (*Anseriformes*), piciforms *(Piciformes*), falconiforms (*Falconiformes*), and some other bird orders that live on water or near it. The number of bird species involved in the WNV circulation appears to be considerably higher in Russia since more than 300 bird species with confirmed WNV infection have been established in the USA [7].

In the lower Volga Delta, high levels of the WNV contamination have been established in cormorants (8.2 %), bald-coots (6.1 %), and great crested grebes (6.3 %); lower ones, in gulls and terns. In the middle Volga Delta, similar levels were identified in bald-coots, herons, gulls, and terns whereas the level was considerably higher in cormorants and reached

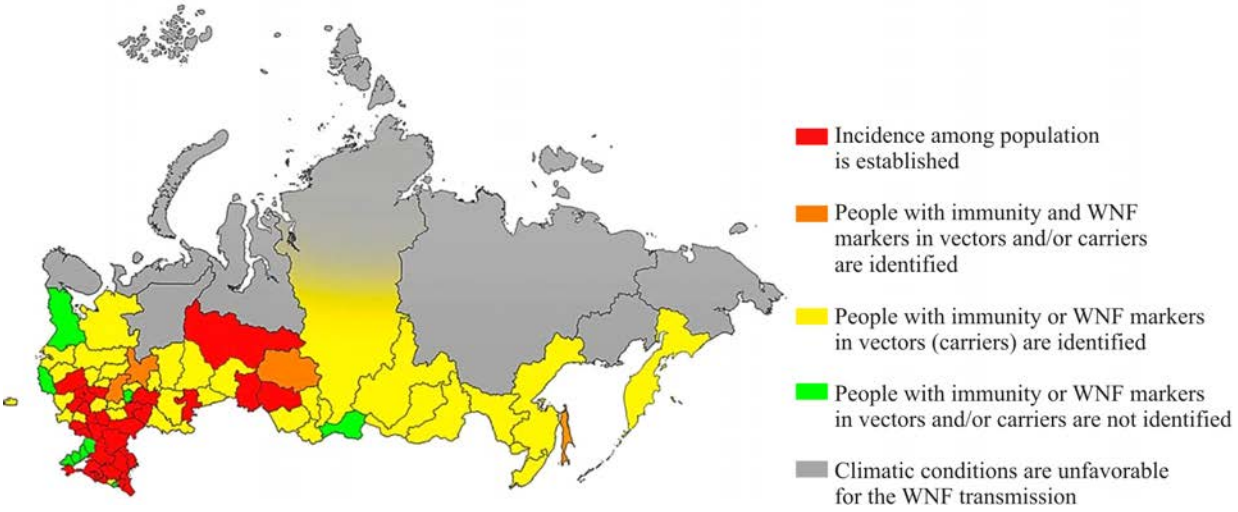

Figure 2. Estimated ranking of the Russia territory to identify evidence of the WNF epizootic and epidemic processes

21.2 % [18, 19]. The same bird species have often turned out to be infected in other regions in southern Russia (the Volgograd and Rostov oblasts, the Krasnodar and Stavropol Krai) and Volga Region (the Saratov oblast) [15, 20, 21].

In anthropogenic biocenoses, the WNV is carried by hooded crows, rooks, jackdaws, jays, blue rock pigeons, and sparrows; their high populations result in the infection spread among synanthropic mosquitos and people [11, 15, 21]. Thus, the WNV contamination in crows reached 17.4 % in anthropogenic biocenoses in the Volga Delta; this allows concluding that crows play a significant role in the WNV circulation [19].

In Western Siberia, WNV RNA and / or AG have been established in bluetails, fieldfares, rubythroats, starlings, tree sparrows, sand martins, European teals, garganeys, rooks, hooded crows, great tits, common redstarts, woodcocks, nuthatches, millerbirds, willow wrens, garden warblers, red-wings, chaffinches, lesser whitethroats, chiffchaffs, yellow buntings, willow tits, and common bullfinches [22]; in the Far East, in European teals, falcated ducks, black vultures, Egyptian herons, common magpies, large-billed crows, black-tailed gulls, tits, and yellow buntings [23, 24].

The role all the aforementioned bird species play in the WNV transmission still remains unclear since the species composition and bird populations have not been identified on every territory; geography of wintering grounds and migration roots has not been analyzed systematically; there have been no experimental studies to identify species-related susceptibility to the WNV, levels or duration of viremia.

It is worth noting that the data presented in this study have been derived by research conducted in some separate areas in Russia. Scheduled monitoring activities performed by the RF Sanitary Service practically never identify any WNV carriers. No mass epizooties or bird deaths are established in Russia, though such events are regularly reported in the USA and Europe. Research articles provide only some singleton (unofficial) mentions of mass bird deaths prior to the WNF outbreaks in 1999 in the Volgograd and Astrakhan region and in 2021 in Moscow. This indicates that interactions and data exchange between the RF Sanitary and Veterinary Services are not effective enough.

As for other vertebrates, the WNV markers have been identified in rodents (in European Russia, in common voles, bank voles, red-backed mice, house mice, small field mice, yellow-necked mice; in Western Siberia, meadow mice, red-backed mice, narrow-sculled voles, sagebrush voles, root voles, house mice, field mice, harvest mice, and musquashes; in the Far East, in Daurian sousliks and East-Asian mice) as well as in insect-eaters (hedghogs, common shrews, tundra shrews, small shrews, lesser shrews, brown-toothed water shrews), carnivores (weasels), and lagomorphs (brown hares and Daurian piping hares) [15, 20, 21, 24, 25]. Among small mammals, rodents seem the most likely to play a role in the WNF circulation since they tend to be feeders for many tick species. This assumption is evidenced by all the tick metamorphosis stages caught on small rodents being infected with the WNV [26]. At the same time, there have been no experimental studies aimed at examining viremia levels, duration of the WNV persistence in rodents and other small mammals or effectiveness of the virus transmission by vectors in the process of blood sucking. This is rather unfortunate since such experiments would be able to shed some light on significance of such species in preservation of the WNF agent.

Some data have been derived over the long-term observation period, which confirm some intensive contacts between large mammals and the WNV on some territories in Russia. The share of farm animals with immunity to the WNV on average amounted to 16.3 % in the Volga Delta (32.5 % in horses; 10 %, cattle; 10.7 %, camels); 11 % in the Central Russia (horses in the Kursk oblast); 8.5 % in the Western Siberia (9.2 % in horses and 7.8 % in caws in the Novosibirsk oblast); 7.6 % in the Far East (Primorskij Krai) [19, 24, 27]. Therefore, farm animals can be used as an eligible indicator of active WNV circulation on examined territories. It is noteworthy that monitoring of farm animals is not actually conducted in Russia (examinations are performed annually only in 1 or 3 regions).

Apart from rodents, the WNV (genotype 4) contamination has been also identified in amphibians such as marsh frogs *Rana ridibanda* that are feeders for some blood-sucking mosquitos including *Uranotaenia inguiculata* [28].

Blood-sucking mosquitos are primary WNV vectors on endemic territories in Russia. Out of 100 species of blood-sucking mosquitos inhabiting Russia, the WNV markers have been identified in the following ones: *Culex modestus* Fic., *Cx. pipiens* L. (non-autogenic *Cx. pipiens* f. *pipiens* and autogenic *Cx. pipiens* f. *molestus*), *Anopheles maculipennis* Mg., *An. claviger* Mg., *An. hyrcanus* Pall., *An. messeae* Pall., *Aedes cinereus* Mg., *Ae. geniculatus* Oliv., *Ae. vexans* Mg., *Ae. caspius* Pall., *Ae. pulchritarsis* Rond., *Ae. albopictus* Sk., *Ae. cataphylla* Dyar, *Ae. flavescens* Mull., *Ae. excrucians* Walk., *Ae. cantans* Mg., *Culiseta annulata* Schr., *Coquillettidia richiardii* Fic., and *U. unguiculata* Edw. [15, 19–21, 29, 30]. The WNV contamination identified in all the aforementioned mosquito species gives solid evidence of their active participation in the WNV circulation; however, epidemiologic significance of specific vectors as well as their competence (effectiveness) remains unexplored.

The results derived by long-term exploratory WNF research in some separate areas in southern Russia allow concluding that all the dominating mosquito species become involved into the WNV circulation. The Astrakhan oblast model was used as an example to show that *Cx. pipiens*, *An. hyrcanus*, *Coq. richiardii*, *An. Messeae* were likely epidemically significant vectors in anthropogenic biocenoses and *An. hyrcanus*, *Coq. richiardii* acted as such in natural biocenoses [19]. In the Volgograd oblast, another active WNF focus, high levels of the WNV contamination were identified in such species as *Cx. modestus*, *Cx. pipiens*, к. *An. maculipennis, An. hyrcanus*. As regards *Cx. pipiens*, the WNV was confirmed to be likely to persist during an inter-epidemic period in wintering mosquito populations.

Obviously, this list of the WNV carriers is not complete since blood-sucking mosquito fauna that inhibits different climatic-geographical zones in Russia is scarcely studied; local mosquito populations that have not yet been covered by 'research area' are likely to play an active role in the WNF epidemic and epizootic processes.

In Russia, WNF circulation is also facilitated by ticks, gamasid ticks and argasid ticks. The WNV markers (antigens, RNA) and isolates have been established in 12 tick species, most frequently in southern Russia in such species as *Hyalomma marginatum*, *H. scupense*, *Rhipicephalus rossicus, Dermacentor reticulatus* [15, 20, 21]. In some years, the WNV contamination in *H. marginatum* ticks was much higher than in mosquitos in anthropogenic biocenoses located in the Volga Delta (0.48 % and 0.047 % respectively). In addition, crows turned out to be highly contaminated with *H. marginatum* tick larvae and nymphs (up to 300 units on one bird); given all the above stated, this may indicate a significant role that belongs to ticks in preserving WNF population [19].

In Western Siberia, the WNV markers have been most frequently detected in ornithophilic ticks *Ixodes persulcatus, I. pavlovskiy*. As regards these two species, their ability to infect with the WNF agent and to perform its trans-phase transmission was experimentally proven as far back as in 1970es. Research data indicate that epizootic activity of WNF foci is largely maintained due to nidicoles, arthropods feeding on colonial nesting birds [30].

Circulating WNV genotypes. The WNV of genotypes 1, 2, and 4 (WNV01, WNV02, and WNV04) is reliably established to circulate in Russia [15, 17, 23, 26, 28, 31]. The WNV01 has been identified in different years in the Astrakhan, Volgograd, Voronezh, Omsk, Novosibirsk, Tomsk, and Kurgan oblasts; in Ingushetia and Mordovia Republics; in Primorskii, Altai, Krasnoyarsk, and Stavropol Krai. The WNV02 has been identified in the Astrakhan, Volgograd, Rostov, Voronezh, Kursk, Lipetsk, Penza, Saratov, Nizhni Novgorod, Omsk, and Novosibirsk oblasts; Stavropol and Krasnodar Krai; Moscow, Tatarstan, Kalmykia, Crimea, Dagestan, Severnaya Osetiya, and Karachaevo-Cherkeskaya Republics; Jewish Autonomous Area. The WNV04 has been identified in the Volgograd and Astrakhan oblasts; Krasnodar Krai; Kalmykia and Crimea Republics.

The Volga Delta, which is located in the Astrakhan oblast, is likely an initial area for the spread of the WNV01 in southern Russia [31]. Periodic occurrence and identification of the WNV01 in other areas, both adjoining and remote from the Astrakhan oblast (south of Western Siberia or Primorye, for example) can be due to the virus being brought there by migrating birds [23, 31]. The WNV01 circulation was

not confirmed in Russia in 2019–2022; however, since molecular and genetic investigations were performed on rather small volumes of materials, no unambiguous conclusion can be made that the virus transmission stopped. We cannot exclude that the WNV02 that had adapted to the conditions in the country was displaced whereas the uninterrupted circulation of the WNV01 persisted in some specific local biotopes. Thus, the WNV01 was repeatedly identified in Italy in 2020 and 2022 where previously it had been last detected in 2017. Given great similarities between 2020 isolates with those that had been circulated in Italy earlier, researchers assumed that the WNV01 was possibly brought onto other territories from some local foci where it circulated [32]. The fact that we identified the WNV01 in Ingushetia and Mordovia Republics in 2023 naturally raises a question of its origin: has the virus spread from some local foci or has it been brought into the country anew from Africa?

We believe the data are still scarce as regards areas where the WNV04 is circulating. This variant is persistently identified only in vectors and some amphibians only in Sarpinskiye Ozora (lakes) located in the Volgograd oblast and Kalmykia [28, 31].

At present, the WNV02 prevails in southern and central European Russia; given that, we should consider peculiarities of its circulation in greater detail.

Occurrence of the WNV02 was first established by sequencing the virus genome identified in samples of *Coq. richiardii* mosquitos caught in the Astrakhan oblast in 2003. The profound profile of this isolate cannot be found in any available sources. WNV02 strains, which were isolated in the Volgograd oblast during the 2007 WNF epidemic, differed considerably from the virus strains isolated in early 2000ties in the south of the Central Europe. They were phylogenetically closer to the strains isolated in Africa and Israel between late 1950ties and 2000ties [17]. This might be evidence of different WNV02 variants being brought independently at that time to the Central Europe and southern Russia.

A similar picture is derived by analyzing strains of the 2nd genetic line isolated in the Southern Russia in the following years. Thus, strains isolated in the Volgograd oblast and adjoining regions between 2010 and 2018 form a separate cluster group that is genetically isolated from the virus isolates identified at the same time in the central European countries, Balkan countries and the Mediterranean region.

Phylogenetic analysis of the WNV02 isolates extracted in the Volgograd oblast in 2019–2020 and partially in 2021 as well as the 2020 isolates extracted in the Rostov and Astrakhan oblasts confirmed that this strain group was genetically isolated and monophyletic. The tree branch topology indicates that these strains have a common ancestor that was formed not later than 2007. We believe these data to be eligible to confirm the hypothesis that the WNV02 circulation was maintained on WNF endemic territories in southern Russia due to the local virus population that had existed for a long time. Additional evidence of the assumption is provided by specific composition of synonymic and non-synonimic amino acid replacements in nonstructural proteins of the WNV isolates identified in the Volgograd oblast in 2018.

However, WNV isolates extracted in 2021 and 2022 on the examined territories in the European part of Russia (Dagestan, Kalmykia, Crimea, Karachayevo-Cherkeskaja Republic, Stavropol Krai, Astrakhan, Volgograd, Rostov, and Voronezh oblasts) belonged to a completely new WNV02 genetic variant that was not included in the GenBank NCBI. In 2022, another genetic variant, which previously had never been found in Russia, also occurred in the Stavropol Krai and Kalmykia.

Organization of the system for epidemiological surveillance over WNF and sanitary-anti-epidemic (prevention) activities. After the first disease cases were confirmed in 1967, epidemiological surveillance over WNF was not systemic until the beginning of the 21st century. Public healthcare tended to neglect the issue probably due to relatively favorable outcomes of the disease, difficulties in its etiological verification due to absence of available laboratory diagnostic techniques, and top priorities being assigned to fighting against such dangerous infections as plague and cholera.

The 1999 outbreak that involved WNF occurrence on a considerably new territory of

the Volgograd oblast, severe neuroinvasive forms and high case fatality rate together with a growing number of the disease cases in the Astrakhan oblast gave grounds for the development of epidemiological control and surveillance in regions; such activities were developed and fixed in the regulation as regional programs for epidemiological surveillance.

Revision of the system for the registration, records, and reports about WNF cases was of fundamental importance. WNF as an independent disease was included into the list of communicable (parasitic) diseases that were subject to mandatory control and registration. Previously the infection was not mentioned in statistical reports and the disease was usually included under the common diagnosis of 'viral fevers' or 'serous meningitis / viral encephalitis, unspecified'.

Further growth of the WNF area together with new registered epidemic outbreaks made it necessary to develop unified principles for organization of the system for epidemiological surveillance over the infection and a set of preventive and anti-epidemic activities and to fix them in the national legislation. It was also very important to organize relevant interdepartmental interaction.

The regulatory documents define WNF as a communicable disease associated with sanitary-epidemiological emergency. Within reinforcement of the national laboratory network, a three-level functionally-based diagnostic structure has been created including the Reference Center for monitoring over the WNF agent (opened in 2008) on the basis of the Volgograd Scientific Research Anti-Plague Institute of the RF Sanitary Service (Rospotrebnadzor).

At present, the state sanitary-epidemiological surveillance over WNF in Russia includes several activities. They are constant dynamic observation of the WNF epizootic and epidemic process; investigating how endemic a given territory is; monitoring of the WNF agent circulation within an epizootic cycle; examining WNV properties and genetic diversity, probable ways for the virus to penetrate the country and spread over its territory; observation of biological, natural, and social factors that influence the epizootic and epidemic processes; predicting an epidemiological situation and control of effectiveness of accomplished activities.

In the Russian Federation, epidemiological control and surveillance activities are coordinated and accomplished under supervision of bodies and institutions of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing (the RF Sanitary Service or Rospotrebnadzor). In addition to Rospotrebnadzor bodies, such activities can also be accomplished by regional executive authorities responsible for health protection as well as by other concerned services and departments within complex plans on WNF prevention or complex plans on sanitary protection of a given territory. Such plans are usually approved by a relevant regional executive authority.

Epidemiological surveillance over WNF, just as in case of any other infection, is accomplished at a territorial (district or city), regional (a republic, Krai, or oblast, federal-subordinated cities), or federal (the country as a whole) level. Volumes and depth of data analysis are determined by tasks that should be solved at each level of epidemiological surveillance and by significance of managerial decisions.

Investigation of how an epidemic process manifests itself involves monitoring of its intensity, dynamics (long-term and within a year), structure of incidence (age-specific, social, clinical, etc.), spatial characteristics of disease cases, case fatality rate, duration of a disease, applying for medical care, hospitalization, and confirming a diagnosis with laboratory tests. Organization of the system for epidemiological surveillance over WNF has some peculiarities in Russia. Infected patients are actively revealed during an epidemic season by conducting laboratory tests to identify WNF in patients who have unspecified fevers, meningitis or meningoencephalitis and are treated at out-patient and in-patient departments.

Serological monitoring involves examining population immunity to the WNV in random population samples in order to identify the intensity of the WNV circulation, to reveal an exact moment when epidemic complications occur, territories and population groups with elevated risks of the infection, and to predict how an epidemiological situation would develop.

Zoological and entomological monitoring includes observation of species structure, numbers and levels of contamination in vectors and carriers, dynamics of the epizootic

process, weather and phenological events that determine the WNV circulation in vectors and carriers. Such monitoring should be accomplished by experts of the Sanitary Service in close cooperation with experts from the Veterinary Service.

Results of the accomplished analysis give grounds for establishing specific epidemiological zones in the natural foci of the infection and for assessing their potential epidemic hazards. Administrative territories are differentiated considering some specific natural and geographical, biological and social factors.

Non-specific prevention is a key component in prophylaxis. Non-specific prevention activities include sanitary work, extermination, and use of personal protective equipment. Occurrences of new infection foci or mass assaults by mosquitos indicate the necessity to conduct some disinsection activities in settlements. Sanitary prophylaxis involves preventing mass reproduction of blood-sucking mosquitos in a given settlement and in a surrounding area (elimination of vectors' habitats, territorial development in a settlement, sanitation of water bodies and parks, etc., maintaining satisfactory sanitary conditions in basements of residential buildings), control of synanthropic bird populations by decreasing their food supply, provision of hygienic education to population to explain how a person can get infected with WNF, how the infection manifests itself, and how it can be prevented by using relevant personal protective equipment.

Conclusion. Since the WNV was first isolated in Russia in 1963 and up to the end of the 20th century, WNF was known to spread in the Astrakhan oblast and some other territories in southern Russia, both its European and Asian parts. The large WNF outbreaks of 1999, which occurred in the Astrakhan and Volgograd oblast and, according to some researchers, in the Krasnodar Krai as well, changed the existing attitudes towards the infection. WNF started to be considered a leading internal threat for the sanitary-epidemiological wellbeing of the population; it required organization of a complex and multi-level system for epidemiological surveillance including monitoring of the WNF incidence, examining population immunity, zoological and entomological monitoring, and monitoring of the WNF infectious agent.

The WNF epidemic process has certain peculiarities in Russia. Rises in the incidence usually occur within a range between 1 and 8 years; WNF cases are predominantly detected in southern Russia; people aged 60 years and older tend to have elevated risks of getting infected with WNF; WNF without the CNS involvement prevails but still there is a persistent growth in the share of neuroinvasive cases. The number of territories where the local WNV transmission is confirmed has grown substantially since 1999 (from 2 to 31 regions). Therefore, we can claim firmly that the WNF area is much greater than researchers who investigated the infection before used to believe. WNF has long gone beyond the border of the area assigned for it and located within the 20 °C isotherm for the warmest month (the south of the moderate climate area). The northern border of the WNF area remains unspecified. We have reason to believe that the WNV can circulate among carriers and susceptible vertebrates even in areas with sub-Arctic and Arctic climate without any favorable conditions for its usual transmission. Probably, this circulation can be maintained by some other mechanisms. Solid evidence of these assumptions can become an object of future research in the area.

The whole scope of the WNV vectors and carriers has not been established so far. Solution to this task requires wide-scale experimental studies to identify how susceptible different vertebrates and arthropods are to the WNV and those able to transmit it. Complex studies are also needed to examine the structure of the WNF parasitic system and how the infection foci maintain their functioning in different landscapes and environmental conditions.

The WNV population that circulates in Russia is heterogeneous and represented by WNV01, WNV02, and WNV04. The WNV02 prevails at the moment; it is also characterized with genetic diversity and this requires constant monitoring of the WNF infectious agent given the continuous introduction of new virus variants along bird migration routes and its ecological plasticity.

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Review

ON POSSIBLE PRACTICAL APPLICATIONS OF THE GUT MICROBIOME RESEARCH IN THE PREVENTION, DIAGNOSIS, ASSESSMENT OF, AND TREATMENT MODIFICATION FOR MULTIPLE SCLEROSIS IN PATIENTS FROM RISK GROUPS

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Research into the gut microbiota (GM) in multiple sclerosis (MS) has the potential to lead to a number of practical applications in the prevention, diagnosis, assessment of, and treatment modification for, MS. Four most promising areas include biomarkers, treatment personalization, drug development as well as disease prevention and mitigation.

Changes in the GM have been observed in individuals with MS; analysis of the GM composition may help to identify individuals at risk of developing the disease or to monitor disease progression. Dietary interventions aimed at improving gut health could be used as a complementary approach to traditional MS treatments in order to reduce inflammation thereby potentially improving MS symptoms and lessening disease progression. Differences in the GM between individuals with MS suggest that personalized treatment approaches based on an individual's microbiome composition could be effective. Manipulating the GM could therefore be a potential avenue for drug development in MS. In addition, the exploration of bacteria or bacterial metabolites as therapeutic agents to modulate the immune system and reduce inflammation is also promising.

Such explorations may even help identify strategies for preventing the development of MS in at-risk individuals. Overall, practical applications of gut microbiome research in MS are still in the early stages and further research is needed to fully understand the mechanisms underlying the relationship between the gut microbiome and MS and to determine the most effective interventions for improving gut health in individuals with the disease.

Keywords: *multiple sclerosis, gut microbiome, prevention, diagnostics, treatment personalization, biomarkers, risk of a disease, diet.*

Research into gut microbiota (GM) in multiple sclerosis (MS) has over time yielded a number of practical directions in research and application of said research when it comes to the prevention, diagnosis, assessment of and treatment modification for MS. Multiple sclerosis (MS) is a demyelinating and neurodegenerative autoimmune disease of the central nervous system (CNS). MS has a mean diagnosis age of 30 and is the most common inflammatory neurological disease in young adults [1]. Since this disease strikes so early and then affects people indefinitely, it is of the utmost importance to be able to not only provide the right treatment, but to also assess the effectiveness of said treatment.

In recent years, there has been increasing interest in the role of the GM in multiple sclerosis and a growing body of research in this area.

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Research into the gut microbiome and multiple sclerosis (MS) is still in its early stages, but there are several possible practical applications of this research in the assessment and treatment modification of MS.

Firstly, analysis of the gut microbiome could potentially be used as a diagnostic tool for MS. Changes in the gut microbiome have been observed in individuals with MS, and analysis of the gut microbiota composition may help to identify individuals at risk of developing the disease or to monitor disease progression.

In 2022, a study published by the IMSMS consortium in *Cell* comprised of a large multi-center study of MS patients and household healthy controls [2]. The study found that gut bacteria in individuals with MS were less diverse than those in healthy individuals, and that specific bacterial species were associated with disease activity and disability. The researchers suggested that changes in the gut microbiome may contribute to the development and progression of MS by promoting inflammation and altering the balance of immune cells.

Secondly, dietary interventions aimed at improving gut health could be used to complement traditional MS treatments since it is known that the GM changes during treatment with drugs [3, 4]. For example, a diet high in fiber and prebiotic and probiotic foods may help restore the balance of beneficial gut bacteria and reduce inflammation thereby potentially improving MS symptoms and slowing down the disease progression.

A *Nutrients* review in 2023 by Kurowska et al. showed that an imbalance in the function as well as composition of the GM is critical in the pathogenesis of neurological diseases [5]. Specifically for MS, dietary intervention as with the Mediterranean or the Ketogenic diets, and consumption of nuts, vegetables, legumes, vitamins, and anti-inflammatories like omega-3 and many others, were associated with improvements. Significant improvements were noted by using the Modified Fatigue Impact Scale (MFIS) and physical and mental components of the Multiple Sclerosis Quality of Life (MSQoL-54) in MS patients. Biomarker-wise, it was also noted that levels of the anti-inflammatory cytokine interleukin 4 (IL-4) increased while levels of serum neurofilament light chain level (sNfL) decreased thus indicating a potential neuroprotective effect with the latter biomarker [6].

In 2022, the article in *Aging and Disease* by Z. Jiang et al. detailed the physiological basis of the ketogenic diet as well as its functions within regulation of neuroinflammation and therefore its protective role in normal brain aging and neurodegenerative diseases [7]. Diseases such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and Huntington's disease were mentioned by name and it would not be a stretch to include MS toward these same findings.

Another study published in *Frontiers in Neuroscience* in 2022 found that probiotic supplementation can have beneficial effects on serum levels of CRP and IFN-γ, for example, both of which are related to systemic inflammation [8].

All these findings suggest that the gut microbiome may play an important role in the development and progression of MS and that dietary interventions aimed at improving gut health may be a promising avenue toward managing the disease. However, further research is needed to fully understand the mechanisms underlying the relationship between the gut microbiome and MS and to determine the most effective interventions for improving gut health, and hopefully overall outcome, in individuals with the dis-

ease. Potentially, personalized nutritional interventions may constitute a non-invasive and effective strategy in combating neurological disorders [9].

Thirdly, the use of probiotics or fecal microbiota transplantation (FMT) may be explored as a potential treatment for MS. FMT involves transferring fecal material from a healthy donor into the gut of a recipient with the aim to restore a healthy gut microbiome. While FMT is not currently an approved treatment for MS, it has shown promise in small studies and may merit future research.

In 2022, Correale et al. (*Nature reviews, Neurology*) reviewed a number of studies that looked at microbiome alteration in multiple sclerosis across different disease courses including clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary-progressive MS (PPMS) and secondary-progressive MS (SPMS) along with the treatments they used and controls. The authors were able to identify several possible therapeutic strategies aimed at GM alteration: probiotics, FMT, dietary modifications as well as bacterial metabolite supplementation, for example using short-chain fatty acids [10].

The results of K.F. Al et al. in 2022 in MSJ showed that FMT was both safe and well-tolerated among the RRMS patient cohort. There is a potential for it to enhance the microbiota that may be protective against MS. Additionally, there is evidence that FMT could reduce small intestinal permeability, which is often elevated in MS patients [11]. Nonetheless, the authors acknowledged that further research involving larger sample sizes and longer follow-up periods is needed to ascertain whether FMT is a viable therapy for MS [12].

Similarly, in a review by Matherson et al. published in 2023 in the *International Journal of Molecular Science*s, the authors aimed to summarize FMT research in neurodegenerative disease in both human and animal studies [13]. The authors acknowledged that the current state of research on gut microbiome modification through FMT as a potential treatment for diseases like MS is still in its early stages and has several limitations. While case studies and animal studies offer valuable insights for future research, clinical trials are still limited or absent. Moreover, FMT protocols vary greatly among studies and standardized procedures are not yet available making it challenging to draw conclusions on a larger scale. For example, different delivery routes, the use of antibiotics beforehand, and the number of FMT infusions can significantly affect outcomes. To address these limitations, future research should consider establishing standard protocols or examining the impact of the aforementioned factors to facilitate comparison between studies. Despite these limitations, the authors posit that the available evidence suggests that FMT may provide relief from symptoms with minimal side effects and warrants further investigation. This is particularly valuable in the context of limited long-term treatment options for these diseases. Therefore, further research, particularly clinical trials, is eagerly anticipated in this field [13].

Finally, understanding the role of environmental factors in shaping the gut microbiome and their potential impact on MS could inform public health efforts to prevent the disease or modify its progression [5, 14, 15]. For example, public health campaigns aimed at reducing exposure to environmental toxins or promoting a healthy diet and lifestyle could help to improve gut health and potentially reduce the incidence and severity of MS.

In a 2022 review article in *Cureus*, Jayasinghe et al. investigated diet and the

gut microbiome and how they relate to the progression of MS disease course [15]. They found the past decade's research has shown multiple instances of interplay between genetics and environmental factors in the pathogenesis of MS. The functions of the gut-brain axis, antioxidants, vitamins, obesity, and various diets are also covered in this review. Research has found that the gut-brain axis plays a crucial role in regulating the immune response and maintaining immune homeostasis, which is significant in the development of MS [16–18]. Moreover, recent studies suggest that modifications to the gut microbiome through dietary changes can trigger inflammation and demyelination in MS. Concomitantly, in RRMS, adopting the ketogenic diet has resulted in improvements in quality of life, fatigue, and depression [19]. Additionally, adherence to the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet has demonstrated a reduction in both MS incidence and cognitive decline. These findings underscore the importance of considering the impact of diet and the gut microbiota in managing patients with MS therapeutically [15].

In order to determine the potential benefits of these approaches on the gut microbiota in individuals with MS, it is necessary to conduct controlled clinical trials with uniform protocols. To ensure the validity of these studies, it is important to enroll large groups of patients who have been carefully phenotyped, including an assessment of their genetic makeup, dietary habits, medication usage, and any coexisting illnesses. These patients should then be compared with carefully selected individuals who do not have the disease. If these studies are properly designed and executed, they may provide insight into whether manipulating the gut microbiota could be a useful addition to the existing MS treatment options [10].

Acquiring this knowledge is crucial not only for understanding the underlying causes of neuroinflammation but also for identifying diagnostic biomarkers and developing novel treatment approaches that target the gut microbiota composition to restore immune cell homeostasis in immune-mediated CNS diseases. Overall, research into the gut microbiome and MS has the potential to inform novel diagnostic and therapeutic strategies, as well as public health interventions aimed at preventing or modifying the disease. Trusting what the gut has to tell us may very well help yield better outcomes.

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Original research article

ASSESSMENT OF NEUROPHYSIOLOGICAL PARAMETERS OF THE NERVOUS SYSTEM IN NON-FERROUS FOUNDRY WORKERS

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A comprehensive assessment of the health status includes the functional exploration of the central and peripheral nervous systems. Results of the neurophysiological examination allow elaboration of effective personified therapeutic and preventive programs for the core personnel of non-ferrous metal industry.

Our objective was to study functional disorders of the central and peripheral nervous systems in smelter operators for further development of risk-based rehabilitation programs for workers engaged in production of non-ferrous metals.

Two cohorts of male workers were examined. The case cohort included 60 smelter operators of a large metallurgical plant situated in the Sverdlovsk Region and the control cohort consisted of 50 unexposed employees. The cohorts were matched by age and years of work experience. The mean age of smelter operators was 37.8 ± 7.9 years and their mean length of current employment was 4.1 ± 4.6 years, while the total length of work under hazardous occupational conditions was 7.1 ± 6.0 years. The case cohort included 39 operators of refinery boilers (mean age: 35.6 ± 7.2 years, mean length of employment: 4.2 ± 4.7 years) and 21 operators of the ore thermal furnace (mean age: 41.9 ± 7.6 years, mean length of current employment: 3.9 ± 4.4 years). All subjects underwent a neurocognitive examination (higher brain function testing), electroneuromyography, the somatosensory evoked response test, and electroencephalography.

The results of examining the higher brain function enabled us to form the neurocognitive profile of the workers. We revealed signs of mild cognitive impairment in 30 % and a decrease in the cognitive reserve in 35 % of the cases. The diagnosed peripheral nervous system disorders included distal sensory polyneuropathy of the upper and lower extremities, carpal and cubital tunnel syndromes, cervical and lumbar radiculopathy.

The comprehensive neurophysiological examination helps detect early changes in the central and peripheral nervous systems. The findings should be taken into account when developing personal medical rehabilitation programs.

Keywords: *neurophysiological examination, polyneuropathy, compression neuropathies, neurocognitive profile, cognitive reserve, somatosensory evoked potentials, prevention and treatment programs, combined toxicity.*

Preserving good health and increasing healthy working life expectancy are the priorities of the government policy in the Russian Federation[1] [1]. A comprehensive assessment of health status that includes testing for functional neurological disorders facilitates elaboration of effective personalized preventive and therapeutic programs implemented within the Concept of Predictive, Preventive and Personalized Medicine [1–4]. The

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issue of a combined effect of occupational toxicants on workers maintains the relevance of searching for early diagnostic and effective preventive and therapeutic measures for exposed personnel [5–9]. Effects of certain toxic pollutants, particularly lead, on the nervous, hematopoietic, and digestive systems have been previously demonstrated; they are manifested by disturbances in epigenetic status; oxidative DNA damage; changes in reticulocyte count; oxidative stress; neurobehavioral changes; gene polymorphisms of glutathione peroxidase, paraoxonase, and metallothionein-4; and calcium metabolism with bone mineral density [10–21]. Dangerous variants of the combined toxicity of zinc oxide and copper oxide nanoparticles have been identified. In addition, it has been established that the exposure to nanoparticles of silver, gold, oxides of copper, iron, aluminum, zinc, lead, nickel, and silicon induces a statistical increase in nuclear DNA fragmentation [7–9].

Since 2019, the project for maintaining health of the core personnel in metallurgical industry has been implemented on the basis of the Yekaterinburg Medical Research Center for Prophylaxis and Health Protection in Industrial Workers [6]. Smelter operators of the refining department of the metallurgical (smelting) shop are at high risk of occupational and work-related diseases associated with exposure to a combination of adverse factors (work heaviness and toxicants, such as lead, copper, zinc, antimony, arsenic, and cadmium). Findings of a neurophysiological examination allow the development of effective personified preventive and therapeutic programs focused on the main targets for pathological processes (central and / or peripheral nervous systems) [6–9, 11].

Our **objective** was to study functional disorders of the central and peripheral nervous systems in smelter operators for further development of risk-based rehabilitation programs for workers engaged in production of non-ferrous metals.

Materials and methods. Two cohorts of male workers matched by age, seniority and level of education were examined at the clinic of the Yekaterinburg Medical Research Center. The control cohort consisted of 50 unexposed employees and the case cohort included 60 smelter operators aged 25 to 53 years (mean age: 37.8 ± 7.9 years) having the work history of 0 to 18 years (mean length of current employment: 4.1 ± 4.6 years). The total duration of work in hazardous conditions was 7.1 ± 6.0 years. The case cohort included 39 operators of refinery boilers aged 25 to 49 years (mean age: 35.6 ± 7.2 years, mean length of employment: 4.2 ± 4.7 years) and 21 operators of the ore thermal furnace aged 27 to 53 years (mean age: 41.9 ± 7.6 years, mean length of current employment: 3.9 ± 4.4 years), all with the work history ranging from 0 to 18 years.

According to the results of a special assessment of working conditions for all cases, the time-weighted average (TWA) concentration of lead was up to 1.94 times higher than its maximum permissible concentration (MPC), which is characteristic of Class 3.1 of working conditions. Concentrations of copper and zinc oxide were below the corresponding MPCs at all workplaces, with the exception of that of the ore thermal furnace operator where the TWA concentrations of both copper and zinc oxide were 1.02 times higher than their MPCs (up to 0.51 mg/m^3 with the average daily MPC of 0.5 mg/m^3). “Control” measurements of the levels of lead and its inorganic compounds in the workplace air of refinery boiler operators showed a 46.6, 30.4, and 48.4-fold excess of the TWA corresponding to Class 3.4 of working conditions in terms of lead compound concentrations and total chemical exposure.

The control cohort consisted of 50 men of similar age (*Me* = 51 (48; 55) years) never exposed to occupational risk factors in the

industrial setting. Workers with traumatic nerve injury, demyelinating diseases of the nervous system, hereditary diseases, diabetes mellitus, thyroid diseases, and a cardiac pacemaker were not eligible for inclusion in the study.

Electroneuromyography was performed using a Dantec® Keypoint® G4 workstation, Denmark, with analysis of indicators (latency of sensory and motor responses (ms), motor and sensory nerve conduction velocity (m/s), amplitude of the motor response (Am, mV) and sensory response (As, μV), F-wave).

When testing somatosensory evoked potentials (SSEPs) using a Neuro-MEP-4 auditory-visual stimulation unit, Neurosoft, Russia, peak potentials and interpeak intervals were measured at different stimulation frequencies of 3–5 Hz. The amplitude of components (potentials), peak and interpeak latencies were analyzed.

Electroencephalography (EEG) was also performed using the Neuro-MEP-4 unit according to a standard method.

A comprehensive neurological examination of the subjects was carried out with assessment of clinical indicators, a neuropsychological testing (Montreal Cognitive Assessment or the MoCA test, with a score of 26–30 points considered to be normal), tests of semantic associations and speech sound disorders with 15 or over words taken as the norm. These tests evaluated the global cognitive function and its components, such as concentration, executive functions, memory, attention, language, abstract reasoning, and visuoconstructional skills.

The study was conducted using non-invasive methods and it complies with the ethical standards of the Bioethical Committee of the Research Institute for Complex Problems of Hygiene and Occupational Diseases, developed in accordance with the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects as amended in 2013 and the "Rules of Clinical Practice in the Russian Federation" approved by Order no. 266 of the Russian Ministry of Health dated June 19, 2003.

Results and discussion. Higher brain function test results helped establish the neurocognitive profile of the examined workers. Findings of the MoCA test showed that 35 % of the cases scored 19–24 points, 35 % scored 26 points (the suggested cut-off score), and 30 % scored 27 points or over. At the same time, a score of 26 or over was registered in 90 % of the controls with no pronounced cognitive impairment detected in this cohort.

Testing of semantic skills and phonological disorders. The findings showed specific features of the neurocognitive profile of the cases, including disorders of spatial orientation (20 %) and poor alternating trail making (15 %), constructional apraxia of the frontal type (the clock-drawing task) (15 %), impaired semantic speech activity (30 %), reduction in phonetically mediated associations (40 %) indicating the subcortical-frontal dysfunction, impaired memorization and reproduction processes (40 %) (frontal-subcortical disorders), impaired conceptual thinking (generalization) (20 %), decreased attention (30 %), and preserved executive functions (100 %). The evaluation of semantic and phonetic test results revealed a decrease in phonetically mediated associations compared to semantically mediated ones as a sign of subcortical-frontal dysfunction. We revealed signs of mild cognitive impairment in 30 % and a decrease in the cognitive reserve in 35 % of the cases. It is worth noting that neither cases nor controls had any complaints at the time of testing.

Electroneuromyography results showed statistically more significant changes in the case cohort ($p < 0.05$). We detected signs of entrapment neuropathies of the upper extremity in 20 % of the cases (increased latency in sensory and motor conduction ve-

locity along the median nerves at the level of the carpal tunnel and along the ulnar nerves at the level of the cubital tunnel, decreased As of the median nerve at the level of the carpal tunnel). In 35 % of the cases, we observed signs of a decreased amplitude of M-response and diagnosed conduction block related to motor axonal neuropathy in the peripheral nerves of lower limbs in 25 % and in the peripheral nerves of upper limbs – in 10 % of them. In 30 % of the cases, we registered sensory conduction abnormalities, such as prolongation of latency, a decrease in the amplitude and nerve conduction velocity; of these, along the sensory fibers of the upper and lower limbs – in 20 % and 10 %, respectively. In 15 % of the cases, ENMG parameters were normal.

The analysis of somatosensory evoked potentials in the control cohort showed that all indicators were normal. During the study, the parameters of peaks of the indicators in the case cohort were also within the normal range (Table 1).

Table 1

Upper extremity somatosensory evoked potentials in the case cohort

Level	Potentials	Latency, ms
C3'-Fz (cortex)	N20	22.1 ± 1.6
	P23	
	N30	
	P45	
C7-Fz (cervix)	N11	
	N13	13.2 ± 0.9
	N14	
	P18	
(Erb's point)	N9	10.7 ± 0.88
	P8	

We revealed signs of afferentation impairment at the subcortical-cortical level when analyzing interpeak intervals in the case cohort. In measurements of upper extremity somatosensory evoked potentials, N13 was assessed as the potential reflecting mainly the postsynaptic activation of the nuclei of the medulla oblongata and N20 – as that mainly reflecting the activity of generators in the thalamus or thalamocortical radiations. The conduction time from the lower parts of the brainstem to the cortex, determined by the time interval between components N13 and N20, was increased. The N13–N20 interval for C7-Fz–C3'-Fz was 8.9 ± 0.6, while the N30–P37 interpeak latency for C7-Fz–Cz-Fz1 was 2.2 ± 1.6. Prolongation of the conduction time from the lower brain stem to the cortex indicates conduction dysfunction at this level (Table 2).

Table 2

Interpeak intervals between upper extremity somatosensory evoked potentials in the case cohort

Level	Interpeak interval	Latency, ms
Erb-Fz – C7-Fz	N9–N13	4.6 ± 0.8
Erb-Fz – C3'-Fz	N9–N20	10.1 ± 0.77
C7-Fz – C3' Fz	N13–N20	**8.9 ± 0.6**

When measuring lower extremity SSEPs, the activity of generators in subcortical structures (N30) and the potential primarily reflecting cortical activation of the somatosensory area of the corresponding projection of the leg (P37) were within normal limits (Table 3).

Table 3

Lower extremity somatosensory evoked potentials in the case cohort

Level	Components	Latency, ms
L3-R (lumbar)	N22	25.2 ± 2.5
C7-Fz (cervix)	N30	30.1 ± 3.0
Cz-Fz (cortex)	P37	42.4 ± 3.3
	N45	50.3 ± 3.2

When analyzing the interpeak activity, we registered a slight prolongation of the

N30–P37 interpeak latency indicating conduction dysfunction at the subcortical-cortical levels (Table 4).

Table 4

Interpeak intervals between upper and lower extremity somatosensory evoked potentials in the case cohort

Level	Interpeak interval	Latency, ms
L3-R – Cz-Fz	N22–P37	19.1 ± 1.55
L3-R – C7-Fz	N22–N30	7.5 ± 1.07
C7-Fz – Cz-Fz	**N30–P37**	12.2 ± 1.6

Thus, we registered a change (slowing down) of afferentation at the subcortical (stem)-cortical level in the cases when testing upper and lower extremity SSEPs.

When analyzing EEG data, no significant differences were found between the cohorts.

Conclusion. The results of analyzing the functional state of the central and peripheral nervous systems in the workers occupationally exposed to a number of toxicants showed the predominance of such distal disturbances of motor and sensory conduction as compression lesions of the nerves, as well as signs of axonal pathology, mainly at the lumbar level. The integrated approach enabled us to determine specific characteristics of the neurocognitive profile and to detect initial frontal-subcortical disorders and a decrease in cognitive reserve. When testing upper and lower extremity SSEPs in the cases, we registered a change (slowing down) of afferentation at the subcortical (stem)-cortical level. Our findings are consistent with those obtained in other studies [4, 5, 10, 13, 14]. The revealed changes have enabled us to elaborate personal medical rehabilitation programs including neuroprotective techniques aimed at the main pathogenetic targets.

We believe that a comprehensive neurophysiological examination should be part of the regular health checkup of workers exposed to toxicants at workplaces, including those engaged in non-ferrous industry, as it helps detect early neurological changes.

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Research article

EXTRACT OF EUROPEAN SPRUCE STROBILES AS A PROMISING TOOL TO MINIMIZE THE RISKS OF INFLAMMATION

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The article is devoted to examining anti-inflammatory activity of dry aqueous extract of European spruce (Picea abies) strobiles using different routes of administration.

Strobiles of European spruce for extracts were harvested on the territory of the Perm region of the Russian Federation in a mixed forest with a predominance of European spruce and Scots pine (Pinus sylvestris). Dry aqueous extract was obtained according to the original patented method. Procyanidins content in spruce strobiles and dry extracts was determined by using acid cleavage of procyanidins to anthocyanidins according to the Porter method. Anti-inflammatory activity was established by using carrageenan-induced paw edema in rats. White laboratory outbred Wistar rats were used in the experiment.

According to the results of the study, the procyanidin content was found to equal approximately 13 % in the samples of spruce strobiles. Intraperitoneal administration of dry extract of strobile spruce at a dose of 100 mg/kg was established to induce pronounced anti-inflammatory activity. Intraperitoneal administration of smaller doses of strobile extract resulted in pronounced anti-inflammatory activity at a dose of 50 mg/kg. A dose of 10 mg/kg successfully suppressed inflammation (50 % edema suppression) 1 and 3 hours after carrageenan administration ($p < 0.05$) according to hydrometric data, but this was not confirmed by photometric data. Oral administration of the extract showed no anti-inflammatory activity. With the rectal route of administration, no pronounced anti-inflammatory activity was found in the studied extract.

The extract of spruce strobiles obtained by the original method contains 56 % procyanidins and exhibits pronounced anti-inflammatory activity when administered intraperitoneally. The use of the extract in oral and rectal routes of administration requires more in-depth study.

Keywords: *European spruce, strobiles, dry extract, procyanidines, intraperitoneal administration, oral administration, rectal administration, anti-inflammatory activity.*

In the Russian Federation, coniferous strobiles are harvested to obtain seeds for forest regeneration. Forest regeneration includes forest seed industry and reforestation. Seed yield from strobiles is only about 2 %. After seeds have been extracted, strobiles remain in forestry in huge quantities. The rich chemical composition of common spruce strobiles is the basis for searching for promising pharmacologically active substances.

We have developed a method for obtaining a dry aqueous extract of common spruce strobiles where one of the leading groups of biologically active substances are condensed tannins or procyanidins.

Proanthocyanidins were first examined by Jacques Masquelier in the 1940s in a study of

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pine bark, which Native Americans boiled to treat scurvy [1]. Procyanidins are derivatives of flavan-3-ols that have a typical C6-C3-C6 flavonoid backbone. In total, about 15 subclasses of proanthocyanidins have been identified, of which procyanidins are the most common. There are dimeric, trimeric, tetrameric and polymeric procyanidins [2].

Procyanidins are of medical interest because of their multiple beneficial properties [3, 4]. Procyanidin D1 has been shown to be effective in rheumatoid arthritis when administered orally for 23 days. The antiarthritic effect was mediated by the regulation of Th17 (T-helpers producing interleukin-17) / Treg (T-suppressors) cell balance; the regulatory effect, in turn, was associated with the inhibitory effect of procyanidin D1 on aromatic hydrocarbon receptor expression [5]. Procyanidin B1 increases the influx of mesenchymal stem cells to wounds and accelerates wound healing in a diabetic mouse model [6]. Procyanidin C1 exhibits antitumor properties by inducing apoptosis in breast cancer cells [7].

Literature sources describe different effects of procyanidins on the immune system. Using a splenocyte proliferation model, it has been shown that procyanidin D1 exhibits an immunosuppressive effect reducing the levels of interferon-α and interleukin–2 in a dose-dependent manner [8].

An aqueous extract of black spruce bark contains a significant amount of procyanidins and exhibits antiradical and anti-inflammatory activity [9]. Type A procyanadins isolated from cinnamon bark – *Cinnamomum verum J. Presl, (Lauraceae family)* exhibit anti-inflammatory activity in rat models of carrageenan edema and adjuvant-induced arthritis [10].

According to the WHO, chronic inflammatory diseases are one of the most important causes of death in the world. Their prevalence in the world is expected to grow steadily over the coming years. Inflammatory diseases include stroke, chronic respiratory disease, heart disease, cancer, obesity and diabetes, etc.[1] [11].

Considering high pharmacological activity of procyanidins isolated from plant sources, it is of interest to identify anti-inflammatory activity of spruce strobile extracts.

The purpose of the research was to study procyanidins levels in a dry aqueous extract of European spruce strobiles and evaluate its anti-inflammatory activity using different routes of administration.

Materials and methods. The object of the study is an extract of European spruce (*Picea abies (L.) Karst., Pinaceae*) strobiles growing in the Perm region (Russia). To obtain the extract, spruce strobiles were harvested on the territory of the Ilyinsky district of the Perm region in a mixed forest with a predominance of European spruce and Pinus sylvestris. After harvesting, raw materials were subjected to air-shadow drying.

The method of obtaining the extract. About 50 g of spruce strobiles crushed to particles passing through a sieve with a hole diameter of 2 mm, are placed in a flask, are added 1.5 liters of water (hydraulic ratio 1:30) and extracted with stirring for 1.5 hours while heating at 80–85 °C. The extraction completed, the raw material is separated from the extract by filtration. The resulting extract is concentrated under vacuum at a temperature of 80–85 °C 10 times from the original volume. Next, the ballast, inactive fraction is separated by cooling the evaporated extract at a temperature of -18 °C for 15 minutes. In this case, a precipitate falls out, which contains a part of the polysaccharide complex, proteins, tannins, and resinous substances. The precipitate is compacted by centrifugation and discarded. Next, the supernatant is evaporated in a vacuum evaporator to a thick mass and dried in an oven at a temperature of 50 °C[2].

The extract is a light brown amorphous powder with a specific odor, soluble in water,

[1] Rukovodstvo po provedeniyu doklinicheskikh issledovanii lekarstvennykh sredstv. Chast' pervaya [Guidelines for conducting preclinical studies of medicines. Part One]. In: A.N. Mironov ed. Moscow, Grif i K, 2012, 944 p. (in Russian).

[2] Pat. RF RU 2756009C1. Sposob polucheniya sredstva, obladayushchego protivovospalitel'noi aktivnost'yu [Method of obtaining a drug with anti-inflammatory activity]: patent for an invention. D.Yu. Apushkin, A.I. Andreev, D.K. Gulyaev, V.D. Belonogova, I.P. Rudakova, V.V. Novikova, date of publication: September 24, 2021 (in Russian).

partially soluble in 50 % and 70 % ethyl alcohol, insoluble in diethyl ether, ethyl acetate, or chloroform.

Obtaining microcapsules in a shell of cellulose acetate phthalate (CAP). Cellulose acetate phthalate (CAP) coated microcapsules are obtained by evaporating a highly volatile solvent in a liquid medium. Initially, 2 g of the powder is ground in a mortar in a dry form, placed in 20 ml of a polymer solution (5 % solution of cellulose acetate phthalate) in a chemical beaker and dispersed for 10 minutes on a magnetic stirrer. Then, 150 ml of vaseline oil is poured into the reactor (chemical beaker). The installation with an anchor stirrer is lowered into the glass and the equipment is turned on. The resulting drug suspension is poured into the reactor in a thin stream with the anchor mixer running and mixed for 15 minutes at 20 °C and a rotation speed of 800 rpm, preventing the mixture from being released. To cure the shells (remove the volatile solvent), the temperature is raised to 40 °C based on 5 °C after 20 minutes with a constantly running stirrer. After hardening (microcapsules do not flatten when pressed with a glass rod on filter paper), the stirrer is turned off. The resulting microcapsules are separated from the dispersion medium (vaseline oil) using a grid with a hole size of 0.2 mm. The microcapsules separated from the oil are washed 3 times with hexane (15–20 ml per portion). The finished microcapsules are left to air dry at room temperature.

Determination of procyanidins content. The procyanidin content in spruce strobiles and its dry extracts was determined using acid cleavage of procyanidins to anthocyanidins according to the Porter method [12, 13].

About 0.2 g of the extract (accurately weighed) (weighed amount of 1.0 grams of strobiles with a particle size that goes through a sieve size of 0.5 mm) was placed in a 100 ml round-bottom flask. 20 ml of 60 % ethyl alcohol was added, closed with a cork and weighed with an error of ± 0.01 g. Next, the flask was attached to a reflux condenser and heated in a water bath at a temperature of 80 °C for 15 minutes (40 minutes for the strobiles). After cooling to room temperature, the flask with stopper was weighed and brought to the initial mass with 60 % ethyl alcohol. The contents of the flask were centrifuged for 10 minutes at a speed of 2000–3000 rpm; 0.1 ml of the obtained extract was transferred into a 50 ml round-bottom flask, 0.9 ml of 60 % ethyl alcohol, 6 ml of acid butanol, 0.2 ml of an iron-containing reagent were added. The resulting mixture was attached to a reflux condenser and heated in a water bath at 80 °C for 50 minutes. The resulting solution was cooled at room temperature.

The optical density of the solution was measured on a SF 2000 spectrophotometer at a wavelength of 540 nm in a cuvette with a layer thickness of 10 mm using a solution consisting of 1 ml of 60 % ethyl alcohol, 6 ml of acid butanol, and 0.2 ml of an iron-containing reagent as a reference one.

The procyanidin content in terms of cyanidin chloride (%) was calculated by the formula:

$$X = \frac{A \cdot 20 \cdot 7.2 \cdot 100}{136 \cdot m \cdot 0.1 \cdot (100 - W)},$$

where

A is optical density of the test solution;

136 is specific absorption rate $E^{1\%}_{1\,\text{см}}$ of cyanidin chloride;

m is mass of raw materials (extract), g;

W is weight loss on drying, %.

White laboratory outbred Wistar rats and white laboratory outbred ICR (CD-1) mice were used in the experiment. Animal preparation included selection by sex, age and health status. Within the selected subpopulation, randomized selection was performed using a random number generator in the experimental groups, the reference group (diclofenac sodium) and the control group. Each group included at least 6 animals[3]. Animals in groups

[3] Rukovodstvo po eksperimental'nomu (doklinicheskomu) izucheniyu novykh farmakologicheskikh veshchestv [Guidelines for the experimental (preclinical) study of new pharmacological substances], 2nd ed. In: R.U. Khabriev ed. Moscow, Meditsina Publ., 2005, 826 p. (in Russian).

were labeled by applying through individual labels. Randomization quality control was performed on the basis of testing the significance of mass shifts and the homogeneity of variances before the experiment.

Design of animal experiments. The dry strobile extract was dissolved in 0.9 % NaCl solution or 2 % food starch solution, and administered to animals intraperitoneally, orally or rectally at doses of 100 (intralaboratory standard screening dose), 50 or 10 mg/kg 40 minutes before administration of a 1 % carrageenan solution (Sigma Aldrich, USA). Enteric-coated tablets of diclofenac sodium, 0.05 g, produced by OOO Ozon, Zhigulevsk, were used as the reference drug. The reference drug was dissolved in 0.9 % physiological NaCl solution or 2 % food starch solution and administered to animals. Animals in the control group received 0.9 % physiological NaCl solution or 2 % starch solution as an equistress effect. There was no reference group for the rectal form, and the control group received a 2 % starch solution in an equal (with the experimental group) volume. A solid dosage form of a plant extract (microcapsules) was administered orally after suspension in a 2 % food starch solution. The dose for the animal was determined based on the active substance (spruce strobile extract) contained in the dosage form. An acute inflammatory reaction was induced by subplantar administration of 0.1 ml 1 % carrageenan. An increase in foot volume, indicating the development of edema, was assessed using an aqueous plethysmometer and an anhydrous plethysmometer, where an optical three-dimensional measuring system is used [14, 15]. The anti-inflammatory effect was evaluated by reduction in the volume of edema in the experimental groups compared to the control group. To assess the anti-inflammatory activity of substances, the following indicators were used:

1) The value of the growth percentage. It characterizes the degree of increase in the volume of the paw in the experimental group compared with the control calculated by the formula:

$$X = \frac{a}{b} \cdot 100\ \%,$$

where X is the value of the growth percentage; a is the background value of the paw volume; b is the value of the paw volume 1 / 3 / 5 hours after administration of carrageenan.

2) The percentage of edema inhibition (characterizes the ability of a substance to inhibit the development of inflammation or reduce the amount of exudate that comes out of the blood vessels into the area of inflammation). It is calculated according to the formula:

$$Y = \frac{c}{d} \cdot 100\ \%,$$

where Y is the percentage of edema inhibition; c is the median percentage increase in the paw volume in the control group 1 / 3 / 5 hours after the administration of carrageenan; d is the median percentage increase in the paw volume in the experimental group 1 / 3 / 5 hours after the administration of carrageenan.

To analyze the experimental data, we used the nonparametric two-sided Wilcoxon signed-rank test for independent samples; corrections for multiple comparisons were not introduced[4] [16]. Outliers were identified and excluded according to the 1.5 IQR rule (outliers removed using 1.5*interquartile range rule).

Results and discussion. At the first phase of the study, we identified the content of procyanidins in strobiles of European spruce and two types of extracts, in the extract obtained by the method described in patent № 2756009C1, and in the extract obtained by conventional hot-water extraction without sediment removal. The presence of a condensed group in the extract of tannins was previously proven using qualitative reactions: a reaction with a 1 % solution of iron-ammonium alum and a Stiasny reaction. For quantification of procyanidins, a modified Porter method [12] was used, which is based on the acid cleavage of procyanidins to anthocyanidins. The results of the study are presented in the Table 1.

[4] Hollander M., Wolfe D.A., Chicken E. Nonparametric Statistical Methods. Canada, John Wiley & Sons, 2013, 848 p.

Table 1

The content of procyanidins in strobiles of European spruce and hot-water extracts

Sample	Content of procyanidins, %
Strobiles of European spruce	13.21 ± 1.57
Hot water extract with sediment removal (Patent RU № 2756009C1)	56.75 ± 2.53
Hot water extract without sediment removal	18.61 ± 0.65

According to the results of the study, the content of procyanidins was found to equal approximately 13 % in samples of common spruce strobiles. The scheme for obtaining a dry aqueous extract of common spruce strobiles, specified in patent № 2756009C1, makes it possible to obtain a substance with a content of procyanidins more than 3 times higher than the content in the extract of common spruce strobiles without removing the sediment. A significant increase in the content of procyanidins can affect the pharmacological activity since many activities are associated with procyanidins, including anti-inflammatory effects [9].

The results of studying the anti-inflammatory activity of the obtained extract when administered intraperitoneally are presented in Table 2.

Table 2 presents data on the experiment, the purpose of which was to determine the presence of pronounced anti-inflammatory activity of dry spruce strobiles extract. Spruce strobile extract showed pronounced anti-inflammatory activity when administered intraperitoneally to rats. Moreover the effect was so strong that the carrageenan edema model itself could not develop unlike the control or the reference groups. Diclofenac was used as a reference drug, as it is one of the most popular NSAID today. Diclofenac showed a pronounced anti-inflammatory activity, but the anti-inflammatory effect of the spruce strobile extract was higher, especially during the third hour of the experiment. Such observations were noted both in photometric and hydrometric measurements.

The RR (relative risk) of developing an increase in rat paw edema in the group receiving diclofenac relative to the group receiving spruce strobile extract is 2.94 at the first hour; at the third hour, 3.94; at the fifth hour, 4.88. OR (odds ratio) that an increase in inflammation will occur in the group receiving diclofenac, in comparison with the group receiving the extract of spruce strobiles, equals 5 at the first hour, 10.15 at the third hour, and 24.4 at the fifth hour. This indicates a more pronounced anti-inflammatory effect of spruce strobile extract in comparison with diclofenac. The use of spruce strobile extract minimizes the risks of developing an inflammatory reaction.

To confirm the effectiveness of spruce strobile extract as an anti-inflammatory agent, it was of interest to investigate anti-inflammatory activity in different animal species. CD-1 mice were used as the second model animal. The results of exploring the anti-inflammatory activity of spruce strobile extract in mice are presented in Table 3.

Table 2

Anti-inflammatory activity of spruce strobile extract when administered intraperitoneally to rats

Substance code / dose	Route of administration	Assessment method	Edema inhibition (%)					
			1 h	p-value	3 hrs	p-value	5 hrs	p-value
Spruce strobile extract 100 mg/kg	ip	Photo	> 95	**0.020**	99.6	**0.004**	> 95	**0.005**
Spruce strobile extract 100 mg/kg	ip	Hydro	84.6	**0.004**	>95	**0.004**	93.8	**0.004**
Diclofenac 10 mg/kg	ip	Photo	67.9	0.2403	61.8	**0.0411**	55.3	0.0651
Diclofenac 10 mg/kg	ip	Hydro	86.1	**0.0022**	72.1	**0.0050**	45.1	**0.0022**

Note: * ip – intraperitoneally; photo – measurement with an anhydrous plethysmometer, where an optical three-dimensional measuring system is used; hydro – measurement with a water plethysmometer, *p* (Wilcoxon signed-rank test) – *p*-value according to the Mann – Whitney test. **Bold indicates *p*-values < 0.05**.

Table 3

Anti-inflammatory activity of spruce strobile extract when administered intraperitoneally to mice

Group	1 h			4 hrs		
	Median Growth Percentage, %		Paw edema inhibition (%)	Median Growth Percentage, %		Paw edema inhibition (%)
Control	26.67	*p*-value	-	31.29	*p*-value	-
Spruce strobile extract	12.75	**0.0021**	52.2	10.63	**0.0021**	66.0
Diclofenac	11.49	**0.0297**	56.9	21.26	0.1244	32.0

Note: **p* (Wilcoxon signed-rank test) – *p*-value according to the Mann – Whitney test. **Bold indicates *p*-values < 0.05**.

The results of the experiment indicate pronounced anti-inflammatory activity of the spruce strobile extract, which was confirmed in screening experiments on two animal species, when assessing the volume of edema by two mutually independent instrumental methods.

Table 4 presents data on an experiment aimed at determining the minimum effective dose (to reduce the amount of substance used) that would also effectively suppress the inflammation model. For this, a small dose range was taken: 50 mg/kg and 10 mg/kg (data on a dose of 100 mg/kg are present in the previous experiment).

Table 4 shows that intraperitoneal administration of spruce strobile extract at a dose of 50 mg/kg to rats resulted in a considerable and statistically significant suppression of the inflammatory response. A dose of 50 mg/kg of spruce strobile extract can be used as a substitute for a dose of 100 mg/kg. A dose of 10 mg/kg, according to hydrometric data, suppresses inflammation (50 % suppression of edema) at the 1st and 3rd hour after the administration of carrageenan ($p < 0.05$), but this is not confirmed by photometric data.

The next stage of our work involved exploring anti-inflammatory activity of the spruce strobile extract when administered orally. Influence of the aggressive environment in the stomach was reduced by using microencapsulation. Since many anti-inflammatory drugs are used as suppositories, another experiment was conducted using this route of administration. The results of experiments with oral and rectal routes of administration are presented in table 5.

Oral administration of the extract had no significant effect on the inflammatory response. When assessing the oral exposure to a dry aqueous extract of common spruce strobiles from the first to the fifth hour, we did not establish any statistically significant difference

Table 4

Anti-inflammatory activity of spruce strobile extract when administered intraperitoneally (dose reduction)

Substance code	Route of administration	Assessment method	Edema inhibition (%)					
			1 h	*p*-value	3 hrs	*p*-value	5 hrs	*p*-value
Spruce strobile extract 50 mg/kg	ip	Hydro	> 95	**0.004**	> 95	**0.004**	> 95	**0.004**
Spruce strobile extract 10 mg/kg	ip	Hydro	58.5	**0.001**	50.2	**0.001**	17.9	**0.001**
Spruce strobile extract 50 mg/kg	ip	Photo	> 95	**0.032**	> 95	**0.008**	> 95	**0.008**
Spruce strobile extract 10 mg/kg	ip	Photo	28.2	0.329	39.4	0.082	5	0.792

Note: * ip – intraperitoneally; photo – measurement with an anhydrous plethysmometer, where an optical three-dimensional measuring system is used; hydro – measurement with a water plethysmometer, *p* (Wilcoxon signed-rank test) – *p*-value according to the Mann – Whitney test. **Bold indicates *p*-values < 0.05.**

Table 5

Anti-inflammatory activity of spruce strobile extract after oral and rectal administration

Substance code	Route of administration	Assessment method	The difference between the experimental and control groups, *p*-value		
			1 h	3 hrs	5 hrs
Spruce strobile extract 50 mg/kg	Orally	Photo	0.862	0.728	0.281
Spruce strobile extract in microgranules 50 mg/kg	Orally	Photo	0.731	0.731	0.731
Spruce strobile extract 50 mg/kg	Rectally	Photo	0.429	0.177	0.247

Note: * Photo – measurement with an anhydrous plethysmometer, where an optical three-dimensional measuring system is used, *p* (Wilcoxon signed-rank test) – *p*-value according to the Mann – Whitney test.

from the control group in the inhibition of inflammation. Similarly, as a result of the experiment with rectal administration, there was no statistically significant difference with the indicators of the control group in terms of the level of anti-inflammatory activity. Oral administration of microcapsules with spruce strobile extract also did not reduce the severity of carrageenan edema.

This study established that the concentration of procyanidins occurs when using a technique involving a stage of sediment removal by a sharp change in temperature. The content of procyanidins obtained by this method is higher than by using standard hot water extraction.

Procyanidins are one of the main groups of biologically active substances in spruce strobile extract. The anti-inflammatory effect of procyanidins is associated with the ability to reduce the production of reactive oxygen species in the focus of inflammation. Reactive oxygen species are involved in the activation of the NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling system and the MAPK (mitogen-activated protein kinase) signaling pathway. The MAPK signaling pathway determines the expression of various genes by regulating several pro-inflammatory factors [17].

Intraperitoneal injection of spruce strobile extract leads to a significant inhibition of the inflammatory response in comparison with the control. The anti-inflammatory activity of spruce strobile extract was confirmed in two animal species at three dose levels (100, 50, 10 mg/kg) using an aqueous and anhydrous plethysmometer for measurement. This study may be a starting point in the development of anti-inflammatory drugs for use in medical and veterinary practice.

There are inconsistent data in the literature on the absorption of procyanidins from the gastrointestinal tract. Some studies state that procyanidins are able to be absorbed from the gastrointestinal tract and undergo glucuronidation and sulfation [18, 19]. In contrast, other studies have shown that procyanidins have very low bioavailability [20]. Bioavailability can also influence the severity of the anti-inflammatory effect of an extract. Our study showed that oral administration of the studied extract did not lead to suppression of the inflammatory response. However, it should be noted that the extract was administered to the animals once; long-term administration of the extract has not been evaluated. The literature reports that the administration of procyanidin D1 for 23 days led to the suppression of the inflammatory response against the background of rheumatoid arthritis [5]. This indicates that the studied extract rich in procyanidins does not show a rapid and pronounced anti-inflammatory effect when taken orally, but may be effective with long-term oral use.

In the environment of gastric juice, many substances are destroyed or change their structure. To reduce the effect of gastric juice on the extract of spruce strobiles, microcapsules with CAP were obtained. Microcapsules are capsules consisting of a thin shell of CAP, spherical or irregular in shape. The use of this approach makes it possible to obtain enteric microcapsules. Our study established that mi-

croencapsulation did not lead to an increase in the anti-inflammatory activity of the spruce strobile extract when administered orally. This indicates that the absence of pronounced anti-inflammatory activity in the spruce strobile extract is not associated with possible changes in the structure of substances in the gastrointestinal tract.

Conclusion. Our study established that a dry aqueous extract of European spruce strobiles, obtained by an original method, contains a significant amount of procyanidins. The experiments on laboratory animals established that the studied extract has pronounced anti-inflammatory activity when administered intraperitoneally. The studied extract is active in two animal species. No pronounced anti-inflammatory activity has been established after oral or rectal administration of the extract. The features of absorption of common spruce strobiles extract and oral use as an anti-inflammatory agent require more in-depth study.

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Competing interests. The authors declare no competing interests.

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Review

MICROPLASTICS POLLUTION IN WATER IS A THREAT FOR HUMAN HEALTH AND THE ENVIRONMENT (LITERATURE REVIEW)

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Microplastics pollution of water bodies and drinking water is a relevant problem caused by wide use of plastics in multiple industries, agriculture, manufacturing of household chemicals and medicines. Microplastics pose a threat for human health both due to physical effects and chemicals in their structure as well as microorganisms that can occur on their surface.

Some foreign studies describe how microplastics are formed and how they can occur both in seawater and fresh water. There are also studies confirming microplastics to be present in seas and rivers in the Russian Federation.

Studies that address microplastics in tissues of aquatic organisms are scarce. According to some foreign authors, microplastics can be absorbed by mollusks, starfish, actiniae, crabs, etc. Russian researchers provide evidence of considerable quantities of microplastics found in the digestive organs of a dace fish caught in the Tom River. Several foreign studies have established effects produced by microplastics on reproduction, eating behavior as well as declining survivability in crustaceans and fish.

Fish products are a well-known significant source of microplastics in human diets. Microplastics bioaccumulation in aquatic biota is seen as a potential health threat for organisms at higher trophic levels, including humans at the top of the food chain.

Unified water sampling techniques are absent; studies that address effects of microplastics on the human body are scarce; there is no available methodology for hygienic standardization of microplastics in water. All this makes it necessary to have some research aimed at identifying sources and causes of microplastics pollution in water bodies including sources of drinking water supply, to assess public health risks, and to provide safe conditions for water use.

Keywords: *microplastics, water bodies, drinking water, risk factor, human health, bioaccumulation, negative impacts, biota, water pollution.*

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The world plastic production has been growing steadily as these materials are used in all spheres of our life. From the very moment plastics were invented and up to now, production outputs have become huge. Between 1950 and 2020, almost 9 billion tons of plastics were manufactured worldwide. At present, only 9 % of them have been recycled; 12 % have been combusted as energy recovery; the remaining 79 % have not been treated and are stored in landfills, illegal dumps, or just in the environment [1].

Nowadays, the global society has some serious concerns about plastic wastes that pollute water objects. Thus, the United Nations Environment Program (UNEP) envisages creating an international legally binding instrument on plastic pollution, including that in the marine environment [2], which should be agreed upon by governments of participating countries. Between May 29 and June 2, the second session of the intergovernmental negotiating committee was held; its major aim was to develop an international legally binding document on cessation of plastic pollution in the environment. Federal executive authorities from Russia, including the Ministry of Foreign Affairs, Ministry of Natural Resources and Environment, and Sanitary Service, as well as representatives of the Russian Academy of Sciences and the Russian Environmental Operator took part in this session of the intergovernmental negotiating committee.

Materials and methods. We analyzed plastic pollution of water objects and aquatic biota relying on data provided in foreign and Russian studies. Microplastics should be given special attention among other plastic pollutants of water objects; this concerns microplastics, which are widely used in industrial and agricultural products, household chemicals, and medications (so called 'primary' microplastics), or those formed by breakdown of larger plastic objects ('secondary' microplastics).

Microplastics can be potentially hazardous for human health due to their physical effects, chemicals in their structure, as well as due to microorganisms in films occurring on their surface.

Microplastics were first reported in plankton samples as far back as in 1970es; however, they were not given much attention by research society until early 2000es. 'Microplastic' as a concept was first introduced in research literature in 2004 by Richard Thompson, a world-leading marine scientist. Some researchers believe that microplastics initially represent larger plastic elements, which then break down to smaller particles sized between 1 and 5 μm [3–12].

Results of investigating microplastics in water objects. The aquatic environment nowadays is attracting more and more attention worldwide. This is due to steadily growing amounts of microplastics consisting of widely spread plastics including polyethylene, polystyrene, polypropylene, polyamides, and polyvinyl chloride. These plastics differ not only in size but also in shapes and specific density and, as a rule are identified in water objects. Microplastics in water are able to absorb various pollutants such as pesticides, pharmaceuticals, personal care items, metals and microorganisms and carry them into various ecosystems.

Studies by A.I. Andrady (2011) and other researchers established that plastics reduce their molecular mass under exposure to solar ultraviolet radiation and some mechanic forces, for example, waves and rising tides. This results in their breakdown into smaller fragments. These plastic fragments are rather fragile and can crumble to powder-like particles, which quite often turn out to be microplastics. Simultaneously, chemicals are washed out from plastics thereby making the aquatic environment more toxic. Therefore, water pollution with microplastics is becoming an urgent issue related to preservation of ecological stability of water objects [13–20]. Fresh water is also prone to microplastics pollution. In 2014, M. Eriksen with colleagues published the first study of open water that aimed to identify plastic pollution in the Great Lakes. Samples were taken in 21 spots in three lakes (the Lakes Superior, Huron, and

Erie) and examined by scanning electron microscopy (SEM). All the samples but one contained plastics. Their average quantity equaled 43,157 particles per km^2.

Samples from Lake Erie had the highest levels of microplastics accounting for 85 % of all microplastic particles collected in all the analyzed samples. The identified particles sized between 0.36 and 0.99 mm. Five categories of microplastics were identified; granules and fragments were the most widely spread accounting for 81 % of the total quantity of particles [21].

So far, field studies focusing on plastic pollution have been accomplished in ten seas in Russia [22].

Considerable amounts of plastic enter Russian Arctic seas with the Atlantic Ocean currents that flow from densely populated areas in Europe and America. The maximum amount of plastic microparticles that equaled 30 items per m^3 was identified in the Barents Sea. Smaller amounts were identified in the Kara Sea (9 items per m^3), the Laptev Sea (7 items per m^3), the White Sea (6.42 items per m^3), and the East Siberian Sea (2 items per m^3), although large rivers of the Russian European North and Siberia (the Northern Dvina, Ob, Yenisei, Lena and some others) flow into these seas. Quantitative contributions made by these rivers to microplastic pollution of the Arctic Ocean and its seas still remain unknown.

Microplastics can enter Russian seas with the Pacific Ocean currents. Elevated microplastics levels in the Chuckchee Sea (up to 26 items per m^3), the Bering Sea (up to 81 items per m^3), and the Sea of Okhotsk (up to 357 items per m^3) may result from this circumstance.

Microplastics levels identified in Inland seas of the Atlantic Ocean did not differ substantially from those identified in the Arctic Ocean seas. The Baltic Sea waters contained microplastics in levels less than 10 items per m^3; the Black Sea waters, up to 7 items per m^3.

Recently, microplastics levels have been analyzed in freshwater of large Russian rivers. Microplastic quantification in water samples established the largest amounts of microplastic particles in Kazanka, a left tributary of the Volga (up to 210 items per m^3); Vychegda, a tributary of the North Dvina (76 items per m^3); the Ob (51 items per m^3); the Tom (44 items per m^3), and the Mesha River, a tributary of the Kama River (41 items per m^3). At the same time, lower levels of microplastic pollution were identified in Ishim (4.56 items per m^3), Volga (up to 4.10 items per m^3), Yenisei (2.95 items per m^3), and Lower Tunguska (2.58 items per m^3). Microplastic pollution was also found in Baykal, its level varying between 0.03 and 3.85 items per m^3. These research results indicate that microplastic levels differ greatly in fresh water of large Russian rivers depending on a region. Further research of the issue requires more detailed investigations in various water objects considering not only their geographic locations but also such factors as industrial objects in close proximity to them, population density, and the like (Figure 1).

Studies that address microplastics in tissues of aquatic organisms are scarce. According to some foreign authors, microplastics can be absorbed by Arctic biota including mollusks, starfish, actiniae, crabs, etc. (Figure 2).

The highest levels of microparticles were identified in blue mussels (4.29–10.81 items per specimen) in the Barents Sea; the lowest ones, in opilio crabs (0.0–0.6 items per specimen) in the Chuckchee Sea. Among the Chuckchee Sea biota, elevated microplastic levels were identified in actiniae (0.2–1.7 items per specimen) and starfish (0.04–1.67 items per specimen) [23–25].

It is noteworthy that investigations with their focus on identifying microplastics in fresh water biota have been given much less attention in research literature.

In Russia, levels of microplastics were first investigated in organisms living in water objects in Russia by experts from the Research Center of the Biological Institute of the Tomsk State University within the project on investigating levels of pollution in the Ob River and its tributaries. They established considerable levels of microplastics (sized between 0.15 and 2.00 μm) in the gastrointestinal tract of a dace fish caught in the Tom River.

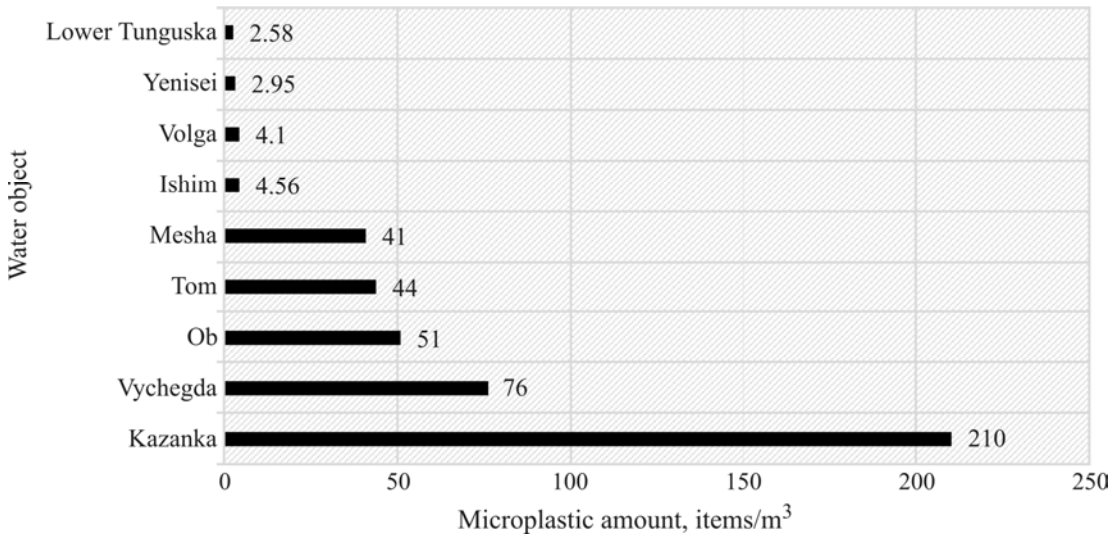

Figure 1. Microplastic levels in rivers in the Russian Federation

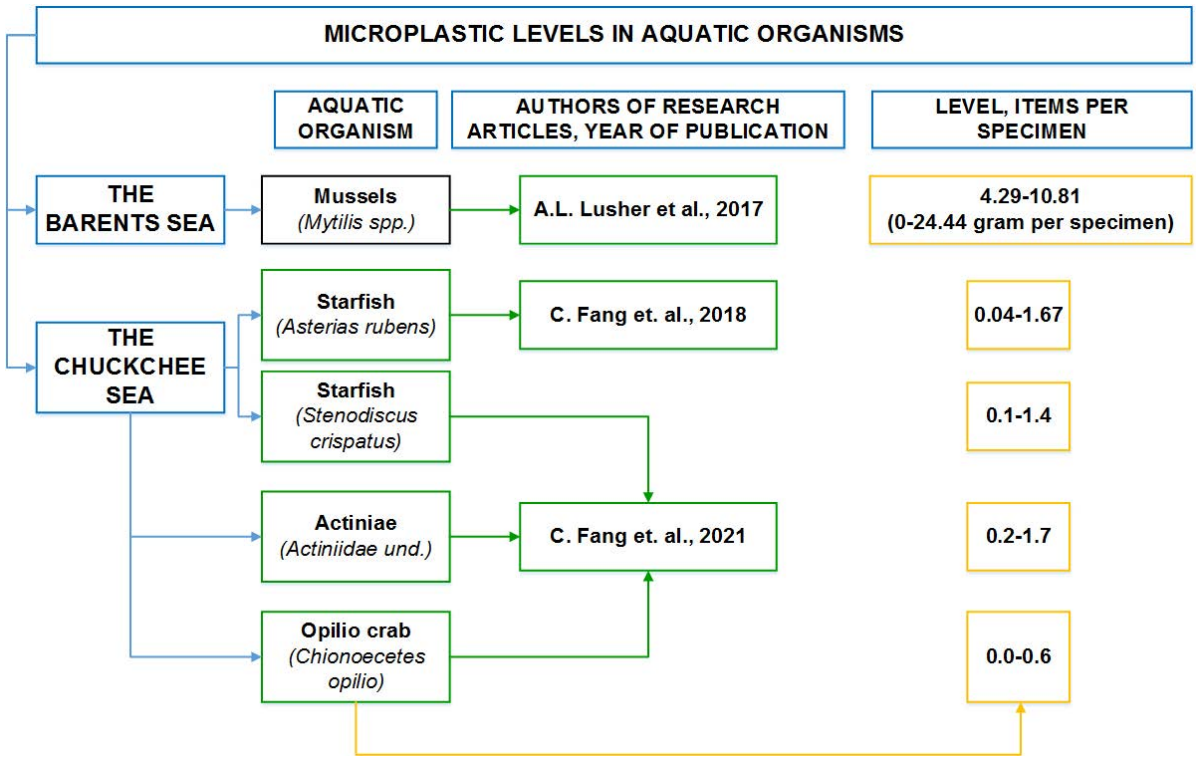

Figure 2. Microplastic levels in aquatic organisms [26–28]

Effects produced by microplastics on living organisms. Data on influence of microplastics on the aquatic environment and biota in Russia are scarce. However, such data can be found in foreign publications reporting some adverse effects produced by microplastics on the reproductive behavior and food habits.

Physical properties of microplastics include size, shape, surface, and ability to absorb chemical pollutants and pathogens along food chains.

As reported in the study [29], microplastic bioaccumulation in the aquatic biota is considered a potential threat for organisms at higher trophic levels. Microplastic pollution can have adverse effects on human health as well since people are at the top of the food chain. Seafood is the most hazardous in this respect; the aforementioned study reports that regular

Microplastic levels in fishes' organs [32–35]

Species / taxons	Organs	Levels	Average length (μm)	Microplastic type
The Nile tilapia *Oreochromis niloticus*	gills	$71.7 \pm 9.3 \times 10^4$ μg/kg	0.1	PS (100 μg /l)
	liver	$36.6 \pm 1.0 \times 10^4$ μg/kg		
	brain	$40.5 \pm 0.6 \times 10^4$ μg/kg		
The red mullet *Mullus barbatus* the Black Sea shad *Alosa immaculata*	gills	-	50–200	PC PA
	liver			
	brain			
The bartail flathead *Platycephalus indicus*	muscles	14 items per specimen	< 250	Not identified
	gills	17 items per specimen	100–250	

consumption of such food products may result in 11,000 microplastic particles annually penetrating the human body.

Drinking water might be another source of microplastic introduction into the body [30]. It is common thinking that bottled water consumption results in 90,000 particles penetrating the body annually whereas tap water contains particles in much lower levels and intake quantities in this case are up to 4000. Microplastics and other toxic products can penetrate the body from package probably due to improper storage conditions and temperatures as well as when people use plastic packages with mechanical damages of their walls.

S.A. Mason with colleagues examined drinking water from 259 bottles of 11 global brands that were bought in different countries. Microplastics were found in 93 % of the analyzed samples [31].

Some studies report that microplastics sized more than 0.15 μm are not likely to be absorbed in the gastrointestinal tract and those sized less than 0.15 μm are able to penetrate from the GIT into lymph and the circulatory system. For example, microparticles were found in lymph and cytoplasm of some fishes (Table).

Microplastics were found in 80 % of liver samples of 13 analyzed fish specimens caught in the Mediterranean Sea. Moreover, after microplastics have entered fish blood flow, they can accumulate in muscles, gills, and liver. Microplastics accumulated in fish organs can migrate into other organisms at higher trophic levels along the food chain.

Several foreign researchers identified microplastic particles in human vein bloodflow tissues, which can be considered evidence of possible transport of microplastics within human tissues, specifically blood vessels [34].

Plastics are made of various chemical compounds. Some of them are hazardous and can be leached into the environment when plastics undergo breakdown. Plastics usually contain some admixtures that make them more durable and elastic. When these admixtures are leached from plastics into the environment, they can affect not only the aquatic environment but human health as well [35].

Conclusion. Data available in research publications indicate that microplastics are potential and priority pollutants of sea and fresh water objects, aquatic biota and drinking water sources in the Russian Federation. However, there are no convincing data on clinically significant health outcomes caused by exposure to microplastics or unified procedures for sampling of water or bottom sediments.

Effects produced by microplastics have not been examined properly and a methodology for establishing hygienic standards of microplastic levels in water has not been developed either. Therefore, is necessary to accomplish investigations aimed at:

- identifying sources and reasons for microplastic pollution in water objects, including drinking water sources;
- developing unified procedures for sampling of water and bottom sediments;
- comprehensive examination of microplastics as a new exposure factor includ-

ing its identification by using up-to-date methods;

- examining influence of microplastics on the human body and developing hygienic standards for their levels in water objects;
- examining protection functions of water intake structures with respect to microplastics in order to provide population with safe and qualitative water.

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Review

INDIVIDUAL STRATEGIES FOR MITIGATING HEALTH RISK UNDER HIGH EPIDEMIOLOGICAL HAZARD (REVIEW OF FOREIGN STUDIES)

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The COVID-19 pandemic created elevated risks for life and health of overwhelming majority of people all over the world. The situation called for global restructuring of activities performed by social institutions as well as for adaptation of people's routine behaviors to this new reality. Common people faced a serious challenge of selecting an optimal self-preservation model that would allow achieving the maximum possible mitigation of health risks. This review covers empirical foreign studies with their focus on people's health-related behavior during the COVID-19 pandemic with its aim being to identify different types of individual strategies for health risk mitigation.

During the pandemic, protective behavior was influenced by social, cultural, sociodemographic, and individual and personality-related factors. Effects of micro-factors (age or education) could be different depending on a country. High healthcare literacy was a factor of selecting a protective behavior model regardless of any other characteristics.

We can spot out three basic strategies for mitigating health risks under high epidemiological hazard: 1) a maximum protection strategy involving adherence to most medical recommendations on prevention of the coronavirus infection; 2) a dominating protection strategy that involves adherence to some basic recommendations (face mask wearing, frequent hand washing, and self-isolation); 3) a mixed strategy that includes periodical adherence to some recommendations on prevention of the infection, on the one hand, and some risky behaviors, on the other hand.

Behavior strategies aimed at mental health protection are various and include, for example, those that are oriented at social networks as much as only possible (a strategy involving search for emotional support or an attempt to keep social contacts), as well as isolation strategies and deviant strategies.

Some studies covered in the review suggest ways to consider peculiarities of individual and family behavior during the pandemics when solving tasks related to risks of infections spread in future.

Keywords: *pandemic, health risks, self-protective behavior, health-related behavior, coronavirus infection, risk mitigation strategies, maximum protection strategy, dominating protection strategy.*

On May 05, 2023 T. Ghebreyesus, the Director-General of the World Health Organization (WHO), declared the COVID-19 pandemic to be officially over[1] thus summing up a more than 3-year period of this topic hitting headlines all over the world. The COVID-19 pandemic has become the most serious challenge for the whole humankind in the 21st century; it is an integral part of the historical context now, along with several other natural regulators of the global population such as pandemic outbreaks of plague, leprosy, cholera, and Spanish flue [1]. According to the WHO global report, the COVID-19 pandemic caused 14.9 million additional deaths in 2020–2021 and resulted in 336.8 million of lost years of life worldwide[2].

Lifestyles had to be changed globally due to anti-epidemic measures introduced by most countries; as a result, a customary worldview turned out to be fragile and vulnerable in the face of invisible and obscure danger. This process stimulates thinking about humans' place, role, and capabilities within the system of their interaction with the world around.

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[1] WHO Director-General's opening remarks at the media briefing – 5 May 2023. *WHO*. Available at: https://www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing---5-may-2023 (September 01, 2023).

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This pandemic has become a striking example of what negative consequences globalization might have thereby providing its opponents with new arguments and starting new discussions in scientific and common discourse [2]. The speed of the virus spread all over the world has clearly shown strength of social connections and density of economic, cultural, and political interdependencies in the global society. Hazards created by the virus persuaded the world it was necessary to combine efforts to fight against the common danger together, at least, for a while.

Social and political aspects of the pandemic have become apparent through selecting specific anti-epidemic procedures introduced in a whole state, starting from total isolation and severe sanctions for breaching it as it was in China and down to efforts to naturally achieve something like 'collective immunity' under minimal social restrictions and with relatively slow vaccination. Different models of fighting against the COVID-19 pandemic had different effects in population incidence and mortality [3].

The pandemic has again attracted the humankind attention to social inequality as a global issue by showing greater vulnerability to the infection among people from traditionally deprived social groups and countries, which are underdeveloped socially and economically [4].

From the very first days of the pandemic, the COVID-19 virus turned out to have an astonishing ability to potentiate hazards posed by already existing health issues, which, in an ordinary situation, would only create some minor difficulties in patients' lives. Such diagnoses as obesity or diabetes mellitus, when they were combined with the coronavirus infection, turned into a powerful health risk factor that could cause a patient's death or result in a very severe disease, complicated treatment and unfavorable outcome [5, 6]. Since some effective mechanisms of public aid were absent, personal responsibility for one's health became such an acute problem as never before. Understanding that the issue was complex in its essence facilitated occurrence of fundamentally new health protective patterns as regards not only the COVID-19 itself but any concomitant diseases as well.

The aim of this study was to identify types of individual strategies aimed at mitigating health risks and adopted by population under high epidemiological hazard. We are making an effort to answer several questions relying on the results of foreign studies in the process. How did the COVID-19 pandemic change self-protective behavior worldwide? To what extent did medical recommendations on prevention of the disease become a part of a new lifestyle? What social and demographic variables had the greatest effects on readiness to follow risk-mitigating recommendations and vice versa? And, finally, what classical and modern theories of self-protective behavior turned out to be the most relevant for explaining these processes?

In our opinion, a very important circumstance should be highlighted since it makes this challenge more difficult than it appears at first. Despite severe global consequences, the pandemic has still turned out to be a quite rapid, many-aspect, and many-sided process. Results derived by studies that were accomplished during the first stages in the pandemic can be totally different from those obtained at some later stages when a level of a perceived risk has become significantly higher and studies have become more fundamental.

Social and demographic factors that determine protective behavior. The theory of planned behavior by I. Ajzen [7] was selected by foreign researchers as the basic conceptual scheme. By using it, they were able to explain individual choices as regards a strategy for health risk mitigation, transformation of a lifestyle, and adherence to healthcare recommendations during the pandemic. Perceived behavioral control, the key category within this concept, reflects the subjective complexity of adherence to various healthcare recommendations and ultimately determines a behavioral pattern. Subjective norms, behavior accepted in a social setting, and cultural peculiarities of a specific society are other variables that contribute to formation of such patterns. Individ-

ual adherence to prevention behavior and analysis of factors that promote its formation became the first and the most significant research challenge within healthcare sociology under the pandemic.

Since the COVID-19 infection was a respiratory one, this made it possible to create clear and universal recommendations on how to prevent it from spreading. They included face mask wearing, frequent hand sanitation, regular disinfection of surfaces, use of sanitizers, avoiding touching one's face, hiding one's face into the bend of elbow when coughing, keeping a proper social distance, and staying home when infected[3]. Although the recommendations were really clear and quite simple, adherence to them turned out to be rather problematic. For example, long-term keeping of a social distance or social isolation can be rather challenging since people tend to adapt to risks, fight against loneliness and try to return to their ordinary lifestyles thereby refusing to observe protective measures [8].

A research team from two research centers in Florida, USA, made an effort to investigate a connection between perceived behavioral control, attitudes, and subjective norms, and whether people used all the aforementioned prevention measures in their everyday life [9]. The authors made several very interesting conclusions that confirmed basic conceptual postulates of the theory of planned behavior. First of all, they again mentioned a more significant role that belonged to behavioral control in formation of most components of preventive behavior against individual attitudes and influences exerted by social settings. In practical terms, this means that some effective measures would include removing barriers that make adherence to recommendations more difficult or emphasizing easier ways of participating in specific preventive behavior. The most obvious examples are automatic hand sanitizers that can be found everywhere and face masks distributed free of charge.

Age has become a variable able to influence adherence to preventive behavior. Just as expected, people from older age groups were more responsible in comparison with younger ones as regards the majority of the recommended behavioral models. A study that was conducted in the USA on a national sample of adult population in the first half of 2020 showed that people aged 60 years and older followed the basic recommendations authentically more frequently (wearing a mask, washing of hands, and social distancing) than people of younger ages [10]. Data obtained by a sociological survey in spring 2020 in Germany showed that responsible healthcare behavior was more likely to be adopted by older respondents but still there was a certain decrease in readiness to keep social distance and adhere to personal hygiene [11]. A study conducted in late 2020 – early 2021 in Greece established that people from younger age groups (18–30 years) more often denied the validity of scientific data and mass media reports about COVID-19 and this resulted in less responsible behavior [12].

Among other social and demographic factors of protective behavior, attention should also be paid to gender-related one: women and girls are traditionally more prone to protective health behavior during the pandemic [13]. Obviously, the persistent gender-related effect exists in any age group as regards preventive behaviors [14]. A possible interpretation could be different personality characteristics, namely, women tend to score higher than men on agreeableness and conscientiousness, and to be more willing to comply with a set of protective health behaviors [15]. Differences in the gender contract and peculiar social roles of men and women can be another possible explanation. For example, women in general tend to be neater and cleaner, take care of sick people more often and therefore adopt more serious attitudes towards safety precautions; women spend more time at home and, consequently, have fewer social contacts, adapt to self-isolation more rapidly and easier, etc. This means that

[3] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. *National Institutes of Health.* Available at: https://www.covid19treatmentguidelines.nih.gov/ (September 05, 2023).

it may be necessary to conduct more targeted information campaigns for men and boys who are traditionally more prone to risky behaviors and tend to underestimate hazard.

Understanding one's individual susceptibility to COVID-19 turned out to be a significant factor determining formation of protective health behavior. A study conducted in late 2020 in Germany established several factors able to create elevated risks; an age older than 50 years (33 %) and an existing basic disease (32 %) were mentioned more frequently. Obviously, all the respondents had high levels of adherence to recommended safety precautions. It was especially true for avoiding direct social contacts; refusing parties, trips or handshakes; keeping social distance and wearing a face mask (each behavior scored higher than 88 %) [16]. Overall, high levels of compliance with infection control measures were identified in other studies conducted in Germany [17].

Choice of a behavioral strategy during the pandemic was also determined by fear of the disease and trust in information sources [18]. An international study conducted in West European countries and the USA during the first pandemic wave established that COVID-19 worry was authentically associated with selecting a protective behavior strategy. Self-efficacy had a much more substantial effect on individual behavior; it was described with self-estimation of competence and ability to act [19]. Overall, health literacy (awareness) was considered the key competence and the mandatory condition for understanding and estimating COVID-19-related instructions provided by healthcare organizations and workers; the ability to use them in everyday practices to control and prevent the infection; as well as protection of one's own physical and mental health and health of close relatives and friends. High health literacy was also a significant factor able to produce positive effects on vaccination [20].

Some foreign studies provide certain data on high health literacy with respect to preventing and treating COVID-19 both by a population in general and by some specific social and occupational groups [21]. Results of a survey conducted in Germany in spring 2020 indicate that up to 80 % of the respondents believed they were very well or well informed about the pandemic [22]. It was very easy or easy for these citizens, from their subjective point of view, to behave in such a way so that they did not infect other people, to understand government instructions on how to protect themselves from the coronavirus, to estimate measures that protected from the infection and behavioral models that created the highest health risks for them, and to make decisions on how to protect themselves from the coronavirus infection relying on information provided in mass media [23]. On the one hand, these results were quite expected considering universal spread of health information in mass media, research articles, and everyday discourse. On the other hand, these results can be considered unreliably optimistic due to two circumstances typical for similar surveys. First, the pandemic had no equal as an event facilitating popularity of online surveys, which became the basic way to collect empirical data. Consequently, the analyzed sample did not include people without access to the Internet. And if we bear in mind that elderly people are obviously expected to prevail among them, we should accept the fact that a very important information block, which concerned the most vulnerable social and demographic group, was neglected by the analysis. Second, the reported data were self-estimations in their essence and did not show how knowledge was transformed into routine behavior.

Extreme presentation of the pandemic and protective health behavior in mass media (social media included) had certain drawbacks, first of all, information overload of audiences [24]. In addition to that, uncertainty grew among people whose health literacy was low. Deficit of health knowledge prevented them from adequate or critical perception of information and created controversial strategies of protective health behavior. Thus, a survey conducted among people in Germany established that most respondents who believed they were well aware of COVID-19-

related issues either did not have any concerns about risks of infection or had very few whereas low concerns were typically mentioned by only 19 % of those respondents who were rather poorly informed of the matter [23]. This regularity seems universal and is not either gender- or age-dependent. Health literacy that helps estimate and use information correctly can be eligible for eliminating this difference. It is worth noting that different sources of information can have different influence on adherence to them and diagnostics of communication channel effectiveness becomes a separate important task.

Individual and personal factors of protective health behavior. People are different as regards concern, readiness, and expectations in an emergency; they have different levels of conscientiousness and responsibility. Knowing how a personality reveals itself during a complicated epidemic situation can help predicting behavior under future outbreaks of communicable diseases and provide relevant recommendations for executive authorities on how to develop effective advice considering individual peculiarities.

The five-factor model of personality (FFM) is the most popular theoretical framework for factoring of the entire variety of personal traits, mostly due to its relative simplicity. The model was developed by conducting some series of studies as far back as 1960ties [25]. The model inserts the personality into the system of five basic coordinates; two of them, namely 'Self-control – Impulsivity' and 'Emotionality – Calmness' are of direct interest within our subject. Conscientiousness is a trait on the first axis and neuroticism is one on the second. It is these traits that are considered basic personality determinants responsible for formation of attitudes towards a disease and protective health behavior [26].

It seems quite logical to assume that people with high conscientiousness take more safety precautions to avoid getting infected with the coronavirus. This conclusion is consistent with data reported in several studies with their focus on health behavior [27], including those focused on COVID-19 prevention. Since conscientiousness is characterized by orderliness, responsibility, impulse control, and self-discipline, people who score high with respect to this trait are more likely to comply with recommendations on safety precautions. People with high scores on extraversion are not prone to estimate duration of the pandemic pessimistically, have sufficient reserves of internal energy, and assess their life and health more positively. It is noteworthy that higher extraversion was also established to be associated with higher concern and it seems to contradict to the aforementioned facts. However, any concerns about the pandemic should not be considered equal to pessimism; to some extent, they can be a justified rational reaction to an objective hazard. The latter circumstance can also occur due to a high correlation between conscientiousness and extraversion, which becomes apparent, among other things, through taking care of family and friends.

Neuroticism reflects proneness to irritation, anger, sadness, concern, anxiety, and hostility. No wonder, that people with high neuroticism reported strong concerns and were pessimistic in their estimates of the COVID-19 pandemic duration [28]. People high in neuroticism have more chronic negative emotions, react to psychological traumatic experiences especially acutely and largely rely on emotion regulation strategies [29]. Despite their overall hypochondriac orientation, people high in neuroticism adhere to fewer safety precautions. However, this is due to elevated proneness to depression that is typical for them, since some studies on COVID-19 report that higher neuroticism was associated with a tendency to keep social distancing and hygienic behavior, for example, hand washing and avoiding touching the face.

A conclusion on the role that belongs to the ethnic factor in formation of behavioral strategies under the pandemic became an important fact typical for the American research. African Americans and Hispanics tended to have greater concerns and relevant readiness to take more precautions [30].

Whites, on the contrary, turned out to be more careless as regards four aspects of the pandemic: concerns, precautions, COVID-19 duration estimates, and preparatory behavior; the latter meant stocking foods or medications to reduce the need to go out during the isolation period. This also correlates with lower social and economic adaptation and wellbeing of the aforementioned ethnical groups, which makes them more responsible under a global crisis [31].

The sociological approach stimulates authors to look for regularities of influence individual psychological traits may have on behavioral patterns in any other hazardous situations. Neurotic reactions are counter-productive just as conscientiousness, fair practices and optimism are useful, and this is obvious and universal in any critical situation. However, similar studies with their focus on factors that shape protective behavioral patterns under the pandemic (or any other global crisis) highlight the idea that individual and psychological peculiarities will unavoidably have lesser role in distribution of data in future. In other words, personality traits cease to be those variables that determine behavioral peculiarities of specific social and other groups in the face of grave dangers threatening a population as a whole.

Role of the family in selecting a risk mitigation strategy. Family support had the key role in choices of protective strategies made by an individual during the COVID-19 pandemic. Studies that were conducted in various periods of the pandemic in North America, Western Europe, and Asia established that support provided by family, relatives, and friends authentically increased likelihood that an individual would choose protective health behavior [32–34]. An interstate study accomplished in summer 2020 on a representative sample made of 6990 people showed that support provided by 'significant others' was a more substantial determinant of choosing health-protective behavior than sex, socioeconomic status, health state, and concerns about the pandemic [35]. A survey conducted among Israeli adolescents during the first (April 2020) and the second (September 2020) lockdown established that risk-inducing behavior (alcohol abuse, tobacco and marijuana smoking) was more typical for children from families with weak family support [36].

It was rather difficult for families to implement social support functions effectively due to unavoidable intra-family transformations associated with the pandemic. Due to anti-epidemic measures, primarily self-isolation and quarantine, families were forced to change their ordinary life, redistribute roles and revise interactions inside the system and contacts with the outer world. The fact that any family was to some extent influenced by the pandemic is obvious at least due to the complexity of family systems, variety of family sub-institutions, intra-family roles and interactions and each family being a unique small social group. The basic questions here are how exactly they were influenced; what sub-institutions and sub-systems were affected the most and the least; and what factors caused the observable effects.

Positive experience of intra-family functioning prior to the pandemic is the key factor that determines positive adaptation of a given family to COVID-19. Such families tend to score high in mental health and internal integration, which provides adequate ability to adapt under uncertainty and chaos. It is these concepts taken from the family stress theory that are usually applied by foreign researchers to describe reactions of family systems to isolation and emotional state of their members [37]. Forced confinement to a closed space, disrupted connections with the outer world, unemployment, and a decrease in living standards could not fail to induce changes in the balance of authority relations, statuses, and roles, education processes, and quality of parent-child and sister-brother relationships. This called for readjusting all the components in the family systems, which, in its turn, led to responses by subsystems and individuals, from reserved acceptance to blunt protest [38, 39].

Within the health protection context, it should be noted that these circumstances cause elevated parental stress, depression and con-

cern. This may create risks of mental disorders and use of psychoactive drugs not only by parents but by adolescents and young students as well. Adolescents also had elevated risks of mental disorders due to weaker support provided by their counterparts and loneliness during the pandemic [40]. Telemedicine and other distant consulting were deemed promising under these new conditions; however, prospects of their use also turned out to be rather ambiguous. At present, new data are reported in some studies that such interventions that rely on technologies and do not provide direct contacts are not effective in working with socially challenged population groups. Therefore, it is necessary to adapt telemedicine services for families in difficult situations to avoid aggravating the existing disparity in access to healthcare. This includes providing access to relevant technologies.

Dynamics of family violence is another significant indicator that describes family health within the pandemic context [41]. It can be considered a destructive but rather expected reaction to family disorganization when any potential conventional means of harmonization have been depleted but the problem has not been solved yet. Universal nature of family violence, that is, absence of any binding to specific risk groups, and its occurrence in any social layer makes it a very sensitive indicator of family stress levels. Comparative analysis of its dynamics during the pandemic and prior to it makes it possible to illustrate influence exerted by anti-epidemic measures on family stress levels [42].

The gender-specific approach, which is typical for western scientific research, considers women and children primary victims of family violence; therefore, other family members rather rarely appear in this context. Statistical analysis of complaints about family violence revealed that the number of complaints about domestic abuse of a spouse grew during the quarantine but the number of complaints about violence towards children went down. The latter is most likely due to a reduction in contacts between children and employees of organizations responsible for detecting infringements of civil rights and activating various mechanisms of social protection.

Two recommendations were the most widely spread in the analyzed studies. First, it was necessary to provide digital access to services; and second, to develop skills of education and healthcare experts as regards using online platforms to identify signs of family violence. It was also recommended to provide better training and funding for workers of psychiatric and social services to effectively prevent family violence, especially during the pandemic. However, let us again highlight the necessity to employ a differentiated approach to using digital technologies and providing equal access to online services for various social groups.

Mental health protection strategies. The necessity to change customary lifestyles, destruction of traditional work or study regimes, forced self-isolation, and confinement to a closed space with the same people for several weeks or even months became a grave challenge for human psyche. This called for selecting effective strategies aimed at mental health protection. According to the WHO reports, prevalence of anxiety disorders and depression grew by 25 % worldwide during the first year of the COVID-19 pandemic[4].

The pandemic can be described in dynamics by changes in its stages: the beginning, crisis, lockdown, re-orientation and the new reality. Each stage has its typical dominating psychological experiences. Thus, German researchers reported the highest generalized anxiety at the lockdown stage since 10 % of the respondents mentioned the symptom being rather severe and this was by far higher than prior to the pandemic. Depression occurred at all stages in the pandemic until the new reality was formed; its levels grew from 5.6 to 22 % [43].

[4] COVID-19 pandemic triggers 25 % increase in prevalence of anxiety and depression worldwide. *WHO*. Available at: https://www.who.int/news/item/02-03-2022-covid-19-pandemic-triggers-25-increase-in-prevalence-of-anxiety-and-depression-worldwide (September 05, 2023).

According to the US Centers for Disease Control and Prevention, as of June 2020, almost one third of adults in the country suffered from anxiety or depression [44]. These levels were almost twofold among older male adolescents, that is, the social group with prevalence of mental disorders already growing significantly in it over the last decade. More than 60 % of people aged between 18 and 24 years were susceptible to depression or anxiety and one fourth of them reported they had been thinking about suicide during the previous month. These estimates give evidence of a considerable growth in depression since its prevalence was about 11 % among adults and about 25 % among American college students prior to the pandemic in 2019.

This rise in prevalence of depression occurred immediately after such safety precautions as social distancing and self-isolation had been introduced. They led to a drastic change in physical activity, sleep, and leisure, especially at the beginning of the pandemic in March and April 2020 against uncertain prospects of the disease spread and unknown duration of forced self-isolation. It was noted that risks of depression were considerably higher for students who had to study during the pandemic adhering to anti-epidemic measures than for their counterparts from previous cohorts [45]. This gives evidence that the pandemic was able to intensify the relationship between maintaining customary lifestyles and mental health. It is noteworthy that an experiment was conducted when a group of students returned to their former levels of physical activity for one and a half month; as a result, their mental health did not improve [46]. This fact may indicate that physical activity does not have any intrinsic value but is rather a form of social interaction that was almost completely shut down by anti-epidemic restrictions. Switching to distance learning also made its contribution to risks for physical and mental health since it aggravated a decrease in physical activity and intensified communicative deprivation even when the actual and virtual reality came closer to each other. The only positive result that can be mentioned here is that these data outline some promising trends in future research with its focus on mental health recovery.

Another obvious assumption is that an association between physical activity and subjective wellbeing is primarily determined by the initial level of mental health and not by a lifestyle. That is, changes in physical activity, duration of sleep or behavioral models of spending free time as such can be early symptoms of depression. Moreover, both physical activity and mental disorders can be determined by basic reactions to the pandemic. In other words, people who are able to keep their customary lifestyle during the pandemic have been more resistant to stress and less prone to anxiety prior to it.

International organizations developed recommendations on how to protect mental health for specific social groups. The United Nations Office for the Coordination of Humanitarian Affairs developed a Guide on Psychological Support for Older Adults during the COVID-19 pandemic[5]; UNICEF, recommendations for adolescents on how to protect mental health in this new reality[6]. Recommendations covered, for example, proper sleep-wakefulness patterns, relaxation, meditation, adherence to information hygiene, and socializing and communication with family and friends. A study conducted in May 2020 in the USA established that the top three strategies to cope with COVID-19 with respect to mental health included acceptance, self-distraction, and use of emotional support [47]. Behavioral detachment, use of psychoactive drugs, and denial were less popular.

[5] Living with the Times, A Mental Health and Psychosocial Support Toolkit for Older Adults During the COVID-19 Pandemic. *Inter-Agency Standing Committee: OCHA Service*. Available at: https://interagencystandingcommittee.org/iasc-reference-group-mental-health-and-psychosocial-support-emergency-settings/living-times-mental-health-and-psychosocial-support-toolkit-older-adults-during-covid-19-pandemic (September 07, 2023).

[6] How to protect your mental health during the coronavirus (COVID-19) pandemic: 6 strategies for teenagers faced with the new (temporary) situation. *UNICEF, Serbia*. Available at: https://www.unicef.org/serbia/en/how-protect-your-mental-health-during-coronavirus-covid-19-pandemic (September 07, 2023).

A survey conducted in Australia found that positive thinking, active stress coping and social support were significant factors for mental health protection [48]. A study conducted between March and August 2020 established four basic coping strategies (problem-focused, emotion-focused, avoidant, and socially-supportive) adopted by the respondents. Of them, the socially-supportive coping was associated with a faster decrease in anxiety and depressive symptoms [49].

To summarize various behavioral patterns typically chosen by people during the COVID-19 pandemic, we can spot out several risk mitigation strategies. The first one is the maximum protection strategy involving adherence to most medical recommendations on prevention of the coronavirus infection (wearing a face mask and gloves, social distancing, strict self-isolation during a lockdown, vaccination, etc.). The strategy can have some variations that are largely determined by culture. For example, a comparative study of behavior adopted in Germany and Japan during the first pandemic year revealed that people in both countries were highly committed to health-protective behavior. In Germany, however, a significantly higher proportion washed their hands frequently and avoided crowds, physical contact, public transport, peak-hour shopping, and contact with the elderly. In Japan, a significantly higher proportion was willing to be vaccinated [50]. The second one is the dominating protection strategy that involves adherence to some basic recommendations (face mask wearing, frequent hand washing, and self-isolation): a survey conducted in China in early 2020 established that it was this strategy that most people adhered to during the first phase in the pandemic [51]. A cross-national study accomplished in Western and Southern Europe revealed that frequent hand washing and face mask wearing integrated into people's routine behavior the most rapidly [52]. A variation of this strategy was adherence to basic prevention together with refusal from vaccination. At the same time, vaccination against the coronavirus infection reduced a level of person's adherence to health-protective practices [53]. The third one is the mixed strategy that includes periodical adherence to some recommendations on prevention of the infection, on the one hand, and some risky behaviors, on the other hand. Thus, an online US national study conducted in August – October 2020 established that 12 % of the respondents 'always' or 'often' disinfected their hands and wore face masks but also 'always' or 'often' failed to keep self-isolation, went shopping, or visited their friends or relatives [54]. Finally, we should mention COVID-19 denialism as a specific behavioral strategy as regards COVID-19-related risks. The strategy is based on denying the very existence of the coronavirus infection and / or scales of its hazards and prevalence [55]. Choice of this strategy is associated with individual health literacy (awareness) and trust in various sources of information.

Conclusion. Our analysis of studies conducted in various countries during the COVID-19 pandemic revealed several variable individual strategies aimed at health risk mitigation, from responsible health-protective behavior to risk-inducing one associated with COVID-19 denial and low trust in information about mandatory prevention measures. Factors that determine choice of an individual behavioral strategy can be divided into a) social and demographic ones (sex, age, ethnicity, place of residence, self-assessment of infection risks, and health status); b) social and psychological (anxiety, neuroticism, and conscientiousness); c) micro-social (social support and information involvement). Family and its successful adaptation to new functioning conditions also play a significant role in determining strategic choice of health-protective behavior.

On the one hand, a situation that involves high epidemiological hazards creates risks of communicable diseases; on the other hand, it creates high levels of anxiety in people since it is always an uncertainty factor. Implemented anti-epidemic measures can be an additional source of stress due to involved changes in everyday life. Orientation at social support and emotional help provided by significant others,

first of all, family, is the most effective strategy aimed at mitigating risks for mental health under such situations.

Multiple studies that investigate behavioral peculiarities of various social groups during the COVID-19 pandemic provide great opportunities for mitigating risks of communicable diseases in future. It seems advisable to do several things. First, we should create an integral system for sanitary education of population, raise health literacy, and provide operative health risk communications. Second, there should be targeted efforts aimed at forming adherence to self-protective behavior in risk groups who do not have sufficient resources to resist a disease. Third, we should develop certain mechanisms of strengthening family connections and prevent family ill-being as an additional risk health risk factor under a stressful epidemiological situation.

Limitations of the study. The review covers only full-text publications in English and German languages that report empirical research results.

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