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Research article

METHODICAL APPROACHES TO ASSESSING ADDITIONAL DISEASE RISK AND LOSS OF LIFE EXPECTANCY AT BIRTH UPON COMBINED EXPOSURE TO POLLUTANTS

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Assessment of health risks and resulting negative health outcomes, including those caused by combined exposure to pollutants, as well as scientific substantiation provided for decisions aimed at managing them, are among priority hygienic tasks solved by Rospotrebnadzor through implementing its functions and powers. In this study, we were interested in developing methodical approaches to assessing additional disease risk and losses of life expectancy at birth upon combined exposure to pollutants. The study design is based on an iteration algorithm, which includes a cascade model of interrelated events Exposure – Biomarker of Exposure – Biomarker of Negative Effect – Negative Outcome (Disease) – Additional Health Risk. Probable losses of life expectancy at birth were predicted based on quantitative estimation of additional risk to isolated risk. We assessed approximately 300 multifactorial models (1000 parameters). The algorithm was tested for actual repeated exposure to airborne copper oxides in a concentration equal to 1.5–3.0 RfC; nickel oxides, 0.5–8.0 RfC; and chromium oxides, 0.2–3.9 RfC. The testing involved using the results obtained by our own long-term profound examinations accomplished over 2014–2023 with 2800 participants, of them 1868 children (aged 4–7 years) and 920 adults (aged 18–59 years).

A predominantly synergic type was established for combined effects produced by copper, nickel and chromium oxides (up to 57.1 % cases). It created an additional risk to isolated disease risk, which was 1.5–6.4 times higher than its acceptable level. Additional health risk for children was caused by diseases of the nervous system; for adults, diseases of the circulatory system, metabolic disorders, and diseases of the nervous system. Probable losses of life expectancy at birth, given the existing additional health risks upon actual combined exposure to copper, nickel and chromium oxides, were equal to approximately one month (30.2 days) under the best-case scenario and approximately one year (376.0 days) under the worst-case one.

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Practical use of the proposed algorithm for assessing additional health risks upon combined exposure to chemicals makes it possible to perform objective analysis as regards the existing sanitary-hygienic situation, to achieve more effective and adequate assessment of the current and planned air protection activities for their timely adjustment, as well as to provide targeted medical and preventive measures until health risks decline down to their acceptable levels.

At the same time, it is necessary to improve approaches to substantiating lists of chemicals that are top priority for regulation upon combined exposure to their mixture. It will help create a convincing basis for differentiation of regulatory measures and concentration of efforts on the highest health risks and health harm.

Keywords: *combined exposure, airborne exposure, additional health risk, cascade model, biomarkers of exposure, biomarkers of negative effects, diseases, prediction, life expectancy at birth.*

Minimization of health risks is an extremely important task Rospotrebnadzor has to tackle within providing sanitary-epidemiological safety of the population[1]. Chemical air pollutants (with diverse composition, structure, etc.), including their combined mixtures with variable composition, are among leading health risk factors creating additional associated population incidence and mortality [1, 2]. Repeated airborne combined exposure existing in regions with stably operating industrial productions can create unacceptable health risks. This induces negative cellular and systemic health impairments, which in future lead to medical and economic losses [3–5]. Over the last year, approximately 600 additional diseases and 4.6 deaths per 100,000 of the total population were associated with exposure to chemical air pollutants in residential areas. This unavoidably results in losses of employable population participating in production of the gross domestic product[2].

Given that, assessment of health risks and resulting negative health outcomes, including those caused by combined exposure to pollutants, as well as scientific substantiation provided for decisions aimed at managing them, are among priority hygienic tasks solved by Rospotrebnadzor through implementing its functions and powers [6]. The methodology for assessing health risks associated with effects of chemical mixtures has been developed for decades following variable principles, adopting variable concepts and priorities; it has been improved due to using the combined potential of interdisciplinary knowledge and achievements [3, 7, 8].

Pioneer research works focusing on investigating peculiarities of combined exposures are represented by experimental studies based on quantification of lethality of biological models using two- or three-factor combinations of chemicals (largely for various metals and metalloids) [3, 9, 10]. Subsequent use of statistical analysis, mathematical modeling, graphic techniques (for example, the least squares method, correlation and regression, isobole analysis etc.) allowed achieving more authentic and adequate results [3, 7]. Still, interspecies differences between experimental animals and humans [11, 12], complexity involved in modeling an actual exposure to chemical mixtures and inconsistency in interpreting a prevailing type of an effect [3, 13] were basic uncertainties able to influence precision and objectivity of estimations.

An approach based on summation of negative effects or dose addition made a substantial contribution to development of the methodology for assessing risks upon combined exposures [9, 14]. Use of the Dose – Response relationship became the key element of this approach [15, 16]. Need in more detailed studies of combined exposure and attempts to bring them to real-world conditions required including quantification of chemicals in bio-

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[1] O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2023 godu: Gosudarstvennyi doklad [On sanitary-epidemiological safety of the population in the Russian Federation in 2023: the State Report]. Moscow, Federal Service for Surveillance over Consumer Rights Protection and Human Well-being, 2024, pp. 4–6 (in Russian).

[2] O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2023 godu: Gosudarstvennyi doklad [On sanitary-epidemiological safety of the population in the Russian Federation in 2023: the State Report]. Moscow, Federal Service for Surveillance over Consumer Rights Protection and Human Well-being, 2024, pp. 126–130 (in Russian).

logical media of the human body and possible health outcomes in susceptible population groups (identification of exposure biomarkers and biomarkers of negative effects) [17–19]. In this respect, researchers started to use a system of cause-effect relations to reveal authentic associations between negative effects and exposure factors. The system was parameterized using a correlation-network approach, multidimensional regression and neural network models etc. [20, 21]. In general, the existing methodology for health risk assessment is a powerful instrument, which provides analysis of a sanitary-hygienic situation on the formalized basis. The aim is to substantiate measures aimed at preventing and mitigating negative health outcomes caused by combined exposure. At the same time, an important issue is to specify levels of additional risks in real world conditions relative to calculated data per risk-realized diseases and to rank chemicals per their priority in a mixture. Peculiarities of combined exposures, that is, interactions more complex than simple summation (synergy, potentiation, antagonism etc.) are not considered in regulatory practices to the full extent but they are much more prevalent (more than 50.0 % cases) [22–25].

In this respect, it is a crucial challenge for hygiene and prevention medicine to expand scientific grounds of the methodology for assessing health risks caused by combined exposure. This will make it possible to develop approaches to regulating levels of chemicals in various combinations in mixtures that create an exposure; this gives solid grounds for a relevant strategy aimed at minimizing health risks and eliminating negative health outcomes.

The aim of this study was to develop methodical approaches to assessing additional disease risk and losses of life expectancy at birth upon combined exposure to air pollutants.

Materials and methods. To achieve the set goal, the study design was based on a proposed iteration algorithm for quantification of additional risk to separate effects creating disease risks and associated predicted losses of life expectancy at birth (LEB) upon combined exposure to a three-component chemical mixture (Figure 1).

Assessment of additional to isolated likelihood of negative effects (Δp_n) at Stages I–III in the proposed scheme was accomplished on the example of a mixture containing aluminum oxide, hydrogen fluoride, and benzo(a)pyrene and was described in detail in a previously published work [26]. Further development of methodical foundations (Stages IV–VIII) includes assessment of additional health risks per additional to isolated likelihood of an associated disease considering its severity.

Additional likelihood of a risk-associated disease (Δp_z) upon combined exposure to a three-component mixture was established per the following formula (1):

$$\Delta p_z = \frac{1}{1+e^{-(b_{z0}+\sum_n b_{zn}\Delta p_n)}} - \frac{1}{1+e^{-(b_{z0})}}, \tag{1}$$

where $\Delta p_{z\,n}$ is additional likelihood of the z-th nosologic form of a disease in case the n-th biomarkers of negative effects deviate from the physiological range due to effects produced by combined exposure to a mixture of chemicals;

$\frac{1}{1+e^{-(b_{z0}+\sum_n b_{zn}\Delta p_n)}}$ is likelihood of the z-th disease in case the n-th biomarkers of negative effects deviate from the physiological range due to effects produced by combined exposure to a mixture of chemicals;

Δp_n is additional likelihood of changes in the n-th biomarkers of negative effects due to combined exposure;

b_{z0} , b_{zn} are the parameters of the mathematical model;

$\frac{1}{1+e^{-(b_{z0})}}$ is background likelihood of the z-th disease in case biomarkers of negative effects deviate from the physiological range in the absence of any chemical exposure.

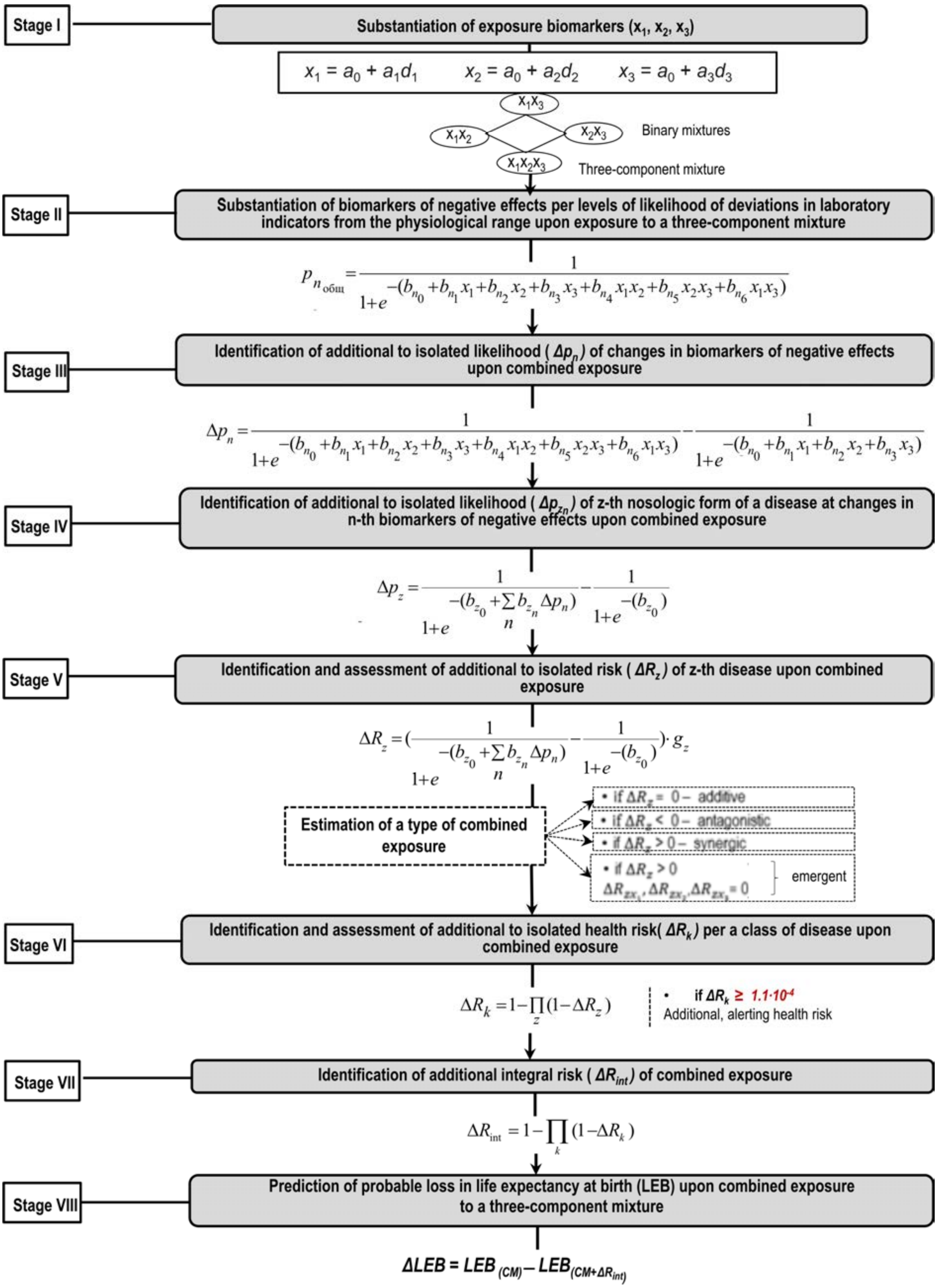

Figure 1. Iteration algorithm for assessing additional to isolated disease risk (ΔR_k) and associated predicted losses of life expectancy at birth (LEB) upon combined exposure to a three-component chemical mixture with diverse composition

Additional disease risk (ΔR_z) caused by exposure to a combination of chemicals was calculated using the following formula (2):

$$\Delta R_z = \left(\frac{1}{1+e^{-(b_{z0}+\sum_n b_{zn}\Delta p_n)}} - \frac{1}{1+e^{-(b_{z0})}}\right)\cdot g_z, \quad (2)$$

where ΔR_z is additional risk of the z-th disease upon combined chemical exposure; g_z is average weighted severity of the z-th disease per one nosologic group [27].

Additional risk for a class of diseases upon combined exposure was calculated per the formula (3):

$$\Delta R_k = 1 - \prod_z (1-\Delta R_z), \quad (3)$$

where ΔR_k is additional risk of diseases per a given class of diseases caused by combined chemical exposure; ΔR_z is additional risk of the z-th disease caused by combined chemical exposure.

The range $1.1\cdot10^{-6}$ – $1.0\cdot10^{-4}$ was used as the indicator showing that additional non-carcinogenic risk was acceptable. At $\Delta R_z > 1.1\cdot10^{-4}$, additional health risk was estimated as 'alerting'[3].

Additional integral risk upon combined chemical exposure was established based on the results of risk evolution modeling for specific health impairments (diseases) using the formula (4):

$$\Delta R_{\text{int}} = 1 - \prod_k (1-\Delta R_k), \quad (4)$$

where ΔR_{int} is the integral risk at age t; ΔR_k is risk of the k-th health impairment kind (a disease per a specific class) at age t.

Probable losses in life expectancy at birth were calculated based on evolution modeling of health risk growth from the cellular-molecular to the whole body level in accordance with the conventional procedure (MR 2.1.10.0082-13)[4]. LEB was calculated given the distribution of mortality rates for the population under the current exposure and given the distribution of these rates added by the value of the additional integral risk in each age group (formula 5):

$$\Delta LEB = \Delta LEB_{(MR)} - \Delta LEB_{(MR + \Delta Rint)}, \quad (5)$$

where $\Delta LEB_{(MR)}$ is the calculated life expectancy at birth given the existing death rate;

$\Delta LEB_{(MR + \Delta Rint)}$ is the calculated life expectancy at birth given the death rate added by the value of the additional integral risk;

MR is the mortality rate that described how likelihood of death is distributed per age.

The whole algorithm was tested for an actual chronic airborne exposure over the period of 2014–2023 using another chemical mixture as an example: copper oxides in levels equal to 0.0000088–0.000082 mg/kg·day (1.5–3.0 RfC); nickel, 0.000003–0.00022 mg/kg·day (0.5–8.0 RfC); and chromium, 0.0000047–0.00053 mg/kg·day (0.2–3.9 RfC).

[3] R 2.1.10.3968-23. Rukovodstvo po otsenke riska zdorov'yu naseleniya pri vozdeistvii khimicheskikh veshchestv, zagryaznyayushchikh sredu obitaniya; utv. Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii ot 06 sentyabrya 2023 g. [Guide R.2.1.10.3968-23 Health Risk Assessment upon Exposure to Chemical Pollutants in the Environment; approved by the RF Chief Sanitary Inspector on September 06, 2023]. Moscow, State Sanitary-Epidemiological Regulation of the Russian Federation, 2023, pp. 80–81 (in Russian).

[4] MR 2.1.10.0082-13. Metody otsenki mediko-demograficheskoi situatsii na populyatsionnom urovne: metodicheskie rekomendatsii, utv. vrio rukovoditelya Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, vrio Glavnogo gosudarstvennogo sanitarnogo vracha RF A.Yu. Popovoi 28.11.2013 [Methods for assessing the medical-demographic situation at the population level: Methodical Guidelines, approved by A.Yu. Popova, the acting Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, the acting RF Chief Sanitary Inspector on November 28, 2013]. *MEGANORM: the system for regulatory documentation*. Available at: https://meganorm.ru/Data2/1/4293772/4293772405.htm (February 07, 2025) (in Russian).

Additional disease risk was calculated using the results obtained by the authors' long-term profound examinations of 2800 people, including 1868 children (aged 4–7 years) and 920 adults (18–59 years), which were conducted in 2014–2023. The resulting data array contained individual levels of copper, nickel and chromium in blood; levels of biochemical, immunological and hematological indicators, which had pathogenetic associations with the analyzed exposure; the main diagnosis (ICD-10).

This study did not require approval of a local ethical committee (it was conducted using data obtained by previous research).

Levels of chemicals identified in blood of the examined participants were used as biomarkers of combined airborne exposure; children: copper, 0.968 ± 0.009 mg/dm^3 (1.1 RfL), nickel, 0.007 ± 0.0004 mg/dm^3 (7.0 RfL), chromium, 0.006 ± 0.0002 mg/dm^3 (8.5 RfL); adults: copper, 0.948 ± 0.053 mg/dm^3 (1.1 RfL), nickel, 0.009 ± 0.001 mg/dm^3 (9.0 RfL, chromium, 0.005 ± 0.0003 mg/dm^3 (7.1 RfL)[5].

Forty-seven biochemical, immunological, and hematological indicators, pathogenetically associated with impacts exerted by the analyzed exposure factors were used as biomarkers of negative effects in critical organs and systems. The studied negative effects describe 18 classes of diseases. They are diseases of the nervous system (G90.8, G90.9) including activity and attention disorders (F48.0, F90), other extrapyramidal and movement disorders (G24.9); diseases of the blood such as iron deficiency anaemia (D50.9), specified and unspecified (D64.8, D64.9), certain disorders involving the immune mechanism (D83.9, D84.9); heart diseases (I34.1, I45.1, I49.9), including ischaemic heart disease (I20) and hypertensive diseases (I10, I11.9); diseases of the upper (J30, J30.3, J31, J32, J35.0, J35.1, J35.8, J37, J39.3) and lower (J42, J44.8, J45, J46) airways; disorders of kidney and ureter (N25), including tubulo-interstitial diseases (N11.9, N18.2) and urolithiasis (N20–N23); metabolic diseases (E78), including obesity and other hyperalimentation (E66, E67); diseases of oesophagus, stomach and duodenum (K25, K29, K30), liver (K76.0), disorders of gallbladder, biliary tract and pancreas (K80, K81, K82.8, K83.4, K83.8, K83.9, K86).

Additional likelihood and risks of diseases were calculated using a cascade of interrelated events, which included the stage-by-stage definition of the model parameters to describe cause-effect relations within the Exposure – Biomarker of Exposure – Biomarker of Negative Effect – Negative Health Outcome (Disease) – Additional Health Risk system. Mathematical modeling was accomplished by the multiple logistic regression in multifactorial statement using software packages with MS-Office[6] applications. Validity and relevance of the modeling results was estimated using the Fischer's F-test and the determination coefficient (R^2). Overall, we estimated approximately 300 digital multifactorial models (1000 parameters).

Results and discussion. Implementation of the first three stages in the algorithm made it possible to establish authentic cause-effect relations and their regression coefficients describing the growth rate of additional to isolated likelihood (Δp_n) that certain biomarkers of negative effects would deviate from safe levels in people from various age groups upon combined exposure to copper, nickel, and chromium oxides (Table 1).

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[5] Clinical Guide to Laboratory Tests. In: Professor Norbert W. Tietz ed.; V.V. Menshikov translation from English ed. Moscow, YuNIMED-press Publ., 2003, 960 p. (in Russian).

[6] Modeling was accomplished by experts from the Department of Mathematical Modeling of Systems and Processes of the Federal Scientific Center for Medical and Preventive Health Risk Management Technologies (D.A. Kiryanov, V.M. Chigvintsev). Table 2 provides data on additional to isolated likelihood (Δp_{zn}) and (ΔR_z) risk of the *z*-th diseases in children and adults, which were obtained at the stages IV and V of the algorithm.

Table 1

Additional likelihood of changes in biomarkers of negative effects upon combined exposure to copper, nickel and chromium oxides

Biomarker of negative effect	Vector of hazardous developing negative effect	Regression coefficient upon isolated and combined chemical exposure							Likelihood of negative effects			Additional likelihood upon combined exposure (Δp_n)
		back-ground	copper (x_1)	nickel (x_2)	chro-mium (x_3)	Cu and Ni ($x_1 x_2$)	Cu and Cr ($x_1 x_3$)	Ni and CR ($x_2 x_3$)	No expo-sure (p_f)	Isolated exposure (p_{if})	Isolated and combined exposure (p_{comb})	
		b_0	b_1	b_2	b_3	b_4	b_5	b_6				
Children aged 4–7 years												
Apolipoprotein B100	Rise	-3.28	-1.67	-447.49	281.14	607.55	0.00	0.00	0.006	0.011	0.080	0.069
Lipid hydroper-oxides	Rise	-3.40	2.14	227.32	-482.46	-173.83	423.99	0.00	0.170	0.186	0.200	0.014
Glutamate dehydrogenase	Rise	-0.77	0.00	-119.84	50.46	156.67	0.00	0.00	0.298	0.329	0.427	0.099
Glutathione peroxidase	Rise	-2.81	0.00	0.00	240.25	220.30	0.00	-20643	0.066	0.079	0.299	0.220
Cortisol	Rise	-1.86	-0.99	-516.55	0.00	454.89	-71.14	7592.51	0.037	0.052	0.031	-0.021
Blood lymphocytes	Rise	1.52	-0.92	39.57	-90.06	0.00	70.89	-6019.3	0.662	0.670	0.635	-0.036
Low density lipoprotein	Rise	-5.95	1.43	0.00	-82.73	73.40	83.54	0.00	0.009	0.010	0.016	0.006
Neuron-specific enolase	Rise	-2.18	-0.56	-99.62	277.85	185.29	-218.91	-3224.4	0.070	0.072	0.125	0.053
Total bilirubin	Rise	-2.53	-0.76	-89.45	-73.43	87.99	46.99	2388.90	0.034	0.038	0.033	-0.004
Total cholesterol	Rise	-2.95	0.09	-50.24	0.00	75.68	0.00	0.00	0.051	0.055	0.062	0.007
Direct bilirubin	Rise	-2.73	-0.34	53.09	-59.43	-23.82	48.41	1329.22	0.046	0.047	0.053	0.006
Superoxide dismutase	Rise	2.71	-6.20	313.75	-1411.9	0.00	1940.8	-66274	0.028	0.086	0.253	0.167
Alkaline phosphatase	Rise	-2.34	-2.45	-102.35	0.00	208.97	31.37	-2516.6	0.010	0.012	0.018	0.007
Hemoglobin	Fall	-2.89	-0.22	-150.74	-15.99	159.22	0.00	1608.03	0.037	0.043	0.042	-0.001
Blood iron	Fall	-3.40	0.28	-54.28	-59.14	71.89	44.70	539.24	0.038	0.041	0.043	0.002
Blood monocytes	Fall	-3.20	1.53	-62.92	0.00	0.00	0.00	24,669.5	0.131	0.133	0.222	0.089
Neurotropin-3	Fall	-1.44	1.49	0.00	0.00	0.00	0.00	0.00	0.476	0.477	0.498	0.022
Phagocytosis percentage	Fall	-0.80	-0.70	-122.52	-19.59	55.20	0.00	2486.08	0.173	0.180	0.126	-0.054
Adults aged 18–59 years												
Alanine aminotransferase	Rise	-3.12	0.92	-241.84	0.00	199.98	-129.46	27,221.3	0.074	0.082	0.096	0.014
Aspartate aminotransferase	Rise	-2.84	0.95	-22.59	-81.94	0.00	0.00	14,060.7	0.112	0.113	0.119	0.005
Glutamate dehydrogenase	Rise	0.62	-1.69	0.00	0.00	62.01	168.52	-6251.18	0.288	0.321	0.513	0.192
Glutamine acid	Rise	-1.42	0.00	390.29	0.00	0.00	135.23	-91,934.5	0.264	0.268	0.185	-0.082
Eosinophilic index	Rise	-2.69	0.00	0.00	-194.21	0.00	137.94	8012.01	0.056	0.061	0.062	0.000
Cortisol	Rise	-2.09	0.00	-878.34	0.00	647.26	-195.42	50,102.7	0.049	0.078	0.045	-0.033
Malonic dialdehyde	Rise	0.60	0.00	0.00	-106.71	0.00	41.05	0.00	0.629	0.635	0.559	-0.076
Blood monocytes	Rise	4.95	-3.50	0.00	-394.77	46.66	602.71	-21,142.0	0.821	0.873	0.890	0.017
Neuron-specific enolase	Rise	-0.79	-2.44	0.00	-598.92	0.00	614.29	24,034.9	0.032	0.047	0.093	0.046
Transferrin	Rise	3.24	-6.95	1153.6	-2995.92	-1063.28	3683.96	0.00	0.019	0.070	0.591	0.521
Alkaline phos-phatase	Rise	-2.41	0.00	-788.67	0.00	845.00	-458.65	52,076.8	0.039	0.064	0.065	0.001
Eosinophils in nasal secretion	Rise	-0.02	-0.83	-53.48	-89.26	61.42	75.83	0.00	0.294	0.315	0.297	-0.018
Absolute phagocytosis	Fall	-2.00	0.00	-67.31	-150.93	0.00	215.63	19,283.8	0.102	0.116	0.189	0.073
Hemoglobin	Fall	-3.34	1.98	-63.38	-296.73	0.00	214.18	25,081.2	0.139	0.158	0.189	0.031
Blood iron	Fall	-1.50	0.00	76.13	-798.50	-219.38	692.75	34,853.8	0.121	0.152	0.134	-0.018
High density lipoprotein	Fall	-0.68	0.00	-52.42	107.04	60.64	-58.25	-3417.67	0.342	0.346	0.380	0.034
Phagocytosis percentage	Fall	-0.24	-2.01	-390.66	294.29	533.68	-341.12	0.00	0.096	0.122	0.184	0.062
Phagocytic index	Fall	1.39	-1.52	-150.97	-34.86	167.53	0.00	0.00	0.462	0.500	0.455	-0.045

Table 2

Additional disease risk caused by combined exposure to copper, nickel and chromium oxides

Class of diseases (ICD-10)	Likelihood of disease for unexposed individuals (p_f)	Severity (g_z)	Additional to background likelihood of diseases upon exposure			Additional to background risk of disease			Additional to isolated exposure and background		Type of combined chemical exposure
			Separately to copper (Δp_{zx1})	Separately to nickel (Δp_{zx2})	Separately to chromium (Δp_{zx3})	Separately to copper (ΔR_{zx1})	Separately to nickel (ΔR_{zx2})	Separately to chromium (ΔR_{zx3})	Likelihood of disease upon combined exposure (Δp_{zn})	Risk of disease upon combined exposure (ΔR_z)	
Children aged 4–7 years											
Certain disorders involving the immune mechanism (D83.9, D84.9)	0.0086	0.116	0.0002	0.0003	0.0001	$2.9 \cdot 10^{-5}$	0.00	$1.1 \cdot 10^{-5}$	0.0002	$2.2 \cdot 10^{-5}$	synergy
Activity and attention disorders (F48.0, F90)	0.0012	0.053	0.0000	0.0005	-0.0002	0.00	0.00	$-1.2 \cdot 10^{-5}$	0.0000	0.00	additivity
Diseases of the nervous system (G90.8, G90.9)	0.0345	0.142	0.0014	0.0232	-0.0096	$2.0 \cdot 10^{-4}$	$3.3 \cdot 10^{-3}$	$-1.4 \cdot 10^{-3}$	0.0011	$1.5 \cdot 10^{-4}$	synergy
Heart diseases (I34.1, I49.9)	0.0021	0.131	0.0000	0.0000	0.0000	0.00	0.000	$-8.4 \cdot 10^{-7}$	0.0000	0.00	additivity
Diseases of the upper airways (J30, J30.3, J31, J32, J35.0, J35.1, J35.8, J37, J39.3)	0.0693	0.016	0.0024	0.0395	-0.0158	$3 \cdot 10^{-5}$	$6.3 \cdot 10^{-4}$	$-2.5 \cdot 10^{-4}$	0.0014	$2.3 \cdot 10^{-5}$	synergy
Diseases of the lower airways (J45, J46)	0.0026	0.105	0.0000	-0.0001	0.0000	0.00	0.00	$-4.2 \cdot 10^{-6}$	-0.0002	$-2.1 \cdot 10^{-5}$	antagonism
Obesity and other hyperalimentation (E66, E67)	0.0233	0.086	0.0005	0.0060	-0.0035	$4.3 \cdot 10^{-5}$	$5.1 \cdot 10^{-4}$	$-3.0 \cdot 10^{-4}$	0.0008	$7.2 \cdot 10^{-5}$	synergy
Diseases of the digestive system (K29, K30)	0.0088	0.173	0.0001	0.0004	-0.0003	$9.9 \cdot 10^{-6}$	$6.5 \cdot 10^{-5}$	$-5.9 \cdot 10^{-5}$	-0.0002	$-2.8 \cdot 10^{-5}$	antagonism
Liver diseases (K76.0)	0.0068	0.221	0.0000	0.0001	0.0000	0.00	0.00	0.00	0.0000	0.00	additivity
Diseases of biliary tract (K83.8, K83.9)	0.0145	0.062	0.0000	-0.0002	0.0000	*0.00*	*0.00*	*0.00*	0.0004	*$2.5 \cdot 10^{-5}$*	emergence
Adults aged 18–59 years											
Iron deficiency anaemia (D50.9)	0.0194	0.017	0.0005	0.0052	-0.0047	$8.5 \cdot 10^{-6}$	$8.8 \cdot 10^{-5}$	$-7.9 \cdot 10^{-5}$	-0.0003	$-5.7 \cdot 10^{-6}$	antagonism
Anaemia, specified and unspecified (D64.8, D64.9)	0.0107	0.022	0.0001	0.0085	-0.0007	$1.4 \cdot 10^{-6}$	$1.9 \cdot 10^{-4}$	$-1.6 \cdot 10^{-5}$	-0.0013	$-2.9 \cdot 10^{-5}$	antagonism
Certain disorders involving the immune mechanism (D83.9, D84.9)	0.0425	0.116	0.0001	0.0004	0.0007	$1.4 \cdot 10^{-5}$	$5.2 \cdot 10^{-5}$	$7.9 \cdot 10^{-5}$	0.0006	$7.3 \cdot 10^{-5}$	synergy
Dystonia (G24.9)	0.0027	0.299	0.0003	-0.0008	0.0031	$7.5 \cdot 10^{-5}$	$-3.0 \cdot 10^{-4}$	$9.2 \cdot 10^{-4}$	-0.0002	$-6.4 \cdot 10^{-5}$	antagonism
Diseases of the nervous system (G90.8, G90.9)	0.3696	0.142	0.0000	-0.0005	-0.0034	0.00	$-1.0 \cdot 10^{-4}$	$-4.9 \cdot 10^{-4}$	0.0049	$7.0 \cdot 10^{-4}$	synergy
Hypertension (I10, I11.9)	0.1136	0.062	0.0027	0.0098	0.0371	$1.7 \cdot 10^{-5}$	$6.1 \cdot 10^{-4}$	$2.30 \cdot 10^{-3}$	0.0098	$6.1 \cdot 10^{-4}$	synergy
Ischaemic heart disease (I20)	0.0153	0.075	0.0019	-0.0051	0.0199	$1.4 \cdot 10^{-4}$	$-4.0 \cdot 10^{-4}$	$1.5 \cdot 10^{-3}$	-0.0007	$-5.0 \cdot 10^{-5}$	antagonism
Heart diseases (I34.1, I45.1, I49.9)	0.0355	0.131	0.0013	-0.0041	0.0100	$1.7 \cdot 10^{-4}$	$-5.0 \cdot 10^{-4}$	$1.3 \cdot 10^{-3}$	-0.0003	$-4.1 \cdot 10^{-5}$	antagonism
Diseases of the upper airways (J30, J30.3, J31, J32)	0.2955	0.016	0.0012	0.0112	0.0092	$1.8 \cdot 10^{-5}$	$1.8 \cdot 10^{-4}$	$1.5 \cdot 10^{-4}$	0.0018	$2.9 \cdot 10^{-5}$	synergy
Obesity and other hyperalimentation (E66, E67)	0.0702	0.086	0.0008	-0.0009	0.0143	$6.7 \cdot 10^{-5}$	$-1.0 \cdot 10^{-4}$	$1.2 \cdot 10^{-3}$	0.0031	$2.7 \cdot 10^{-4}$	synergy
Metabolic diseases (E78)	0.0404	0.091	0.0007	0.0074	0.0057	$6.7 \cdot 10^{-5}$	$6.7 \cdot 10^{-5}$	$5.2 \cdot 10^{-4}$	0.0030	$2.7 \cdot 10^{-4}$	synergy
Diseases of the digestive system (K25, K29, K30)	0.1822	0.173	0.0005	0.0089	0.0099	$7.9 \cdot 10^{-5}$	$1.5 \cdot 10^{-3}$	$1.7 \cdot 10^{-3}$	0.0016	$2.7 \cdot 10^{-4}$	synergy
Liver diseases (K76.0)	0.0385	0.221	0.0001	-0.0009	-0.0003	$2.7 \cdot 10^{-5}$	$-2.0 \cdot 10^{-4}$	$-7.6 \cdot 10^{-5}$	0.0001	$2.3 \cdot 10^{-5}$	synergy
Diseases of biliary tract (K80, K81, K82.8, K83.4, K83.8, K83.9, K86)	0.3439	0.062	0.0370	-0.2041	0.2688	$2.3 \cdot 10^{-3}$	$-12.7 \cdot 10^{-3}$	$1.7 \cdot 10^{-2}$	-0.0511	$-3.2 \cdot 10^{-3}$	antagonism

Table 3

Additional disease risk per classes of diseases caused by combined exposure to copper, nickel and chromium oxides

Class of disease (ICD-10)	Additional risk (ΔR_k)	
	children	adults
Circulatory system (I20, I34.1, I45.1, I49.9)	$1.7\cdot10^{-6}$	**$5.2\cdot10^{-4}$**
Nervous system (G90.8, G90.9, G24.9)	**$1.5\cdot10^{-4}$**	**$6.4\cdot10^{-4}$**
Nutritional and metabolic disorders (E66, E67, E78)	$7.3\cdot10^{-5}$	**$5.4\cdot10^{-4}$**
Respiratory system (J30, J30.3, J31, J32, J35.0, J35.1, J35.8, J37, J39.3, J42, J44.8, J45, J46)	$2.6\cdot10^{-6}$	$1.8\cdot10^{-5}$
Blood and blood-forming organs and certain disorders involving the immune mechanism (D50.9, D64.8, D64.9, D83.9, D84.9)	$2.2\cdot10^{-5}$	$3.7\cdot10^{-5}$
Digestive system (K25, K29, K30, K76.0, K80, K81, K82.8, K83.4, K83.8, K83.9)	$4.4\cdot10^{-7}$	0.0
Activity and attention disorders (F48.0, F90)	$1.3\cdot10^{-6}$	0.0

Having analyzed frequency of the identified combined exposure types, we established that synergy prevailed in both age groups accounting for up to 57.1 %. Frequency of synergy grew with age by 1.4 times. Additivity and emergence were established only in children in 30.0 % and 10.0 % of the cases accordingly.

Synergic combined exposure to copper, nickel and chromium oxides was shown to create additional to isolated disease risk per classes of diseases; it grew fourfold and more with age (Table 3).

Additional risk of diseases of the nervous system was established for children aged 4–7 years; it was estimated as ‘alerting’ and was 1.5 times higher than its acceptable level. Additional risk of diseases of the circulatory system, nervous system, and metabolic disorders was up to 6.4 times higher than its acceptable level for adults aged 18–59 years.

The integral additional health risk for children amounted to $1.3\cdot10^{-4}$ and was estimated as ‘alerting’; for adults, between $1.8\cdot10^{-3}$ and $3.0\cdot10^{-3}$, estimated as ‘high’.

Expected probable loss in life expectancy at birth would equal approximately one month (30.2 days) under the best-case scenario and about one year (376.0 days) under the worst-case one upon combined exposure to the analyzed chemicals due to diseases of the nervous system, heart diseases, and metabolic diseases (obesity).

Therefore, the proposed and tested algorithm makes it possible to assess specific features of combined chemical exposure per additional to isolated health risk on the basis of cause-effect relations between markers of exposure and negative effects; it also allows substantiating age-differentiated priority classes of diseases (diseases of the nervous, genitourinary, circulatory system etc.), which cause losses in life expectancy at birth. At the same time, several problems requiring a scientific and methodical solution have been outlined in studies when an attempt has been made to assess risks of combined chemical exposures. They include the necessity to check adequacy of additional health risk assessment upon combined exposure considering types of effects, which deviate from additivity (synergy, antagonism, etc.) and to develop approaches to substantiating priority chemicals subject to immediate regulation when they act in a mixture. Results obtained by finding solutions to the outlined problems may provide a convincing basis for differentiating measures aimed at easing off regulatory burdens and concentrating efforts on the greatest health risks and harm.

Conclusion. Practical use of the proposed algorithm for assessing additional expected disease risk upon combined exposure to chemicals makes it possible to perform objective analysis as regards the existing sanitary-hygienic situation, to achieve more effective and adequate assessment of the current and planned air protection activities for their timely adjustment, as well as to provide targeted medical and preventive measures until health risks decline down to their acceptable levels.

As expected, implementation of state regulations as regards levels of a hazardous chemical mixture containing copper, nickel and chromium oxide in ambient air in settlements can secure a growth in LEB, which on average will be equal to 30.2 days.

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Research article

SPECIFIC CONCENTRATION LIMIT AS A TOOL FOR CLASSIFYING MIXTURES BY HUMAN HEALTH HAZARDS. PART 1. CHARACTERISTICS, SCOPE, REGULATORY ASPECTS OF IMPLEMENTATION IN THE EAEU

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The Globally Harmonized System of Hazard Classification and Labeling of Chemicals (GHS) makes it possible to classify mixtures by hazardous properties using the calculation method and cut-off values/concentration limits (CV/CL). However, the CV/CL of hazardous components adopted in the GHS do not take into account their individual toxicological profile, which can lead to either underestimation or overestimation of the hazard posed by the entire mixture. To overcome these shortcomings of the GHS and to classify mixtures more accurately, specific concentration limits (SCL) are used along with CV/CL in the European Union (EU). The article presents: the characteristics and scope of SCL in accordance with the types of human health hazards included in the GHS, the possibility of setting numerical values of SCL higher than CV/CL, priority in their joint use and the mathematical criterion underlying the application of SCL. Example classification of model mixtures corrosive/irritative to skin based on SCL of their components is considered in a situation when the additive approach is applicable. The obtained results are compared with the classification based on the CV/CL without considering the SCL. Advantages and difficulties of SCL implementation in order to protect citizens from adverse effects of chemical factors while maintaining required production volumes in the chemical industry are discussed from the perspective of a mixture manufacturer and a regulatory authority. The author evaluated the possibility of SCL implementation for toxicological assessment of mixtures, considering the approved technical regulations of the EAEU «On the safety of chemical products» (TR EAEU 041/2017) and the standards that have come into force.

Keywords: *specific concentration limit, cut-off value, mixture, chemicals, classification, Globally Harmonized System of Classification and Labelling of Chemicals (GHS), technical regulation.*

The Globally Harmonized System of Hazard Classification and Labeling of Chemicals (GHS)[1] is the regulatory basis employed in many countries to regulate turnover of chemical products (CP) [1, 2]. An advantage of the GHS use is a possibility to classify mixtures by hazardous properties using relevant calculations[2]. However, the method adopted in the GHS does not take into account individual toxicological profiles of all mixture components, which can lead to either underestimation or overestimation of the hazard posed by the entire mixture [3–5].

An epidemic of allergic contact dermatitis can be a good example when underestimation has some serious consequences. It happened in the EU in 2010–2018 due to common use of a preservative methylisothiazolinone (CAS 220-239-6) in household chemicals, varnishes, paints and other chemical products [6–8] as well as in perfumes and cosmetics after consumers had refused from using paraben-containing products [9].

Since the mass fraction of methylisothiazolinone in CP was below 0.1 %, that is, below CV/CL established for the hazard class 1 skin

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[1] Globally Harmonized System of Classification and Labeling of Chemicals (GHS), 10th revised ed. New-York, Geneva, United Nations, 2023. Available at: https://unece.org/sites/default/files/2023-07/GHS%20Rev10e.pdf (February 09, 2025).

[2] State Standard GOST 32423-2013. Mixtures classification of hazard for health. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200108173 (February 09, 2025) (in Russian).

sensitizers, these chemical products were not classified using the calculation method as posing such health threats; in reality, they often caused allergic reactions [10].

Since izothiazolinones have sensitizing effects in levels substantially lower than CV/CL [11], the break of the foregoing epidemics called for stricter legal rules of their use. In particular, SCL equal to 0.0015 %[3] was fixed for methylisothiazolinone, that is, 66 times lower than CV/CL. This chemical was prohibited for use in leave-on perfumes and cosmetics[4], and its permissible mass fraction in rinse-off products was lowered from 0.01 % to SCL[5]. The taken measures reduced manifestation frequency of allergic contact dermatitis to methylisothiazolinone [12].

An example when hazard was overestimated is classification of acid- and base-containing mixtures using CV/CL equal to 1 % for the hazard class 1 per such indicators as skin irritation / corrosion and eye damage / irritation in a situation when the additive approach is not applied. Actually, many strong acids and bases produce corrosive effects on skin and eyes in considerably higher concentrations in spite of extreme pH values [3, 13, 14].

The aim of this study was to describe a method for classifying chemical mixtures per their health hazardous properties, which is adopted in the EU and based on using SCL; to estimate its advantages and difficulties in using it as well as a possibility to implement it in the EAEU. Methods for SCL identification will be described in a separate article.

SCL description and field of application. According to the definition[6], specific concentration limit (SCL) is a limit assigned to a substance indicating a threshold at or above which the presence of that substance in a mixture leads to the classification of this mixture as hazardous.

It should be noted that SCL are commonly used only in the EU whereas such practices are much less frequent in, for example, the USA or Canada although valid regulatory documents in these countries allow using concentration limits different from CV/CL to classify CP[7].

The EU legislation[6] stipulates the following conditions for SCL use:

– SCL is established by CP manufacturers, importers or downstream consumers (users);

– SCL is eligible for both physical threats and human health hazards;

– since several hazard classes are applied for many hazard types, SCL can be both one-sided ($C \geq 5.5$ %) and two-sided ($0.5\ \% > C \geq 2$ %) similar to CV/CL established in the GHS;

– SCL, just like CV/CL, is established in mass fractions for liquid and solid mixtures and in volume fractions for gaseous ones;

– SCL has a priority over CV/CL when a mixture is classified;

– SCL can be both higher and lower than CV/CL [15].

It is specifically noted that SCL can be higher than CV/CL in exceptional cases only

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[3] Comission Regulation (EU) 2018/1480 of 4 October 2018 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures and correcting Commission Regulation (EU) 2017/776. *OJEU*, 2018, Ser L, vol. 61, no. L251, pp. 1–12. Available at: http://data.europa.eu/eli/reg/2018/1480/oj (February 09, 2025).

[4] Commission Regulation (EU) 2016/1198 of 22 July 2016 amending Annex V to Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products. *OJEU*, 2016, Ser L, vol. 59, no. L198, pp. 10–12. Available at: http://data.europa.eu/eli/reg/2016/1198/oj (February 09, 2025).

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[6] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. *Publications Office of the European Union*. Available at: http://publications.europa.eu/resource/cellar/c6b6a31d-8359-11ee-99ba-01aa75ed71a1.0004.02/DOC_2 (February 09, 2025).

[7] Sullivan K. Can the European Union's specific concentration limits for skin sensitization be used in the United States and Canada? *SCHC Spring Meeting*, 2019. Available at: https://www.knoell.com/en/news/eus-specific-concentration-limits-for-skin-sensitization-use-in-the-us-and-canada (February 09, 2025).

when there is reliable and convincing evidence that a hazard posed by a component in a mixture does not manifest itself in concentrations below SCL.

Since SCL identification requires additional efforts to conduct a toxicological assessment, such limits have been established for few types of chemicals[6]. The author believes that cases when solid grounds are provided for establishing SCL above CV/CL will cease to be a rare exception as new data will be accumulated on hazardous properties of chemicals in future.

SCLs are mentioned in the EU harmonized classification of chemicals[6]; possibility of their use depends on a hazard type and class[8].

SCLs are never used to classify mixtures per acute toxicity or aspiration hazards. SCLs can be fixed both above and below CV/CL for all hazard classes as regards skin irritation / corrosion, serious eye damage / irritation, skin and respiratory sensitization, mutagenic effects on embryo cells, carcinogenic effects and reproductive toxicity. Possibility to use SCL for specific toxicity as regards target organs (both upon single and repeated exposure) depends on a hazard class. SCL can be only below CV/CL for the hazard class 1; SCL is not applicable for the hazard class 2: SCLs can be fixed both above and below CV/CL for the hazard class 3 (toxicity upon repeated exposure).

In case components in a mixture are of the same type and have the same hazard class, and SCLs are established for *n* out of them whereas only CV/CKL are established for *m* out of them, such a mixture is classified by determining the sum (1) if the additive approach is applicable[8]:

$$\sum_{i=1}^{m} \frac{C_i}{CV/CL_i} + \sum_{j=1}^{n} \frac{C_j}{SCL_j}, \qquad (1)$$

where C_i (C_j) is the mass (volume) fraction of the *i* (*j*) component in the mixture, %.

In case the sum (1) is equal to or above 1, the whole mixture is assigned the hazard class, which corresponds to the hazard class of its components. Otherwise, a similar calculation is performed for a lower hazard class.

Examples of using SCL for mixture classification. Let us consider some examples when model mixtures 1-3 are classified per the hazard type 'skin irritation / corrosion' using SCL within the additive approach. Their relevance results from significance of this health hazard [16] and a considerable proportion of additive effects between toxicants that pose it [17].

Compositions of the mixtures and SCL for their components are given in Table 1–3. To reduce the number of examples, we assume that the analyzed mixture components, chemicals A–F, have the hazard class 1. CV/CL for such components equal to $C \geq 5$ % for the hazard class 1 and $1\ \% \leq C < 5$ % for the hazard class 2 in conformity with the GHS.

Table 1

Initial data for classifying the mixture 1

Mixture component	Mass fraction, %	SCL, %	
		For class 1	For class 2
A	3	$C \geq 7$	$1 \leq C < 7$
B	5	$C \geq 10$	$3 \leq C < 10$
Water	92	-	-

Table 2

Initial data for classifying the mixture 2

Mixture component	Mass fraction, %	SCL, %	
		For class 1	For class 2
C	2	$C \geq 1$	$0.5 \leq C < 1$
D	1.5	$C \geq 2$	$1 \leq C < 2$
Water	96.5	-	-

Table 3

Initial data for classifying the mixture 3

Mixture component	Mass fraction, %	SCL, %	
		For class 1	For class 2
E	4	$C \geq 8$	$2 \leq C < 8$
F	3	Not available	Not available
Water	93	-	-

[8] Guidance on the Application of the CLP Criteria. Part 1: General Principles for Classification and Labelling. Guidance to Regulation (EC) No 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. *European Chemicals Agency*, 2024, Version 5.0, 55 p. Available at: https://echa.europa.eu/documents/10162/2324906/clp_part1_en.pdf/bc58ea9e-2e72-732e-2d34-5d34180ec33f (February 09, 2025).

The following sums are to be calculated for classifying the mixture 1 using SCL:

– for the hazard class 1: 3/7 + 5/10 = 0.43 + 0.50 = 0.93 < 1;

– for the hazard class 2: 3/1 + 5/3 = 3.00 + 1.67 = 4.67 ≥ 1.

Therefore, taking SCL into account allows giving the hazard class 2 to the mixture 1. In total, the mass fractions of the components with the hazard class 1 are 3 % + 5 % = 8 %, which is above CV/CL established by the GHS for this hazard class where they equal 5 %. Consequently, if we are guided only by CV/CVL, we should assign the hazard class 1 to the mixture 1.

For the mixture 2, calculating the sum (1) using SCL for the hazard class 1 yields the following result: 2/1 + 1.5/2 = 2.00 + 0.75 = 2.75 ≥ 1, which means the mixture should be assigned the hazard class 1.

In total, the mass fractions of the components with the hazard class 1 are 2 % + 1.5 % = 3.5 %, which is below CV/CL for the hazard class 1, equaling 5 %, but above CV/CL for the hazard class 2, equaling 1 %. Consequently, if we are guided only by CV/CVL, we should assign the hazard class 2 to the mixture 2.

The foregoing examples show the situations when SCL is not taken into account and this leads to both overestimating hazard posed by a mixture (the mixture 1) and underestimating them (the mixture 2).

The example of the mixture 3 describes a situation how to use SCL in case it has not been established for each component in it.

Since there is no SCL established for the component F in the mixture, the established CV/CL are used in calculating the sum (1). The results are 4/8 + 3/5 = 0.50 + 0.60 = 1.10 ≥ 1 for the hazard class 1. Therefore, this hazard class can be assigned to the mixture 3.

Using SCL: advantages and difficulties. The author believes that SCL use for classifying mixtures is interesting both from the point of view of manufacturers who produce chemical products and regulatory authorities as well.

In case SCL is higher than CV/CL, a concentration of a component in a mixture can be increased quite safely and, accordingly, volumes of production involving use of this component and the mixture as whole. This will have a positive effect on financial state of chemical manufacturers.

Establishing SCL lower than CV/CL makes it possible to protect a large number of consumers from health hazards posed by a mixture, reduce a number of poisonings and potential legal actions associated with health harm to downstream consumers as well as reputation losses borne by a manufacturer and a regulatory authority who permitted this mixture to be marketed.

Certain difficulties involved in implementing SCL include the necessity to determine their numeric values and to develop relevant methods for doing it. SCL establishing increases costs borne by CP manufacturers; however, first of all, they can be compensated for by expanding a sphere where a chemical product is allowed for application and by increasing production volumes. Secondly, these costs can be distributed between, for example, manufacturers who supply components and who produce end mixtures within joint notification of a chemical or registration of a mixture.

Using SCL together with CV/CL makes the mixture classification procedure more complicated, which requires additional training for personnel who deal with it. However, classification can be automated by using relevant software; some simplest calculators can be found online[9].

Evident significance of using SCL in regulation has been described above. In addition, SCL allow more precise classification of mixtures by calculations, which makes for a decline in CP manufacturers' costs since additional testing using *in vivo* methods is no longer required. At the same time, a reduction in the number of animals used for tests is widely appreciated due to not only some humanistic concerns [18] but also difficulties in

[9] Khrolenko M. Online mixture classification calculator. Available at: https://mixclass.net (February 09, 2025).

planning up-to-date toxicological experiments. The latter require strict control and consideration of many factors, which can involve accidental or systemic errors [19] as probable reasons for differences in toxicometric indicators published by different research teams.

However, it is objectively difficult to quantify advantages of using SCL as regards more precise classification since this requires free access to a database containing many mixtures, which have been estimated by using two foregoing methods. Calculated classification in such a database should be represented by two values, one of them obtained by using SCL and the other without it. Bearing in mind that SCLs are not established for every chemical, as well as the fact that exact compositions of mixtures are, as a rule, unknown due to protection of commercially significant information, wide validation of the SCL concept has not been accomplished so far.

A study [20] rather indirectly assesses SCL advantages as it comparatively analyzes the classification results obtained for plant protection products by using calculations and animal tests. Satisfactory coincidence of identified hazard classes was established for skin irritation / corrosion (the proportion of false negative results, that is hazard underestimation, is 22 %) and eyes irrigation / damage (the proportion of false positive results is 66 %); unsatisfactory results were obtained for skin sensitization (the proportion of false negative results is 34 %). The latter might be due to high CV/CL established in the EU for the hazard classes 1 and 1B per skin sensitization, namely 1 % (mass fraction). It is noteworthy that a similar proportion of false negative results was obtained by using *in vitro* methods. Unfortunately, the study does not provide any information about frequency of using SCL when performing classification by calculations. This does not allow using this and similar studies [3–5] to the full to estimate advantages of using the SCL concept when classifying a wide range of chemical products.

Regulatory and legal aspects of SCL implementation in the EAEU. At present, the valid standards used in the EAEU to classify CP[10] do not involve using SCL. Therefore, SCL implementation requires alterations made in these standards or development of new ones.

It is also noteworthy that the system comprising hazard classes of chemical products and CV/CL adopted within it in the EU[11], where SCL is commonly used for mixture classification, is very different from a system adopted in the EAEU [21]. These differences make it impossible to automatically transfer elements of CP regulation based on using SCL in the EU in regulation of chemical products adopted in the EAEU.

Although a possibility to use SCL is not mentioned in any valid standards and Technical Regulations of the EAEU 041/2017[10], the author believes that the existing regulatory-legal base allows implementing them into CP regulation.

First of all, EAEU TR 041/2017 is based on the GHS, which stipulates that hazardous properties of a component in a mixture can manifest themselves in a concentration both higher and lower than its CV/CL[12].

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[10] State Standard GOST 32423-2013. Mixtures classification of hazard for health. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200108173 (February 09, 2025) (in Russian); EAEU TR 041/2017. O bezopasnosti khimicheskoi produktsii: Tekhnicheskii reglament Evraziiskogo ekonomicheskogo soyuza, Prinyat Resheniem Soveta Evraziiskoi ekonomicheskoi komissii ot 3 marta 2017 g № 19 [On Safety of Chemical Products: Technical Regulations of the Eurasian Economic Union, approved by the Council of the Eurasian Economic Commission on March 3, 2017 No. 19]. *Information and legal system of regulatory and legal acts of the Republic of Kazakhstan*. Available at: https://adilet.zan.kz/rus/docs/H17EV000019 (February 10, 2025) (in Russian).

[11] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006. *Publications Office of the European Union*. Available at: http://publications.europa.eu/resource/cellar/c6b6a31d-8359-11ee-99ba-01aa75ed71a1.0004.02/DOC_2 (February 09, 2025).

[12] Globally Harmonized System of Classification and Labeling of Chemicals (GHS), 10th revised ed. New-York, Geneva, United Nations, 2023. Available at: https://unece.org/sites/default/files/2023-07/GHS%20Rev10e.pdf (February 09, 2025).

Secondly, certain SCLs are planned to be introduced in the EAEU by approving the List of Chemicals with Carcinogenic and Mutagenic Effects, Reproductive Toxicity, and Chronic Toxicity for Water Environment as Appendix to the Procedure for Creating and Keeping the Register of Chemicals and Mixtures of the Eurasian Economic Union[13]. Thus, for example, this List establishes SCL for benzo(a)pyrene (carcinogenic, hazard class 1A) as equal to 0.005 %, which is 20 times lower than its CV/CL.

Third, after TR EAEU 041/2017 comes into force, CP toxicological assessment aimed at creating safety profiles and subsequent state registration will make it possible to use information about chemicals, which has already been accumulated by the humankind and is available in various databases. A draft of the Procedure for Creating and Keeping the Register of Chemicals and Mixtures of the Eurasian Economic Union[13] already envisages the possibility to use EU databases containing information about SCL. Bearing this in mind, we can state that numeric SCL values, which can be found in them, are actually legalized in the EAEU.

In case SCLs are implemented, the Appendix No. 4 to the EAEU TR 041/2017 will need revising. Since SCL covers such hazards as mutagenicity, carcinogenicity and reproductive toxicity, stricter control of mixtures that contain carcinogens, mutagens and reproductive toxicants will rely on using not their CV/CL enlisted in this Appendix but their SCL instead.

Conclusions:

1. CV/CL use for mixture classification can both overestimate and underestimate their hazard.

2. SCL allows classifying mixtures more precisely using the calculation method and thereby optimizing their use as regards both protecting downstream consumers from their adverse effects and increasing volumes of CP production.

3. SCL implementation for mixture classification will require making certain alterations in the EAEU legislation, revising the existing standards and (or) developing new ones, which can provide relevant algorithms for using the calculation method within toxicological assessment of mixtures considering the sum (1).

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Research article

COMPREHENSIVE ASSESSMENT OF SCHOOLCHILDREN'S DIETS

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For a comprehensive assessment of schoolchildren's diets, a methodology was developed using the diet quality index (DQI) based on data on frequency of food consumption.

The aim of this work is to develop a method for comprehensive assessment of schoolchildren's diets, to test it using data on frequency of food consumption and to investigate the relationship between DQI and various characteristics of the surveyed.

The method was developed using a database of diet monitoring data for students of secondary schools obtained by Rospotrebnadzor in 2023 within implementation of the Population Health Protection Federal Project of the Demography National Project in 2023 in 85 subjects of the Russian Federation. Data on frequency of food consumption were used to develop and test the method. Statistical data analysis was performed using the IBM SPSS Statistics 20.0, USA. To assess the statistical significance of differences between the groups, parametric methods of variance analysis were used: Student's t-test and ANOVA.

Based on data on frequency of food consumption, a method has been developed for comprehensive assessment of schoolchildren's diets using DQI. Nineteen groups of food products were selected: 9 groups of foods that are most important for formation of a healthy diet and 10 groups of foods with an excess content of critically important nutrients, consumption of which should be limited.

DQI below the average value (below 42.8 points) was detected in 52 % of schoolchildren. Almost half of the children (48.8 %) had DQI within the range of 35–50 points. In 27.5 % of children, DQI of less than 35 points was detected. The study also included analysis of relationships between DQI established for schoolchildren and sex, age and other socio-demographic characteristics.

The developed DQI makes it possible to quickly conduct comprehensive assessment of diet quality and can be used to analyze effectiveness of implemented measures aimed at NCDs prevention.

Keywords: *Diet Quality Index (DQI), actual diet, frequency of food consumption, food products, critically important nutrients, healthy diet, sex, age.*

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The age between 7 and 18 years involves the most intensive somatic growth accompanied with elevated mental and physical loads. Children especially need optimal nutrition in this period. A schoolchild's diet should include food products, which are major sources of necessary macro- and micronutrients. Furthermore, food products with excessive contents of critically significant nutrients (fats, including saturated fatty acids, salts, and added sugars) should be consumed in limited amounts. Non-optimal nutrition can lead to adverse health outcomes in schoolchildren and cause some mental and physical developmental delays thereby increasing risks of growth retardation, underweight or overweight, as well as obesity [1, 2].

It is quite relevant to develop a unified index for analyzing actual schoolchildren's diets. This index can be used to assess diet quality for children both as a whole and individually as well as to establish total effects produced on diet quality by frequency of consumption of food products necessary for a healthy diet and sources of critically important nutrients. This simplifies diet assessment and simultaneously makes it more comprehensive.

Analysis of large-scale epidemiological studies aimed at assessing diet quality and health is a complex multidisciplinary task. Having a tool, which allows prompt and effective assessment of diet quality and helps establish its interrelations with various characteristics of examined participants, for example, sociodemographic ones, makes it possible to solve the outlined task quite effectively.

Various diet quality indexes have been actively developed in many countries including the USA, China, South Korea, Thailand, Vietnam, and Malaysia [3–6]. Thus, the Healthy Eating Index (HEI) was first introduced in the USA in 1995; it is based on results obtained by analyzing food consumption with the 24-hour dietary recall (24HR) method. The index has been developed and updated several times since its introduction [7]. A similar Healthy Eating Index (HEI) was developed and implemented in Russia [8].

In world practice, another employed tool is the Diet Quality Index (DQI), which is calculated using data obtained with the Mediterranean Diet Score (MDS). This index is usually applied in countries where the Mediterranean Diet is quite common [9]. A similar approach was developed by the Federal Research Centre of Nutrition, Biotechnology and Food Safety and tested using micro-data obtained by sample observations of population's diets accomplished by Rosstat on national representative samples in 2013 and 2018 [10]. Data collection using a food frequency questionnaire is less time- and resource-consuming in comparison with the 24-hour dietary recall (24HR) method. Its basic advantage is relative simplicity of conducting a survey, which allows prompt assessment of diet quality in general or for various population groups.

The aim of this study is to develop a method for comprehensive assessment of schoolchildren's diets, to test it using data on food frequency and to investigate the relationship between DQI and various characteristics of the surveyed. Establishing relationships between DQI and various sociodemographic determinants (sex age, family incomes, etc.) as well as some other characteristics (schoolchildren's nutritional status, dietary patterns, adherence to healthy eating, etc.) is of particular interest.

Materials and methods. The method for comprehensive assessment of schoolchildren's diets has been developed based on data obtained by monitoring diets of schoolchildren by Rospotrebnadzor in 2023 within implementation of the Population Health Protection Federal Project of the Demography National Project in 85 Russian regions. Scientific and methodical support as well as the survey coordination was provided by the Federal Research Centre of Nutrition, Biotechnology and Food Safety, Rospotrebnadzor's Novosibirsk Research Institute of Hygiene and Rospotrebnadzor's Federal Center for Hygiene and Epidemiology. The study was accomplished in conformity with the Methodical Guidelines MR 2.3.0316-23 Nutrition Hygiene. Preparing and Conducting Monitoring of Schoolchildren's

Table 1

The sample profile

All children	Number, people			p-value
	137,184	Boys	65,517	< 0.001
		Girls	71,667	< 0.001
including:				
6–10 years old (primary school)	53,440	Boys	26,350	< 0.001
		Girls	27,090	< 0.001
11–15 years old (middle school)	47,753	Boys	23,297	< 0.001
		Girls	24,456	< 0.001
older > 15 years (high school)	35,990	Boys	15,869	< 0.001
		Girls	20,121	< 0.001

Diets[1]. The study protocol was approved by the local ethics committee of the Federal Research Centre of Nutrition, Biotechnology and Food Safety (the meeting protocol No. 5 dated April 30, 2019) as well as the local ethics committee of the Rospotrebnadzor's Novosibirsk Research Institute of Hygiene (the meeting protocol No. dated January 10, 2023)[2].

A sample representative for each Russian region and a plan for locating a sample were created based on the registers of secondary schools in Russian regions by Rospotrebnadzor's Federal Center for Hygiene and Epidemiology (OKVED (all-Russian Classification of Economic Activities) are 85.13 and 85.14). The minimal number of schools in a regional sample was 50. The study was conducted by interviewing schoolchildren and their parents. The total number of participating children was 137,184; the sample profile is provided in Table 1. Schoolchildren were distributed in age-specific groups within the categories *primary school, middle school and high school*.

The questionnaire included questions about how frequently a specific food product was consumed; they were formulated per the following categories: *'every day', '3–4 times a week', 'once a week', '2–3 times a month', 'once a month', 'never'*. The questions were then consolidated into four categories: *'everyday', '3–4 times a week', 'several times a month', 'once a month or practically never'*. Several variables were included in the analyzed data array to establish relationships between DQI and various sociodemographic and some other characteristics: sex, age, family income, parents' education, age-specific body mass index, having a meal before school, and adherence to healthy eating principles.

The research data were analyzed with IBM SPSS Statistics 20.0, USA. The internal consistency of the questions about frequency of consuming various food products was assessed using Cronbach's alpha. Its value was determined as equal to 0.75, which indicates sufficient consistency and reliability of the study results. DQI distribution was accomplished with QQ graph (for $n > 5000$). Since the data followed the normal distribution, the central tendency was estimated with DQI simple mean, standard error of mean, standard deviation (SD) and 95 % confidence interval (when calculating DQI distribution among all the surveyed children in %). Significance of intergroup differences was assessed with parametric dispersion analysis methods: the Student's t-test for a hypothesis about different mean values for two samples (sex, adherence to healthy eating principles); ANOVA for comparing mean values of three or more groups and establishing presence of significant intergroup differences (age, having a breakfast at home, parents' education, income level, a child's nutritional status). The significance threshold alpha (α) was fixed at 0.001.

Nineteen out of twenty four groups from the questionnaire have been selected for DQI

[1] MR 2.3.0316-23. Gigiena pitaniya. Podgotovka i provedenie monitoringa pitaniya obuchayushchikhsya obshcheobrazovatel'nykh organizatsii: metodicheskie rekomendatsii, utv. Federal'noi sluzhboi po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka 28 fevralya 2023 g. [Nutrition Hygiene. Preparing and Conducting Monitoring of Schoolchildren's Diets: Methodical Guidelines, approved by the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing on February 28, 2023]. *GARANT.RU: information and legal portal*. Available at: https://www.garant.ru/products/ipo/prime/doc/406449045/ (September 04, 2024) (in Russian).

[2] Monitoring data as regards schoolchildren's diets were obtained within implementation of the Population Health Protection Federal Project of the Demography National Project.

calculation[3]. Two clusters were created: 9 product groups, which are especially significant for making a healthy diet and mitigating risks of macro- and micronutrient deficiency, and 10 product groups, which are major sources of critically significant nutrients (salt, fats, including saturated fatty acids, and added sugars) and should be consumed in limited amounts. The first cluster included: 1) grain products (cereals and other grain-based foods); 2) meat products (beef, pork, etc.); 3) poultry; 4) milk and sour milk products (milk, kefir, ryazhenka and other liquid milk products); 5) curd and curd-based dishes; 6) eggs; 7) fish; 8) vegetables (except from potato); 9) fruits. The second cluster included: 1) variable sausages; 2) fast food; 3) chips, dried crust; 4) ketchup; 5) mayonnaise; 6) cakes and pastries; 7) chocolate candies; 8) buns and pies; 9) sweetened carbonated drinks; 10) sugary drinks.

Consumption of all product groups was estimated in scores per the foregoing frequency categories; the algorithm employed to assign scores is given in Figure 1. The maximum score 5 was given for daily consumption of food products from the first cluster or for absent consumption of products from the second cluster. Cereals and grain-based foods were the only exception. This group is large and includes many food products any healthy diet is based on and several portions of them should be consumed every day [11]. Daily consumption of products from this group was given 10 scores. If no products from the first cluster were consumed or products from the second cluster were consumed daily, the given

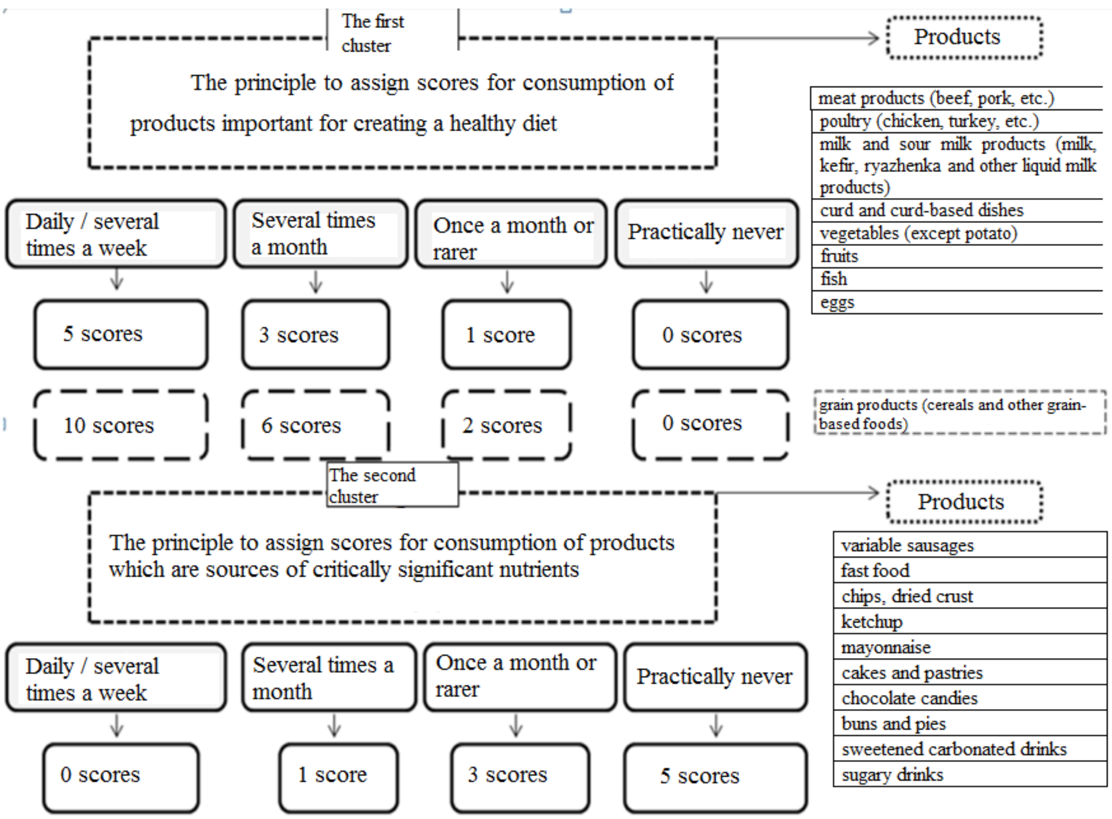

Figure 1. The algorithm for identifying scores necessary to calculate DQI

[3] MR 2.3.0316-23. Gigiena pitaniya. Podgotovka i provedenie monitoringa pitaniya obuchayushchikhsya obshcheobrazovatel'nykh organizatsii: metodicheskie rekomendatsii, utv. Federal'noi sluzhboi po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka 28 fevralya 2023 g. [Nutrition Hygiene. Preparing and Conducting Monitoring of Schoolchildren's Diets: Methodical Guidelines, approved by the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing on February 28, 2023]. *GARANT.RU: information and legal portal*. Available at: https://www.garant.ru/products/ipo/prime/doc/406449045/ (September 04, 2024) (in Russian).

score estimate was 0. Diet Quality Index (DQI) was calculated by summing up the scores given for consumption of products from all 19 groups. Its maximum value is 100 scores and indicates that all products, which are macro- and micronutrient sources, are consumed daily whereas products, which are sources of critically significant nutrients, are absent in a diet.

Mean DQI values were distributed into the categories '*low*', '*medium*', '*high*' and '*very high*' by ranking per percentiles, 25^{th}, 75^{th} and 99^{th}. The DQI value below the 25^{th} percentile was considered low (< 35 scores); between the 25^{th} and 75^{th}, medium (35–50 scores); between the 75^{th} and 99^{th}, high (51–73 scores). The DQI value above 73 scores was considered 'very high'.

To estimate the relationship between the DQI and schoolchildren's nutritional status, sex- and age-specific Z-scores were calculated for body mass index Z-score for age (BAZ) in conformity with the international standards for growth and development of children aged 5–18 years issued by the World Health Organization[4] (WHO) using ANTHROPlus[5]. Z-score measures the exact number of standard deviations or sigma (σ), by which an examined indicator deviates from a standard population median [12]. The following estimation criteria were used for the nutritional status of children aged 5–18 years: underweight at BAZ < -2, normal weight at -1 < BAZ < +1, overweight at +1 < BAZ < +2, obesity at BAZ > +2[6].

Results and discussion. Sex-dependent mean DQI values for children from all age groups are provided in Table 2. DQI was shown to be significantly higher for girls than for boys ($p < 0.001$).

Table 2 also provides the score estimate of consumption of all products groups that constitute DQI. The lowest mean score was revealed for frequency of consuming fish as well as curd and curd-based dishes (1.2 and 1.7 scores accordingly out of maximum 5 scores). Frequency of consuming cereals and grain-based foods was given 5.4 scores, the maximum possible score being 10. Frequency of consuming beef, pork and poultry was estimated as higher than the mean score (2.5), 2.8 and 2.9 scores accordingly. Consumption of milk and sour milk products was given 3.2 scores. Frequency of consuming products, which were sources of critically significant nutrients, was also given low scores; that is, these products were consumed regularly (daily or several times a week). Thus, frequency of consuming chocolate candies was given 0.8 scores; buns and pies, 0.9 scores; sugary drinks, 0.9 scores; cakes and pastries, 1.7 scores; variable sausages, 0.8 scores. In general, we established that schoolchildren did not consume sufficient amounts of grain-based foods, cereals, curd, and fish; instead, they regularly consumed products with high contents of critically significant nutrients, and this indicates that their diets were not balanced or healthy.

DQI above the mean index value (42.8 scores) was identified for 48 % (CI: [47.7–48.3]) of the schoolchildren. The DQI value was at the mean level, that is, within 35–50 scores for practically half of them (48.8 %, CI: [48.5–49.1]). Very high DQI (above 73 scores) was established only for 0.9 % (CI: [0.8–1.0]) of the schoolchildren. Low DQI (below 35 scores) was identified for 27.5 % (CI: [27.2–27.7] of the participants; children from this group had unhealthy diets due to excessive contents of products, which were sources of critically significant nutrients (Figure 2).

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[4] WHO Multicenter Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height, and body mass index-for-age: Methods and development. Geneva, WHO, 2006.

[5] WHO AnthroPlus for Personal Computers Manual: Software for assessing growth of the world's children and adolescents. Geneva, WHO, 2009. Available at: https://cdn.who.int/media/docs/default-source/child-growth/growth-reference-5-19-years/who-anthroplus-manual.pdf?sfvrsn=ddd24b2_1 (September 06, 2024).

[6] MR 2.3.1.0253-21. Normy fiziologicheskikh potrebnostei v energii i pishchevykh veshchestvakh dlya razlichnykh grupp naseleniya Rossiiskoi Federatsii: metodicheskie rekomendatsii, utv. Federal'noi sluzhboi po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka 22 iyulya 2021 g. [Physiological needs in energy and nutrients for various population groups in the Russian Federation: Methodical Guidelines, approved by the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing on July 22, 2021]. *GARANT.RU: information and legal portal*. Available at: https://www.garant.ru/products/ipo/prime/doc/402716140/ (September 06, 2024) (in Russian).

Table 2

Mean score given in conformity with frequency of consuming various food products

Food products*	Mean (*n* = 137,184)	SD	Sex			
			Male (*n* = 65,517)		Female (*n* = 71,667)	
			Mean (*n* = 65517)	SD	Mean (*n* = 71667)	SD
Cereals and grain-based foods	5.4	3.3	5.6	3.3	5.4	3.3
Beef, pork, etc.	2.8	1.6	2.9	1.6	2.8	1.6
Poultry	2.9	1.4	2.8	1.4	2.9	1.4
Milk, kefir, ryazhenka and other liquid milk products	3.2	1.8	3.2	1.8	3.2	1.8
Curd and curd-based dishes.	1.7	1.5	1.7	1.5	1.7	1.5
Vegetables (except potato)	3.5	1.5	3.4	1.5	3.5	1.5
Fruits	3.9	1.4	3.9	1.5	4.0	1.4
Fish	1.2	1.1	1.3	1.2	1.2	1.1
Eggs	2.4	1.5	2.5	1.5	2.4	1.5
Variable sausages	0.8	1.2	0.7	1.1	0.8	1.2
Fast food	2.4	1.6	2.4	1.6	2.5	1.6
Chips and dried crust	2.2	1.7	2.1	1.7	2.2	1.7
Ketchup	2.1	2.0	2.0	2.0	2.2	2.0
Mayonnaise	2.1	2.0	2.0	2.0	2.1	2.0
Cakes and pastries	1.7	1.4	1.8	1.4	1.7	1.3
Chocolate candies	0.8	1.2	0.9	1.2	0.8	1.1
Buns and pies	0.9	1.1	0.9	1.1	0.9	1.1
Sweetened carbonated beverages напитки	1.8	1.8	1.7	1.7	1.9	1.8
Sugary drinks	0.9	1.1	0.9	1.4	1.0	1.5
Diet Quality Index (DQI)	42.8	11.4	42.7	11.4	43.0	11.5

Note: *product groups are given in conformity with the Methodical Guidelines MR 2.3.0316-23.

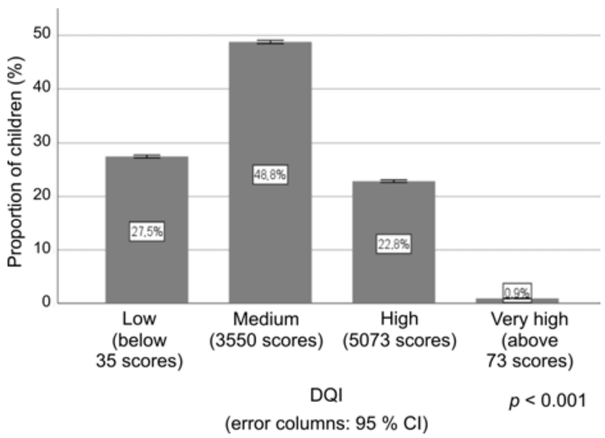

Figure 2. DQI distribution among all surveyed children

The highest DQI was established for primary schoolchildren, 44.6 among boys and 44.3 among girls (Figure 3). The mean DQI value was established to decline in the high school category, 41.0 and 41.7 scores accordingly.

Analysis of the relationship between DQI and having a meal at home before going to school established an authentically higher mean DQI value in children who had breakfast at home regularly ($p < 0.001$) (Figure 4). Thus, DQI was 45.9 scores for primary schoolchildren who had breakfast at home; 43.7 for middle schoolchildren; 43.0 for high school children. DQI values established for children from the same age groups who did not have breakfast at home were 41.9, 39.1 and 38.2 scores accordingly.

Analysis of the relationship between the mean DQI value and family incomes (the latter were estimated by schoolchildren's parents) established a higher mean DQI value for children from families with high incomes (45.4 scores for girls and 44.4 scores for boys) against their peers from families with lower incomes (42.2 scores for girls and 41.4 scores for boys) ($p < 0.001$). The graph that shows how the mean DQI values are distributed depending

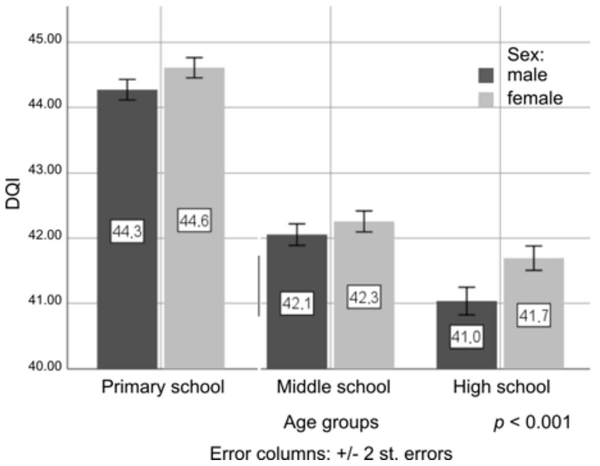

Figure 3. Sex- and age-specific distribution of mean DQI values

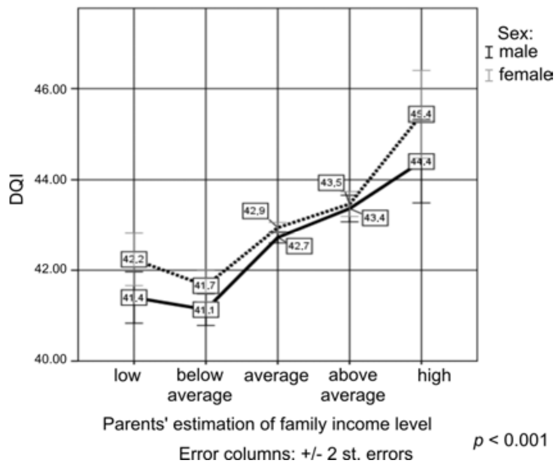

Figure 5. Mean DQI values depending on family income

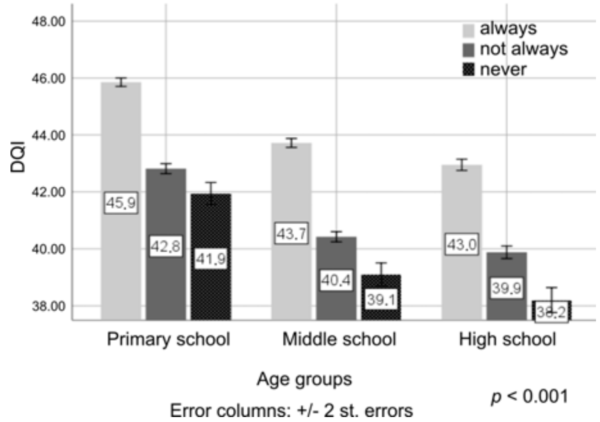

Figure 4. Distribution of mean DQI values depending on breakfast at home before going to school

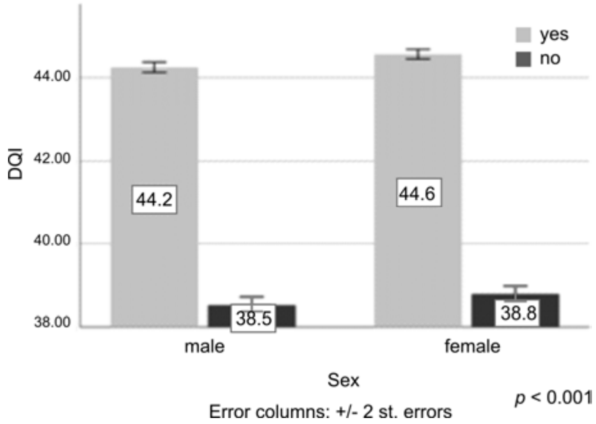

Figure 6. Mean DQI values depending on a family adherence to healthy eating

on family incomes is given in Figure 5. We did not establish any significant differences in DQI values between the children groups with 'low family incomes' and 'below the average family incomes' ($p > 0.001$).

Higher DQI, both among boys and girls, was established in families adhering to principles of healthy eating; 44.2 and 38.5, boys; 44.6 and 38.8, girls ($p < 0.001$) (Figure 6).

The developed DQI was tested depending on levels of awareness about healthy eating principles established in schoolchildren's families and readiness to adhere to them (Table 3). DQI equaled 43.2 scores for schoolchildren from families with some knowledge about healthy eating principles; it was 38.5 scores for schoolchildren from families without such knowledge. DQI values were also higher for those schoolchildren, whose families followed a basic recommendation to have vegetables in two or more meals, than for their peers, whose families did not adhere to this principle (44.0 and 39.5 scores accordingly). A similar result was obtained as regards all other basic recommendations on healthy eating included in the questionnaire: daily fruit consumption in quantity not less than 250–300 grams, giving preference to bread and bakery products made of whole grain flour or second quality flour, daily consumption of fish and 2–3 milk products (including milk-based dishes and drinks). The DQI value was higher for children from families adhering to these principles against their peers, whose families did not follow healthy eating principles (based on $p < 0.001$ in calculating the

Table 3

DQI depending on family adherence to healthy eating principles

Statements about healthy eating (HE)*	DQI			
	True	SD	False	SD
Is a child and his or her family aware of healthy eating principles?	43.2	11.4	38.5	10.2
Having vegetables (except form potato) in 2 and more meals every day	43.9	11.5	39.7	10.5
Fruits included in a daily diet of a family in quantity not less than 250–300 grams	44.0	11.4	38.8	10.5
When choosing bread and bakery products, preference is given to those made of whole grain or second quality flour with bran etc.	44.7	11.8	41.5	10.9
Daily diets include fish	44.2	11.4	41.8	10.9
Daily consumption of 2–3 milk products (including milk-based dishes and drinks)	44.2	11.4	40.1	11.0

Note: $p < 0.001$ between positive and negative answers per each foregoing healthy eating principle. Healthy eating principles are stated in conformity with the Methodical Guidelines MR 2.3.0316-23.

Table 4

Diet Quality Index depending on parents' education

Education		DQI	
		Mean	SD
Mother's education (n = 108,496)	Secondary	41.2	11.0
	Vocational	42.6	11.1
	Higher	44.3	11.8
Father's education (n = 95,911)	Secondary	41.2	11.1
	Vocational	42.6	11.2
	Higher	44.1	11.6

Student's t-test between positive and negative answers per each foregoing healthy eating principle).

Table 4 provides the results obtained by analyzing DQI depending on parents' education. Obviously, the higher education parents have, the higher DQI is established for their children. Thus, the DQI value is 44.3 scores for children, whose mothers have a higher education whereas it equals only 41.2 scores for those with mothers having only secondary education (differences are valid at $p < 0.001$). The similar trend can be traced when analyzing DQI depending on fathers' education.

We also analyzed the relationship between DQI and schoolchildren's nutritional status. DQI was 42.7 scores for boys and 43.0 for girls with normal body weight ($-1 \leq BAZ \leq 1$). The DQI value equaled 42.9 for boys and 43.3 for girls with overweight including obesity ($BAZ > +1$) ($p < 0.001$). We did not find any authentic differences between DQI values for children with underweight, normal body weight, overweight or obesity ($p > 0.05$) (Figure 7). A similar study with adult participants established higher DQI values for people with overweight and obesity [9]. This is likely due to people with overweight or obesity consuming products from all groups more frequently and in greater amounts, including products that are a significant component of a healthy

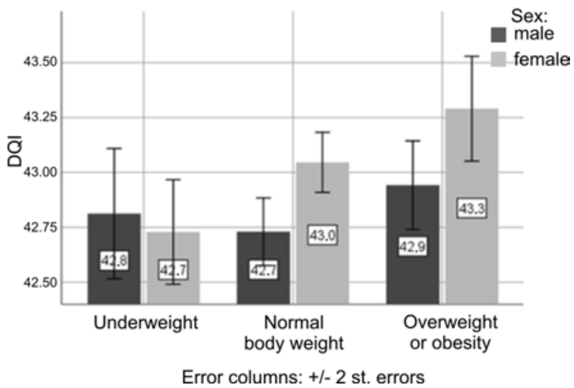

Figure 7. Mean DQI values depending on schoolchildren's nutritional status

diet and consumption of which was given the maximum scores.

DQI, which has been developed for comprehensive analysis of schoolchildren's diets, made it possible to assess their diet quality relying on consumption frequency established for various product groups. Such diet quality indexes are used worldwide to assess diet quality in many studies, including those focusing on children. Thus, diet quality was assessed for children in Australia using an index, which was developed based on food frequency [13, 14]. It allowed estimating diet diversity and finding children with diets not conforming to healthy eating principles. Participants who scored less than the median total food score of 36 were more likely to have suboptimal micronutrient intakes [15]. In our study, DQI below the mean value was established for more than a half (52 %) of the surveyed schoolchildren and low DQI values (below 35 scores) were found for approximately one quarter of the participants.

Mediterranean Diet Quality Index (KIDMED) is employed in European countries to assess diet quality among children and adolescents. It is considered a reliable instrument for assessing adherence to the Mediterranean diet in these age groups [16]. In the study [17], respondents took part in a survey answering 16 questions about consuming various products, both significant for a healthy diet and unhealthy ones [17]. In Spain, the KIDMED index turned out to be higher in large cities and only slight variations were seen for sex and age [18]. The authors showed that the mean index value was authentically higher in girls than in boys. These data are consistent with our findings. Next, DQI values tend to decline with age. This might be associated with stricter parents' control of food consumed by primary schoolchildren and resulting higher consumption of food products necessary for a healthy diet.

The HELENA European study on healthy eating and healthy lifestyles among adolescents assessed diets using the DQI-A index. The authors established a positive association between DQI-A scores and diet quality perception levels in children with normal weight, underweight and overweight. In the authors' opinion, special recommendation on diets for children should be developed in order to achieve better diet quality [19, 20]. In our study, the DQI value was higher in children, whose families were aware of healthy eating principles and adhered to them when making their diets, than in their peers, whose families were either not aware of these principles or did not adhere to them.

Our study found several groups of food products that were not consumed as frequently as they should within an optimal healthy diet such as cereals and grain-based products, fish, and curd. Insufficient consumption of cereals and grain-based products can be a risk factor of deficiency as regards vitamins B, minerals and dietary fiber. Low frequency of curd consumption can be a risk factor of lower bone tissue density. Fish is a major source of easily digestible proteins, polyunsaturated fatty acids omega-3 and phosphor; therefore, low fish consumption creates an elevated risk of deficiency as regards the foregoing nutrients. We also established that schoolchildren regularly consumed products, which were sources of critically significant nutrients. This may indicate that their diets are imbalanced, including excessive calorie contents (due to excessive consumption of fats and added sugars) and insufficient consumption of macro- and micronutrients important for a healthy diet.

Food frequency analysis as a method for assessing actual diets makes studies on dietary patterns much easier and also allows estimating a habitual diet over a short time. Use of DQI based on food frequency analysis makes it much easier to perform complex diet assessment and allows comparing diet quality in various population groups or changes in it in dynamics over time. It seems quite possible to assess diets using DQI both at the population and individual levels. Limitations of the developed method for complex diet assessment include the major disadvantage intrinsic to the frequency method of actual diet analysis; that is, subjectivity of data collection since they are obtained relying on a respondent's individual memory. However, the risk of getting inaccurate data is minimized by conducting a survey competently.

Conclusion:

1. The schoolchildren’s mean DQI was 42.8 scores. DQI values were below the mean score in 52 % of the participants and within the 35–50 score range in 48.8 %. However, the DQI value below 35 scores was established in approximately one quarter of the schoolchildren (27.5 %), which can be a risk factor of chronic non-communicable diseases. We should remember that BMI characteristics such as overweight or obesity themselves are risk factors causing such diseases. DQI was found to decline with age since the highest values were identified in the primary school category and the lowest in the high school category. DQI was higher for children in families with higher incomes (as estimated by parents) than in their peers from low-income families. In addition, DQI values were higher in children whose parents were better educated and had some interest in healthy eating principles.

2. Use of this index for individual diet quality assessment makes it possible to reveal what food products, when consumed, have a negative effect on a diet in each specific case. Thus, regular consumption of fruits and vegetables (products necessary for healthy eating) does not level daily consumption of products with excessive contents of fats, salt and / or added sugars; that is, low scores given for such consumption can affect the total score estimate. Therefore, DQI allows establishing combined effects produced on a diet by food products, which are necessary for healthy eating, and those, which are sources of critically significant nutrients.

3. DQI can be used for analyzing data obtained by large-scale epidemiological studies, which require comprehensive assessment of their results and can be important for these studies. The developed index makes it possible to conduct comprehensive assessment of diet quality and to develop necessary measures aimed at correcting an unhealthy diet. It can also be used to analyze effectiveness of implemented measures aimed at NCDs prevention.

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Research article

HYGIENIC AND HEALTH RISK ASSESSMENT OF WATER SUPPLY SYSTEMS IN ZONES INFLUENCED BY LARGE AGRICULTURAL PRODUCTIONS

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The research objects in this study are represented by some areas in Bashkortostan, which adjoin zones influenced by large agricultural productions; water from water sources used by people for drinking, household, cultural and recreational needs; sanitary-epidemiological indicators of water quality that describe pollution of water sources; levels of health risks associated with drinking water quality.

The aim of this study is to perform hygienic assessment, health risk assessment included, of water supply systems in zones influenced by large agricultural productions as a basis for substantiating relevant measures aimed at providing hygienic safety for the population (exemplified by Bashkortostan).

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We have performed sanitary-hygienic assessment of water resources located in close proximity to agricultural productions including water in surface water objects, underground water sources of non-centralized water supply (wells and springs) and centralized water supply systems. Existing sanitary-hygienic problems were found and described; substantiation was provided for the necessity to organize and implement activities aimed at preventing and mitigating health risks for population. We established main sources and reasons for occurrence of adverse chemicals and pathogens in water objects in areas where animal husbandry, poultry and vegetable-growing farms are located; substantiated a list of priority indicators recommended for control of water quality in various water sources; determined relevant safety criteria that describe adverse impacts exerted by polluted water on human health.

We have established that water quality deviating from safe standards creates elevated health risks in the analyzed areas and can make for growing incidence of non-communicable and communicable diseases among population. Hygienic recommendations and targeted measures have been developed based on our findings; they are aimed at reducing the existing technogenic burden on water objects in areas with developed agricultural industry. The obtained data are recommended to be used by institutions, bodies and organizations responsible for the state sanitary-epidemiological and environmental surveillance over water quality in water objects located in areas influenced by agricultural productions.

Keywords: *underground and surface waters, water form centralized drinking water supply systems, water use, pollution of water sources, sanitary-hygienic assessment, health risk, agricultural territories.*

Special attention is now being paid to finding solutions to sanitary and hygienic issues against growing anthropogenic effects on the environment and an associated increase in risks for humans' life and health. The main goal here is to improve quality of the environment, which is achieved by using such instruments as recovering hydrochemical properties of water systems, reducing the proportion of contaminated sewage water drained in rivers, and improving quality of drinking water supplied to the population[1]. Water quality in underground and surface sources of drinking water supply holds a significant place in promoting health protection, reducing mortality and increasing life expectancy at birth [1–3].

Activities performed by agricultural enterprises have substantial impacts on quality and composition of water in surface and underground water sources used by people for drinking, household and recreational needs. Drainage water from agricultural enterprises, which penetrates natural water systems, tends to contain elevated levels of dissolved organic compounds, pesticides, chlorides, sulfates, nitrogen compounds, and microelements including toxic heavy metals. Several studies have reported considerable levels of pollution in surface and underground water sources located in areas affected by such enterprises [4–9].

Large-scale use of pesticides is a considerable contamination factor. Volumes, in which pesticides are manufactured and used, grow annually. According to the Russian Union of Crop Protection Chemicals Manufacturers and Ministry of Agriculture of the Russian Federation, the share of Russian crop protection chemicals on the market grew from 45 % in 2016 to 70 % in 2022[2]. As highly biologically active substances, pesticides are able to circulate in the environment (water and soil), which often causes poor organoleptic properties of water (smell, color, foaming, and turbidity), leads to contamination of heavy metals salts in surface and underground waters, promotes bacterial contamination in water objects by stimulating growth of microorganisms, as well as weakens self-purification processes in water areas [10–14].

Active use of nitrogen fertilizers in crop cultivation is the largest source of man-made nitrogen pollution in surface and underground

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[1] O Strategii nauchno-tekhnologicheskogo razvitiya Rossiiskoi Federatsii: Ukaz Prezidenta Rossiiskoi Federatsii ot 28 fevralya 2024 goda № 145 [On the Strategy for Scientific and Technological Development of the Russian Federation: the RF President Order dated February 28, 2024 No. 145]. *Prezident Rossii*. Available at: http://www.kremlin.ru/acts/bank/50358 (September 11, 2024) (in Russian).

[2] Za pyat' let dolya rossiiskikh sredstv zashchity rastenii uvelichilas' s 45 % do 70 % [Over five years, the share of Russian crop protection chemicals grew from 45 % to 70 %]. *Ministry of Agriculture of the Russian Federation*, April 06, 2022. Available at: https://mcx.gov.ru/press-service/news/za-pyat-let-dolya-rossiyskikh-sredstv-zashchity-rasteniy-uvelichilas-s-45-do-70/ (September 15, 2024) (in Russian); Za pyat' let dolya rossiiskikh sredstv zashchity rastenii uvelichilas' s 45 % do 70 % [Over five years, the share of Russian crop protection chemicals grew from 45 % to 70 %]. *Delovoi kvadrat*, April 07, 2022. Available at: https://www.d-kvadrat.ru/novosti/20052 (September 15, 2024) (in Russian).

waters across the globe. Excessive use of nitrogen-based fertilizers (synthetic and / or natural) has a specifically harmful effect since the greatest part of nitrogen, which is not absorbed by plants, transforms into nitrates; the latter are easily washed off from soils into watercourses and underground waters [15, 16].

People who live in rural areas are exposed to the highest health risks since they commonly use non-centralized water sources (surface water objects, springs and wells) for drinking and household needs. As opposed to centralized water supply, such sources are not well protected from both natural and human impacts. Sanitary-epidemiological safety and proper laboratory control of water quality is not provided for a major part of such sources. Thus, safety of their use as regards epidemiological and radiation aspects or harmlessness of their chemical compositions cannot be guaranteed.

All foregoing issues related to safe water use are relevant for the Republic of Bashkortostan (RB), a leading agricultural region in the Russian Federation. The Republic owns 3.4 % (7.069 million hectares; of them, plowed fields accounting for 3636.7 thousand hectares) of all agricultural lands in Russia and produces 3.2 % of the total agricultural production in the country [17]. The agricultural sector is developing quite actively in Bashkortostan and operates practically in the whole range of agricultural brunches including animal husbandry (cattle, pig, sheep, horse, and poultry breeding) and plant cultivation (grains, legumes, oil and sugar-bearing cultures, potatoes and other vegetables). This creates elevated human impacts on water sources located in the basins of the Volga, Kama, Belaya and Ural rivers.

The aim of this study is to perform hygienic assessment, health risk assessment included, of water supply systems in zones influenced by large agricultural productions as a basis for substantiating relevant measures aimed at providing hygienic safety for the population (exemplified by Bashkortostan).

Materials and methods. The research was accomplished in some residential areas adjoining large agricultural enterprises operating in various brunches: in Sterlitamakskii district (animal husbandry, poultry breeding, and plant growing on the open ground); Ufimskii district (poultry breeding, protected cultivation and plant growing on the open ground); Alsheevskii, Buraevskii, Davlekanovskii, Karmaskalinskii, Tuimazinskii, Chekmagushevskii and Chishminskii districts (plant growing on the open ground).

The research objects in this study with its focus on assessing sanitary-hygienic state of water objects used by people for drinking, household, cultural and recreational needs are represented by some sections of water ways located close to large agricultural productions (Table 1). Selected observation points were located higher and lower along the stream than sewage disposals from agricultural objects. Samples were taken in various seasons in conformity with the State Standard GOST[3].

Population exposure was estimated using data provided by the testing center of the Ufa Research Institute of Occupational Hygiene and Human Ecology (over 2021–2023) and Bashkir Agency on Hydrometeorology and Environmental Monitoring (over 2007–2020). Quality of water from wells and springs in rural settlements was estimated per 21 indicators. The total research volume included more than 13,000 research units.

Samples were taken and analyzed to establish sanitary and hygienic characteristics of underground waters used by population as non-centralized drinking water supply sources (Table 2).

Underground water contamination was estimated per 32 priority indicators. The total research volume covered approximately 11,200 units. In addition, the analysis included the results of laboratory tests obtained by the Center for Hygiene and Epidemiology in Bashkortostan within conducting social and hygienic monitoring (SHM).

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[3] GOST R 59024-2020. Water. General requirements for sampling (published with alterations No.1), approved and enacted by the Order of the Federal Agency on Technical Regulation and Metrology dated September 10, 2020 No. 640-st. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200175475 (September 07, 2024) (in Russian).

Table 1

Observation points for monitoring of surface water quality

No.	Water object	Observation points
1	Kalmashka River	Chishminskii district, close to agricultural lands
2	Lebyazh'e Lake	Ufimskii district, close to fields
3	Sosnovoe Lake	Ufimskii district, close to greenhouses
4	Soldatskoe Lake	Ufimskii district, on agricultural lands
5	Avdonskii Pond	Ufimskii district, close to a poultry farm
6	Asava River	Sterlitamakskii district, close to a pig farm
7	Kuganak River	Sterlitamakskii district, close to a pig farm
8	Yamansaz River	Sterlitamakskii district, at the boundary of agricultural fields
9	Belaya River	Sterlitamakskii district, close to agricultural lands
10	Mesel'ka River	Sterlitamakskii district, close to agricultural lands
11	Dema River	Al'sheevskii district, close to fields
12	Aslykul' Lake	Davlekanovskii district, close to land spots (plowed fields)
13	Miyaki River	Miyakinskii district, close to agricultural lands
14	Chermasan River	Chekmagushevskii district, close to fields

Table 2

Observation points for monitoring of water quality in underground sources in rural settlements in Bashkortostan

No.	Settlement	Water source
1	Ufimskii district, Avdon settlement, 3 km away from a poultry farm	Shaft well
2	Ufimskii district, Avdon settlement, 2 km away from a poultry farm	Shaft well
3	Ufimskii district, land spots for berry, fruit and vegetable growing	Well
4	Ufimskii district, cottage settlement Tsvety Bashkirii	Well
5	Ufimskii district, Alekseevka settlement, close to greenhouses	Well
6	Ufimskii district, Bachurino settlement, close to plowed fields	Well
7	Ufimskii district, Zubovo settlement, close to plowed fields	Well
8	Chishminskii district, Chishmy settlement, close to an agricultural enterprise	Well
9	Chishminskii district, Chishmy settlement, close to plowed fields	Well
10	Chishminskii district, Chishmy settlement, close to a fruit garden	Well
11	Chishminskii district, Novoabdullino village, close to plowed fields	Shaft well
12	Chishminskii district, Sanzharovka village, close to plowed fields	Well
13	Karmaskalinskii district, Novomusino village, close to a community farm	Well
14	Ilishevskii district, Verkhnemancharovo settlement, close to a grape-growing farm	Private well
15	Buraevskii district, Buraevo settlement, close to a poultry farm	Well
16	Tuimazinskii district, close to greenhouses	Well
17	Iglinskii district, Karamaly settlement, close to an animal husbandry and vegetable-growing complex	Spring
18	Sterlitamakskii district, Ishparsovo village, close to plowed fields	Community well
19	Sterlitamakskiidistrict, Roshchinskii settlement, close to Roshchinkii pig-breeding farm	Well
20	Sterlitamakskii district, Kantyukovka settlement, close to plowed fields	Well
21	Sterlitamakskii district, Naumovka settlement, close to plowed fields	Well
22	Sterlitamakskii district, Burikazgan village, close to plowed fields	Spring
23	Sterlitamakskii district, Zalivnoe settlement, close to plowed fields	Well
24	Sterlitamakskii district, Yuzhnoe village, close to plowed fields	Well
25	Sterlitamakskii district, Pervomaiskii settlement, close to plowed fields	Well
26	Sterlitamakskii district, Begenyashskoe village, close to plowed fields	Well

Quality of water taken from centralized drinking water supply systems in settlements was estimated per 51 indicators using data provided by the laboratories of the Center for Hygiene and Epidemiology in Bashkortostan, Bashkommunvodokanal (a water supplier), and Ufa Research Institute of Occupational Hygiene and Human Ecology. The total volume of analyzed water quality indicators equaled 14,600 units.

To estimate epidemiological safety of water in analyzed areas, water samples were taken and analyzed per 8 microbiological indicators: total bacterial count (22 ± 1.0 C°), total bacterial count (37 ± 1.0 C°), total (generalized) coliforms, enterococci, sulphite-reducing clostridia spores, bacteria from Escherichia coli and Pseudomonas aeruginosa species, and causative agents of intestinal infections. The total research covered 1810 research units.

Quality of water and water sources was estimated in conformity with the regulatory sanitary documents SanPiN 1.2.3685-21[4] and SanPiN 2.1.3684-21[5]. Levels of carcinogenic and non-carcinogenic health risks associated with water quality were calculated, assessed, analyzed and interpreted in conformity with the approved methodology (Guide R 2.1.10.3968-23)[6]. Exposure to chemicals in drinking water was assessed for oral intake into the body for adult people. Recommended standard physiological constants for an adult human were employed in calculating affecting doses (body mass of 70 kg, water intake of 2 liters a day, duration of exposure equal to 30 years (non-carcinogenic risk) and 70 years (carcinogenic risk)). The total volume of analyzed indicators equaled approximately 32,000 units.

Research results were statistically analyzed using Microsoft Excel and descriptive statistics methods.

Results and discussion. Agricultural lands (pastures and plowed fields), poultry-breeding and animal husbandry farms (sheds for poultry and animals, drainage water tanks, catch pits and manure storages), warehouses for keeping fertilizers and pesticides, as well as rural settlements, cottage villages and agglomerations of berry, fruit and vegetable gardens were established to be main sources of human impacts exerted on water systems in the analyzed areas in Bashkortostan.

The research results have shown iron, manganese, nickel, mercury, sulfates and oil products to be priority chemical contaminants of surface water sources (water ways and water objects) since their levels do not conform to hygienic safe standards (Table 3).

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[4] SanPiN 1.2.3685-21. Gigienicheskie normativy i trebovaniya k obespecheniyu bezopasnosti i (ili) bezvrednosti dlya cheloveka faktorov sredy obitaniya (s izmeneniyami na 30 dekabrya 2022 goda), utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha Rossiiskoi Federatsii ot 28 yanvarya 2021 goda № 2 [Sanitary Rules and Norms SanPiN 1.2.3685-21. Hygienic standards and requirements to providing safety and (or) harmlessness of environmental factors for people (last amended as of December, 2022), approved by the Order of the RF Chief Sanitary Inspector on January 28, 2021 No. 2]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573500115 (September 11, 2024) (in Russian).

[5] SanPiN 2.1.3684-21. Sanitarno-epidemiologicheskie trebovaniya k soderzhaniyu territorii gorodskikh i sel'skikh poselenii, k vodnym ob"ektam, pit'evoi vode i pit'evomu vodosnabzheniyu naseleniya, atmosfernomu vozdukhu, pochvam, zhilym pomeshcheniyam, ekspluatatsii proizvodstvennykh, obshchestvennykh pomeshchenii, organizatsii i provedeniyu sanitarno-protivoepidemicheskikh (profilakticheskikh) meropriyatii (s izmeneniyami na 14 fevralya 2022 goda), utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha Rossiiskoi Federatsii ot 28 yanvarya 2021 goda № 3 [Sanitary Rules and Norms SanPiN 2.1.3684-21. Sanitary-epidemiologic requirements to maintenance of territories in urban and rural settlements, to water objects, drinking water and public water supply, ambient air, soils, living spaces, exploitation of industrial and public premises, organization and c implementation of sanitary and anti-epidemic (prevention) activities (last amended as of February 14, 2022), approved by the Order of the RF Chief Sanitary Inspector on January 28, 2021 No. 3]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573536177 (September 11, 2024) (in Russian).

[6] R 2.1.10.3968-23. Rukovodstvo po otsenke riska zdorov'yu naseleniya pri vozdeistvii khimicheskikh veshchestv, zagryaznyayushchikh sredu obitaniya [Guide R 2.1.10.3968-23 Health Risk Assessment upon Exposure to Chemical Pollutants in the Environment]. Moscow, Rospotrebnadzor, 2023 (in Russian).

Table 3

Priority indicators of water quality in surface sources located in rural areas in Bashkortostan

Sampling points	Levels, mg/l								
	Nitrates	Nitrite nitrogen	Oil products	Chlorides	Sulfates	Total iron	Nickel	Manganese	Mercury
MPL, mg/l	45	3.0	0.1	350	500	0.3	0.02	0.1	0.0005
Belaya River	1.83 ± 0.10	0.02 ± 0.003	0.08 ± 0.006	279.6 ± 38.3	46.9 ± 7.4	0.43 ± 0.10	0.011 ± 0.002	0.20 ± 0.03	-
Dema River	8.48 ± 0.90	0.009 ± 0.0008	0.32 ± 0.06	37.2 ± 3.6	321 ± 15.4	0.34 ± 0.08	0.014 ± 0.02	0.04 ± 0.01	-
Kalmashka River	5.7 ± 0.60	0.014 ± 0.002	-	22.0 ± 3.5	143 ± 14	0.10 ± 0.02	0.095 ± 0.027	0.090 ± 0.025	0.0001 ± 0.00004
Lebyazh'e Lake	9.4 ± 0.90	0.011 ± 0.003	-	87.9 ± 7.9	247 ± 25	0.059 ± 0.01	0.070 ± 0.019	0.010 ± 0.003	0.0006 ± 0.0001
Sosnovoe Lake	-	< 0.003	-	88.6 ± 8.0	208 ± 21	0.25 ± 0.05	0.093 ± 0.026	0.018 ± 0.005	0.0007 ± 0.0001
Soldatskoe Lake	6.1 ± 0.70	< 0.003	-	17.7 ± 2.8	205 ± 21	0.075 ± 0.02	0.095 ± 0.027	0.053 ± 0.015	0.0044 ± 0.0007
Aslykul' Lake	0.13 ± 0.02	0.004 ± 0.0009	0.13 ± 0.02	52.9 ± 9.2	779 ± 52.1	0.028 ± 0.004	0.005 ± 0.001	0.028 ± 0.007	0.0010 ± 0.0003
Avdonskii Pond	-	-	-	34.7 ± 3.8	94 ± 9	0.062 ± 0.017	0.014 ± 0.004	0.010 ± 0.003	0.0001 ± 0.00004
Asava River	-	-	-	19.1 ± 3.1	123 ± 12	0.15 ± 0.03	0.11 ± 0.02	0.12 ± 0.02	0.0005 ± 0.0001
Kuganak River, up the stream	-	-	-	33.3 ± 3.7	81 ± 8	0.078 ± 0.022	0.010 ± 0.003	0.11 ± 0.02	0.0010 ± 0.0002
Kuganak River, down the stream.	-	-	-	34.7 ± 3.8	300 ± 30	0.092 ± 0.026	0.010 ± 0.003	0.12 ± 0.02	0.0021 ± 0.0003
Yamansaz River	-	-	-	10 ± 1.9	258 ± 26	0.19 ± 0.04	0.017 ± 0.005	0.21 ± 0.04	0.0001 ± 0.00004
Mesel'ka River	-	-	-	13.5 ± 2.2	155 ± 15	0.21 ± 0.04	0.010 ± 0.003	0.15 ± 0.03	0.0006 ± 0.0001
Miyaki River	14.9 ± 2.8	0.02 ± 0.003	0.37 ± 0.07	16.5 ± 3.3	148.6 ± 17	0.46 ± 0.10	0.009 ± 0.002	-	-
Chermasan River	8.07 ± 0.80	0.015 ± 0.008	0.19 ± 0.02	32.5 ± 7.6	345.6 ± 21	0.092 ± 0.01	0.008 ± 0.001	0.182 ± 0.02	0.0014 ± 0.0003

Note: «-» means data not available.

Safe standards (MPL) for water objects used for drinking and household water supply are violated per levels of such chemicals as mercury (up to 8.8 MPL), nickel (up to 5.5 MPL), oil products (up to 3.7 MPL), manganese (up to 2.1 MPL), sulfates (up to 1.6 MPL), and iron (up to 1.5 MPL). Levels of pesticides, ammonium nitrogen, nitrates, nitrites, hydrogen sulfide, chlorides, phenols, zinc, copper, cadmium, lead, chromium, arsenic and others have been established to be within safe ranges established for open water sources.

Mercury is the most widely spread chemical contaminant in the analyzed agricultural areas as it is identified in elevated levels in open water sources. The highest levels of the toxicant have been found in water in the Kuganak River (up to 4.2 MPL), Chermasan River (up to 2.8 MPL), Mesel'ka River (up to 1.2 MPL), Soldatskoe Lake (up to 8.8 MPL), Aslykul' Lake (up to 2.0 MPL), and Sosnovoe Lake (up to 1.4 MPL). Mercury has not been found in water samples taken from the Dema River, Belaya River and Miyaki River.

Nickel has also been detected in elevated levels. Thus, nickel levels have reached 0.11 mg/l in water from the Asava River in some periods and this is 5.5 times higher than MPL; water from the Kalmashka River and Soldatskoe Lake, 0.095 mg/l (4.7 MPL); Sosnovoe Lake, 0.093 mg/l (4.6 MPL); Lebyazh'e Lake, 0.070 mg/l (3.5 MPL).

Manganese also tends to be identified in elevated levels in the analyzed water objects. The highest manganese levels have been established in the Belaya River and Yamansaz River (2.0–2.1 MPL), Chermasan River (1.80 MPL), and Mesel'ka River (1.5 MPL).

Levels of oil products have been established to not conform to safe standards in water from the Miyaki River (3.7 MPL), Dema River (3.2 MPL), Chermasan River (1.9 MPL), and Aslykul' Lake (1.3 MPL). Average long-term levels of oil products in water taken at the analyzed water intake points in the Belaya River have not exceeded MPLs. We have not been able to determine levels of oil products in water taken from other water areas.

Levels of iron have been found to not conform to safe standards in water samples taken from three water objects: the Miyaki River (up to 1.5 MPL), Belaya River (up to 1.4 MPL), and Dema River (up to 1.1 MPL).

Water from the Aslykul' Lake has been established to contain elevated levels of sulfates up to 1.6 times higher than the relevant MPL. Levels of sulfates higher than MPL have not been detected at any other observation point in other water areas.

Likely non-carcinogenic and carcinogenic health effects have been assessed for population as regards oral, inhalation and subcutaneous exposure to chemicals in water from open sources. The assessment results give evidence of insignificant health risks with their levels being either minimal or permissible (HI < 3.0; CR < 1.0E-05).

Assessment of sanitary-epidemiological safety has revealed that water in some open water sources does not conform to safe standards per several microbiological indicators. Thus, water samples taken from the Kalmashka River have been found to contain total coliforms (TCs) in levels reaching 720 CFU/100cm^3 and enterococci in levels up to 18 CFU/100cm^3; Kuganak River, TCs (up to 1140 CFU/100cm^3), enterococci (up to 11 CFU/100cm^3), Escherichia coli (up to 170 CFU/100cm^3); Lebyazh'e Lake, TCs (up to 610 CFU/100cm^3), Escherichia coli (up to 130 CFU/100cm^3), causative bacterial agents of intestinal infections; Sosnovoe Lake, TCs (up to 590 CFU/100cm^3), enterococci (up to 16 CFU/100cm^3); Soldatskoe Lake, TCs (up to 780 CFU/100cm^3).

Our research results give evidence of great human-induced effects produced on surface water flows and water objects located in agricultural areas in Bashkortostan; this is manifested through chemical and bacteriological contamination of water in them.

Heavy metals and sulfates as contaminants located in water sources in the analyzed areas may occur in them due to drainage water coming from animal husbandry and poultry-breeding complexes, manure storage facilities at farms and fields as well as due to active use of fertilizers and pesticides.

Elevated mercury levels established in water objects can also be explained by pesticides (mercury-containing fungicides and herbicides) having been used in these areas for a long time[7] [13, 18].

In addition, we cannot neglect the fact that water objects are located too close to oil extraction enterprises (Chishminskii, Davlekanovskii, Chekmagushevskii and other districts), processing and petrochemical productions (Ufimskii and Sterlitamakskii districts) in some analyzed agricultural areas in Bashkortostan. Consequently, they are likely to be additionally influenced by waste disposals containing a wide range of soluble and insoluble pollutants such as oil products, sulfates and heavy metals. According to the observation results, levels of pollution in surface water areas tend to be somewhat higher in such areas and they depend on a distance from oil productions and petrochemical plants; the most significant ones are identified within a 5 km radius.

High levels of bacterial contamination established in the analyzed water objects indicate that water is considerably contaminated with organic compounds and various nitrogen forms. Identified pathogens and potential pathogens such as Escherichia coli, causative agents of intestinal infections, and enterococci are microbiological indicators of fecal contamination.

Contamination with pathogens and potential pathogens may occur in water objects due to water drainage coming from poultry-breeding and animal husbandry complexes or high volumes of manure being washed off from plowed fields. Also, both Russian and foreign studies report that pesticides penetrating water objects promote high levels of bacterial contamination in water objects due

[7] Borisenko N.F., Kuchak Yu.A. Vliyanie rtut'organicheskikh pestitsidov na okruzhayushchuyu sredu i zdorov'e naseleniya [Effects of mercury-organic pesticides on human health and the environment]. *Gigiena i sanitariya*, 1989, no. 12, pp. 65–69 (in Russian).

to their ability to influence microbial communities by stimulating growth of some groups and inhibiting reproduction of others [11, 18–24].

Therefore, our research results allow us to conclude that water in surface water sources located in some agricultural areas in Bashkortostan does not conform to ecological-hygienic and sanitary-epidemiological requirements. This makes household and recreational water use unsafe for people living there and may promote growing incidence of both communicable and non-communicable diseases among the population.

Assessment of water quality in water sources for household and drinking water supply. Household and drinking water is supplied to people living in settlements located in the analyzed areas predominantly from non-centralized water supply sources (wells and springs). Drinking water is partially supplied by using a centralized water supply system to people living in the Ufimskii district (Avdon settlement, Alekseevka settlement and Zubovo settlement), Sterlitamakskii district (Roshchinskii settlement), Chishminskii district (Chishmy settlement), Buraevskii district (Buraevo settlement), and Iglinskii district (Iglino settlement) of Bashkortostan.

Sanitary-epidemiological examinations of water quality in underground sources (wells and springs) have been accomplished in some areas in Bashkortostan to estimate safety of water used by people in agricultural areas as non-centralized drinking water supply.

The results obtained by the complex estimation of water quality in underground sources give evidence that in most cases water from wells and springs in some agricultural areas in the republic does not conform to sanitary-hygienic or sanitary-epidemiological requirements (Table 4).

According to our findings, several major pollutants have been identified in drinking water in the analyzed areas in levels higher than the relevant safe standards including nitrates (up to 7.2 MPL), iron (up to 5.0 MPL), nickel (up to 4.6 MPL), mercury (up to 4.0 MPL), and manganese (up to 4.0 MPL). In addition, samples taken from some water sources contain elevated calcium (up to 2.4 MPL) and magnesium (up to 1.6 MPL) levels making water in them too hard (up to twofold higher than the safe level). Levels of ammonia, ammonium nitrogen, nitrites, pesticides, hydrogen sulfide, sulfates, phenols, chlorides, zinc, copper, lead, cadmium, chromium, arsenic, strontium, cobalt, silicon, and oil products in underground water sources have been established to be within the relevant safe ranges. Analysis of microbiological indicators that describe water quality has established non-conformity with safe standards for some water sources per total bacterial count (up to 1000 CFU/cm^3), occurrence of TCs, sulfate-reducing clostridia spores, E. coli, Citrobakter spp. and causative agents of intestinal infections.

Nitrates are the most common pollutant in underground water sources in the analyzed rural areas. Thus, high levels of nitrates have been found in 10 underground water sources: wells located in Buraevo settlement (up to 7.2 MPL), Novomusino village (up to 4.3 MPL), Begenyashskoe settlement (up to 3.8 MPL), Chichmy settlement close to plowed fields (up to 2.3 MPL), outskirts of Tuimazy town (up to 1.6 MPL), Sanzharovka village (up to 1.5 MPL), Novoabdullino village (up to 2.9 MPL), and Verkhnemancharovo village (up to 2.3 MPL); springs, in Karamaly settlement (up to 2.2 MPL) and Burikazgan village (up to 1.3 MPL).

The second significant hazardous factor is water contamination with heavy metals (nickel, mercury, iron, and manganese). Unsafe nickel levels have been established in a community well in Ishparsovo village (up to 4.6 MPL), a well in Chishmy settlement near a fruit garden (up to 3.3 MPL), a private well in Roshchinskii settlement (up to 3.2 MPL), wells in Alekseevskii settlement, near Tsvety Bashkirii cottage settlement (up to 2.9 MPL) and Bachurino village (up to 2.8 MPL); a shaft well in Avdon settlement (up to 2.4 MPL).

Table 4

Priority sanitary-chemical indicators for describing quality of underground waters in some agricultural areas in Bashkortostan

Sampling points	Estimated indicators, mg/l														
	NO_3-	NO_2-	Cl^-	SO_4	Fe	H_{total}	Ca	Mg	Ni	Mn	Hg	Cr	Cd	Pb	As
MPL, mg/L	**45**	**3.0**	**350**	**500**	**0.3**	**10.0**	**25-130**	**50**	**0.02**	**0.1**	**0.0005**	**0.05**	**0.001**	**0.01**	**0.01**
Ufimskii, Avdon, section 613	1.8	<0.003	10	117	0.044	7.3	122	15	0.040	<0.005	<0.0001	<0.01	<0.0001	0.0018	<0.005
Ufimskii, Avdon, section 614	4.2	<0.003	14.9	150	0.02	6.9	114	14	0.048	<0.005	0.0009	<0.01	0.0005	0.0013	<0.005
Ufimskii, Tsvety Bashkirii (well)	0.3	<0.003	53.9	28	0.029	9.5	144	28	0.058	0.02	<0.0001	<0.01	<0.0001	<0.001	<0.005
Ufimskii, Tsvety Bashkirii (well)	0.7	<0.003	76	122	0.83	10.8	152	40	0.051	0.305	0.0011	<0.01	<0.0001	<0.001	<0.005
Ufimskii, Alekseevka	-	<0.003	11.3	198	0.044	5.3	92	9	0.059	0.006	0.0020	0.015	<0.0001	0.0013	<0.005
Ufimskii, Bachurino	12.4	<0.003	9.7	123	0.086	6.5	89	24	0.056	0.007	0.0015	<0.01	0.0008	<0.001	<0.005
Ufimskii, Zubovo	3.3	<0.003	-	-	0.95	10.0	160	24	-	-	-	-	-	-	-
Chishminskii, Chishmy, farmland	103	<0.003	40	118	<0.01	9.3	127	37	<0.010	<0.010	<0.0001	<0.01	<0.0001	<0.001	-
Chishminskii, Chishmy, Shosseinaya St.	5.8	<0.003	32	360	0.082	13.0	166	58	<0.010	0.015	<0.0001	<0.01	<0.0001	<0.001	-
Chishminskii, Chishmy, plowed fields	11.8	<0.003	12.8	146	0.25	7.7	124	18	0.066	0.007	0.0003	<0.01	<0.0001	0.0043	<0.005
Chishminskii, Novoabdullino village	133	-	-	-	0.33	11.0	132	51	-	-	-	-	-	-	-
Chishminskii, Sanzharovka	66.6	<0.003	-	-	0.014	5.9	82	22	-	-	-	-	-	-	-
Karmaskskii, Novomusino	192	-	-	-	0.65	15.6	183	78	-	-	-	-	-	-	-
Ilishevskii, Verkhnemancharovo	103	<0.003	-	-	0.014	5.8	67	30	-	-	-	-	-	-	-
Buraevskii, Buraevo	323	<0.003	-	-	0.020	18.9	309	43	-	-	-	-	-	-	-
Tuimazskii	73.6	<0.003	-	-	0.010	10.0	100	61	-	-	-	-	-	-	-
Iglinskii, Karamaly	99.6	<0.003	-	-	0.014	5.9	82	22	-	-	-	-	-	-	-
Sterlitamakskii, Ishparsovo	-	-	84.4	84	0.80	16.5	188	87	0.092	0.40	0.0010	0.012	<0.0001	<0.001	<0.005
Sterlitamakskii, Roshchinskii	18.7	<0.003	73	95	0.079	13.2	165	61	0.065	0.042	0.0010	<0.010	<0.0001	<0.001	<0.005
Sterlitamakskii, Burikazgan	58.4	<0.003	24.1	23	0.27	8.0	110	49	0.0014	0.014	<0.0001	<0.010	<0.0001	<0.001	<0.005
Sterlitamakskii, Yuzhnoe	43.9	<0.003	14	300	1.5	11.0	150	69	0.013	0.100	<0.0001	<0.010	<0.0001	<0.001	<0.005
Sterlitamakskii, Pervomaiskii	22.4	<0.003	90	390	0.55	18.0	284	51	0.001	0.004	<0.0001	<0.010	<0.0001	<0.001	<0.005
Sterlitamakskii, Begenyashskoe	170.5	<0.003	95	70	0.20	17.9	277	60	0.0012	0.022	<0.0001	<0.010	<0.0001	<0.001	<0.005

Note: «-» means data not available.

Elevated mercury levels have been established in Alekseevka settlement (up to 4.0 MPL), Bachurino village (up to 3.0 MPL), Ishparsovo village, Roshchinskii settlement, Tsvety Bashkirii cottage settlement (up to 2.0 MP:), and Avdon settlement (up to 1.8 MPL).

Elevated iron levels have been found in underground water sources located in Yuzhnoe village (up to 5.0 MPL), Zubovo village (up to 3.5 MPL), Tsvety Bashkirii cottage settlement (up to 2.8 MPL), Ishparsovo village (up to 2.7 MPL), Novomusino village (up to 2.2 MPL), Pervomaiskii settlement (up to 1.8 MPL), and Novoabdullino village (up to 1.1 MPL).

Unsafe manganese levels have been identified in water from two wells located in Ishparsovo village (up to 4.0 MPL) and Tsvety Bashkirii cottage settlement (up to 3.0 MPL).

Elevated levels of alkaline-earth metal salts such as calcium and magnesium are another significant adverse property of underground water sources. They are responsible for high water hardness (more than 10.0 mg-eq/dm^3). Thus, water hardness has been found to exceed its safe level in wells located in Buraevo village (up to 1.9 times), Pervomaiskii settlement and Begenyashskoe village (up to 1.8 times), Novomusino village (up to 1.6 times), Chishmy settlement and Ishparsovo village (up to 1.6 times), Roshchinskii settlement (up to 1.3 times), Novoabdullino village, Yuzhnoe village and Tsvety Bashkirii cottage settlement (up to 1.1 times).

Sanitary-epidemiological studies of underground water quality have revealed water samples not conforming to safe standards per the following indicators: total bacterial count, Zalivnoe settlement (up to 160 CFU/cm^3), Vasil'evka village (up to 300 CFU/cm^3), Roshchinskii settlement (up to 500 CFU/cm^3); total coliforms, Avdon, Zalivnoe, Sanzharovka, Vasil'evka, Bachurino, and Burikazgan villages and settlements; presence of sulfate-reducing clostridia spores, Avdon settlement; Escherichia coli, Avdon, Naumovka, Vasil'evka, and Burikazgan villages and settlements; causative agents of intestinal infections, Avdon settlement. Water in non-centralized water supply sources located in other analyzed areas (Chishmy settlement, Kantyukovka village, Ishparsovo village, Alekseevka settlement) conforms to sanitary-epidemiological requirements. Tests aimed at identifying enterococci and Pseudomonas aeruginosa have not established non-conformity with safe standards in all analyzed water sources either.

Therefore, our findings are evidence that underground waters as sources of non-centralized drinking water supply in agricultural areas in Bashkortostan are affected by human activities and do not conform to safe standards.

Priority chemical pollutants occurring in underground waters include nitrates, nickel, mercury, iron, manganese, calcium, and magnesium; general water hardness is another harmful factor.

High levels of nitrates in underground waters are indicative of the fact that soil in these areas has been abundantly fertilized with nitrogen-based compounds including animal husbandry and poultry-breeding wastes (manure). This might be due to plants being incapable to absorb nitrogen fertilizers completely; the remains are then transformed into nitrates and are either accumulated in soil or lost as part of drainage. Use of nitrogen-based fertilizers (natural and synthetic) in high volumes combined with high water solubility of nitrates support their washing off into underground waters thereby polluting underground water sources [5, 15].

Human-induced pollution in underground water sources with toxic heavy metals just as open water sources in the analyzed areas is likely to be associated with drainage water coming from animal husbandry and poultry-breeding complexes, manure storage at farms and plowed fields as well as with active use of fertilizers and pesticides.

High levels of nickel in underground waters can be partially due to infiltration (washing off) of the metal from soils where it occurs due to decay of soil minerals, death and decay of plants as well as due to precipitations. Animal husbandry wastes and improper use of herbicides are another reason for accumulation of nickel and other metals in soils of agricultural land spots. Motor transport with its volumes growing every year may be another contributing factor.

High hardness of water in underground sources in the analyzed areas caused by calcium and magnesium ions obviously occurs due to natural geological factors involving salts being washed off from rocks.

Pathogens and potential pathogens, which occur in drinking water, give evidence of considerable contamination with feces and organic compounds. Possible reasons might include drainage water from animal husbandry complexes penetrating underground waters or infiltration of manure from soils of plowed fields; violated sanitary-epidemiological requirements to organization and operations of water intake facilities can also contribute to the matter.

Generalization of all research results allow us to conclude that water in underground sources (wells and springs) located in the analyzed agricultural areas in the republic does not conform to sanitary-hygienic and sanitary-epidemiological requirements. It is unsafe to be used as drinking water by people since it can create elevated risks of communicable and non-communicable diseases.

Exposure to elevated levels of nitrates, iron, manganese, nickel, mercury, magnesium, and calcium in drinking water creates possible health risks for people living in the analyzed agricultural areas. These risks are associated with diseases of the digestive organs, cardiovascular, nervous, immune and genitourinary systems as well as the hematopoietic system.

Microbial contamination of drinking water with bacterial pathogens poses a serious threat of intestinal infections. The highest risks of intestinal infections due to bacteriological contamination of drinking water have been established for people living in Zalivnoe, Vasil'evka, Roshchinskii, Avdon, Sanzharovka, Bachurino, Burikazgan, and Naumovka settlements and villages.

To achieve more objective assessment of hygienic safety as regards household and drinking water supply to the population in the analyzed agricultural areas, we have assessed likely non-carcinogenic and carcinogenic health risks associated with quality of water from non-centralized water supply sources.

According to the calculations, high levels of nitrates are the most significant health risk factors associated with chemicals in underground drinking water. The highest hazard indexes (HI above 3), which determine high non-carcinogenic health risks upon exposure to nitrates in drinking water, have been established for people living in Buraevo settlement (HQ = 4.77), Novomusino village (HQ = 3.44), and Begenyashskoe village (HQ = 3.03). So, people in these settlements face higher health risks associated with likely adverse health outcomes related to the hematopoietic system.

An alerting level of health risks (HI = 1.1–3.0) for the hematopoietic system, which are associated with high levels of nitrates in underground waters, has been established for some water sources in Chishmy settlement (HQ = 1.84), Burikazgan village (HQ = 1.10), Karamaly settlement (HQ = 1.78), Tuimazinskii district (HQ = 1.31), Verkhnemancharovo village (HQ = 1.84), Sanzharovka village (HQ = 1.20), and Novoabdullino village (HQ = 2.40).

Acceptable (permissible) levels of non-carcinogenic health risks have been established when estimating effects produced by toxicants on other organs and systems in the body (the genitourinary system, kidneys, nervous system, and developmental processes).

We have assessed carcinogenic health risks associated with exposure to carcinogenic pollutants (lead, cadmium and hexavalent chromium) in drinking water from non-centralized water supply sources. As a result, the greatest carcinogenic threat has been established to be posed by water sources located in Alekseevka settlement (CR = 7.7E-05) and Ishparsovo village (CR = 6.2E-05). Hexavalent chromium identified in water from these sources creates an alerting individual carcinogenic risk (more than 1 case per 1000 people).

Levels of the total carcinogenic risk associated with cadmium and lead in underground water are within permissible (acceptable) ranges. Thus, in Avdon settlement, the total carcinogenic risk is equal to 2.4E-06 (2.4 cases per 1 million people); Bachurino settlement, 3.7E-06 (3.7 cases per 1 million people). The major contribution is made by cadmium. The lowest total carcinogenic risk associated with lead in drinking water is equal to 4.4E-07 and has been established for a well located in Chishmy settlement.

Our analysis of data obtained by monitoring of water quality in centralized drinking and household water supply systems has revealed that water supplied to population in most analyzed areas, in general, conforms to sanitary-epidemiological requirements. Elevated water hardness is the only exclusion; it has been identified in some settlements: Zubovo (up to 1.2 MPL), Chishmy (up to 1.8 MPL), Buraevo (up to 1.11 MPL) and Avdon (up to 1.3 MPL).

Water smell in distribution networks is within its safe standards ranging between 0 and 2 scores. Such indicators as ‘color’ and ‘turbidity’ have also been within safe levels for the last 5 years.

Total mineralization as an indicator describes levels of chemicals (non-organic salts, organic compounds) dissolved in water. On average, its levels have been within its permissible range equaling 400–700 mg/l, the MPL being 1000 mg/l. Solid residue amounts have been reaching this maximum permissible level (976 mg/l) in some periods only in the distribution network in Avdon settlement.

Levels of nitrates (NO_{2}-) identified in the distribution network of Chishmy, Zubovo, and Iglino settlements vary between 0.006 and 0.009 mg/l, which is several hundred times as low as the MPL (3.0 mg/l). Levels of nitrates have been established to be below the limit of detection (0.003 mg/l) in other analyzed settlements (Alekseevka, Roshchinskii and Buraevo settlements).

Levels of nitrates (NO_{3}-) in drinking water identified at all sampling points have been considerably lower than the relevant safe standard (45.0 mg/l) and equaled 1.9–7.2 mg/l.

We should also note that centralized drinking water supply systems are very well protected from introduction of pesticides (hexachlorocyclohexane, 2,4-dichlorophenoxyacetic acid, DDT and simazine). Although plant growing is quite intensive in the analyzed areas (vegetable growing, grains and legumes), pesticides have not been identified in drinking water.

Levels of other hazardous carcinogens identified in water have been lower than maximum permissible ones and therefore they do not create unacceptable health risks.

Our calculations of likely carcinogenic and non-carcinogenic health risks caused by chemicals in water from centralized water supply systems give evidence of their levels being insignificant, either permissible or minimal.

Epidemiological safety of water from centralized drinking water supply systems in the analyzed settlements is confirmed by bacteriological tests aimed at estimating such indicators as total coliforms, total bacterial count, and Escherichia coli. The results give evidence that the foregoing microorganisms are absent.

According to our findings, water from centralized water supply systems, as opposed to non-centralized water sources, is more protected from harmful chemical and biological effects and, consequently, is more eligible for being used by people as drinking water.

The results obtained in this study have given grounds for developing hygienic recommendations and targeted activities aimed at reducing human impacts on water objects and improving drinking water quality in those areas in the republic where agricultural

Table 5

Substantiation of the necessity to develop hygienic measures for making management decisions aimed at providing safe household and drinking water supply in agricultural areas (exemplified by Bashkortostan)

Water use objects	Unfavorable factors associated with water use			
	Water being unsafe per sanitary-chemical indicators*			Water being unsafe per sanitary-microbiological indicators*
	Higher than MPL, times		Health risk level in conformity with the Guide R 2.1.10.3968-23	
	1.1–4.9 times	5 times or more		
Non-centralized drinking water sources	Ni, Hg, Mn, Ca, Mg, $H_{total.}$	NO_3, Fe	High (HI > 6.0; CR > 1.0E-04)	TBC, SRCS***, E. coli, Citrobakter spp., BCAII****
Centralized drinking water sources	$H_{total.}$	No	Permissible (HI < 3.0; CR < 1.0E-05)	No
Water objects used for household and recreational needs	Mn, Fe, OP**, SO_4	Hg, Ni	Permissible (HI < 3.0; CR < 1.0E-05)	TCs, E.coli, enterococci, BCAII****

Note: * means per SanPiN 1.2.3685-21 Hygienic standards and requirements to providing safety and (or) harmlessness of environmental factors for people; **OP is for oil products; ***SRCS, sulfate-reducing clostridia spores; ****BCAII, bacterial causative agents of intestinal infections.

production is well developed. We have created a list of priority pollutants occurring in water from various water sources (Table 5).

The list has been sent to relevant bodies and organizations responsible for monitoring of water quality in water objects so that they can adjust the existing systems for monitoring and control in areas where agricultural enterprises, which are subject to mandatory control, are located.

Obviously, the system for protection of water objects in agricultural areas in Bashkortostan should contain some measures aimed at mitigating human-induced pollution, effective and control and prediction of pollution levels, relevant and effective decisions that help eliminate possible large-scale pollution, and providing safe water use. The system should include the following items:

– organizing automated monitoring of surface waters for recreational use (the Belaya River in Sterlitamakskii and Ufimskii districts, Dema River in Chishminskii district, Chermasan River in Chekmagushskii district, Kiganak River and Asava River in Sterlitamakskii district, Miyaki River in Miyakskii district, Aslykul' Lake) and optimizing laboratory control of water use safety performed by water suppliers and surveillance authorities;

– conducting regular scheduled inspections to check occurrence of groundwaters, their levels and quality in areas where sanitary-epidemiological requirements have been established to be violated (Alekseevka, Avdon, Tsvety Bashkirii, Zubovo, Bachurino settlements and villages in Ufimskii district; Roshchinskii, Ishparsovo, Burikazgan, Yuzhnoe, Begenyashskoe, Kantyukovka settlements and villages in Sterlitamakskii district; Chishmy, Novoabdullino, Sanzharovka settlement and villages in Chishminskii district, Buraevo settlement in Buraevskii district, Verkhnemancharovo settlement in Ilishevskii district, Tuimazy settlement in Tuimazinskii district);

– selecting a place to locate a water intake facility based on geological and hydrogeological data and results obtained by sanitary inspections of a neighboring area performed by authorized experts. A place where a water intake facility is to be built should be located in an unpolluted area not less than 50 meters up the ground water flow from the existing or potential pollution sources: dump wells, outdoor toilets, warehouses for storing fertilizers and pesticides, local enterprises, sewage systems, dumps, and cattle burial grounds;

– organizing sanitary protection zones around water intake facilities;

– systemic purification, washing and, if necessary, preventive disinfection of engineering communications (especially after emergencies) and / or timely replacement of water supply networks. In case emergencies or technical violations occur at water supply networks resulting in drinking water quality deterioration, water supply network owners (juridical or physical persons) should immediately take all necessary measures to eliminate them and inform Rospotrebnadzor institutions about such situations. In case chemical pollution persists in drinking water, a decision should be made to liquidate a water intake facility or non-centralized water supply source;

– orientating social-hygienic and environmental monitoring towards measuring priority indicators;

– creating a system for effective management as regards water supply in rural areas, a system of government responsibilities and actions aimed at providing safe water to rural communities including additional treatment facilities to make drinking water safer for consumers and additional funds allocated for investment projects aimed at developing water supply networks;

– creating an analytical database on the actual situation with water supply in rural areas;

– conducting a comprehensive inventory of water supply networks in rural areas involving estimation of their operating conditions and drinking water quality;

– developing local targeted programs and mandatory implementation of activities within the existing Clean Water municipal programs when developing, building, reconstructing and repairing water supply networks and sewage systems in rural settlements;

– developing and approving industrial control programs and plans of laboratory tests to check quality of drinking water supply. Juridical and physical persons who perform this industrial control should submit a report (every month or quarter), which covers laboratory research programs and is aimed at informing relevant Rospotrebnadzor institutions about cases when water quality has been established to not conform to safe standards;

– organizing a social service for maintaining and repairing water supply networks, wells and water treatment facilities in rural areas in the republic. Any facility is prohibited for operation without a contract on maintenance and repairing;

– providing field workers and workers employed at animal husbandry farms with bottled drinking water;

– providing socially significant objects (schools, preschool children facilities, hospitals etc.) with on-premise water treatment facilities;

– providing rural settlements with drinking water reserves;

– organizing a system for sanitary education for rural residents covering safety of household and drinking water supply.

The following measures are still relevant as secondary prevention: achieving greater healthcare activity of population and creating a culture of health protective behavior; making healthcare services more qualitative and available in rural areas; active involvement of rural residents in sanitary-hygienic programs aimed at preventing morbidity and mortality due to their leading causes.

Conclusion. Therefore, our study has shown that the existing water supply in rural areas cannot fully guarantee sanitary-epidemiological safety and harmlessness for people's health. Health risks are higher than their permissible levels and obviously it is necessary to develop hygienic measures aimed at making relevant management decisions on improving household and drinking water supply in rural areas.

The following ways can be used when selecting an optimal strategy for health risk mitigation:

– a considerable limitation imposed on disposal of hazardous chemicals into water areas achieved by improving and updating agricultural production technologies and equipment;

– creating and developing a system for biogeochemical barriers within agricultural landscapes and agricultural ecosystems to prevent toxicants from migrating to water supply sources;

– purifying soils by targeted growing and subsequent processing of plants (cultures) capable of accumulating heavy metals, pesticides and other hazardous chemicals;

– organizing and conducting medical and preventive activities in areas considered unsafe per sanitary and epidemiological indicators until health risks decline to their permissible levels.

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Research article

ASSESSING AND RANKING OF BROWNFIELDS PER HEALTH RISK CRITERIA: EXPERIENCE GAINED IN THE PERM REGION

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Everywhere objects of accumulated environmental damage (brownfields) pollute surrounding areas and create elevated incidence rates among population. The necessity to establish an order for elimination of such objects is a primary task set within the General Cleaning Federal Project.

The aim of this study was to assess and rank regional brownfields per their hazards for people's lives and health in order to establish the order for their elimination.

Human health risk assessment under exposure in brownfield-influenced areas was conducted by experts of the Center for Hygiene and Epidemiology in the Perm region in accordance with the Rospotrebnadzor's certified methodology based on the fuzzy set theory. Forty to fifty indicators were estimated for each object considering specific features and types of brownfields. The analysis covered 29 objects located in the Perm region. Background materials were examined on each object; overall, 1100 additional laboratory tests were performed to assess quality of environmental objects (ambient air, soils, natural and drinking water.

According to the results obtained by the complex assessment, 4 brownfields were ranked as 'high risk objects' (R = 0.75÷0.62); 16 were ranked as 'medium risk objects' (R = 0.51÷0.41); 9 were ranked as 'moderate risk objects' (R = 0.39÷0.25). Among the identified high risk objects, three were represented by industrial waste landfills of mining and chemical enterprises; one was an unregulated dump. High risk objects were characterized with substantial volumes of accumulated wastes of formed economic activities, long existence period and unregulated effects on the environment; they were located within settlements where safe standards for the quality of the environment were violated in residential areas per indicators, which were typical brownfield markers.

Medium and moderate risk objects were located in small settlements or beyond their boundaries and safe standards for the quality of the environment were not violated in residential areas.

Data on health risks and priorities for funding and implementing activities aimed at eliminating objects of accumulated environmental damage were submitted to Rospotrebnadzor and executive authorities of the Perm region.

Keywords: *brownfield, General Cleaning Federal Project, health risk criteria, categorizing, ranking.*

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Wastes, which were created by former economic activities and have existed for a long time, are an uncontrolled source of pollution. They pose hazards for environmental objects and the human environment as a whole. Long-term unregulated pollution of soils, ambient air, and natural water objects, drinking water sources included, is bound to affect human health [1–5].

Issues related to identifying, assessing and eliminating objects of accumulated environmental damage (brownfields) are common for many developed countries; efforts to resolve them have been made over decades. Since 90ties last century, Germany, Denmark, the Netherlands and other countries have started to actively implement relevant activities aimed at identifying brownfields and eliminating them [6–11]. Countries that have accumulated useful experience in eliminating brownfields usually follow several basic principles: first, an area should be examined to detect any hazardous chemicals; next, actual harm or a threat of harm should be estimated; last, cause-effect relations should be established between revealed harm and economic activities performed by an economic entity[1]. If an owner or a former owner or a brownfield is known, they are made to take necessary measures to eliminate environmental damage at their expense. In case an owner is not known, the responsibility for eliminating environmental pollution belongs to regional or federal authorities.

Everywhere, priority in redevelopment of polluted areas is given to the most hazardous objects with most detrimental effects on the environment and human health [10–12]. To emphasize how relevant the issue is and to demonstrate what great efforts are taken by state authorities to provide safety for citizens, legislation in some countries stipulates creating and maintaining web-sites and registers of brownfields [11, 12].

Some experts from the World Bank believe that the issues related to brownfields are as acute and large-scale in Russia as they are in the USA[2], where Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (Law on Superfund) has been valid since 1980[3]. The Law is supplemented with the Superfund Amendments and Reauthorization Act (SARA)[4]. The document establishes the rules and procedure for assessing brownfields, makes it possible to estimate caused harm and establish the most polluted areas in the country.

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

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[1] Directive 2004/35/CE of the European Parliament and of the Council of 21 April 2004 on environmental liability with regard to the prevention and remedying of environmental damage. *An official website of the European Union*. Available at: https://eur-lex.europa.eu/eli/dir/2004/35/oj/eng (February 04, 2025); Environmental Liability Directive Guidelines. Denmark, The Environmental Protection Agency and the Agency for Spatial and Environmental Planning, 2012; Guidelines for Part 17.2 of the Dutch Environmental Management Act: measures in the event of environmental damage or its imminent threat. The Netherlands, 2008.

[2] Proshlyi ekologicheskii ushcherb v Rossiiskoi Federatsii [Past Environmental damage in the Russian Federation]. *World Bank, Department for Sustainable Development, European and Central Asia region*, May 2007, pp. 39. Available at: http://expert.gost.ru/EC/DOC/PECU.pdf (February 04, 2025) (in Russian).

[3] Superfund: CERCLA Overview. *US EPA*. Available at: https://www.epa.gov/superfund/superfund-cercla-overview (February 04, 2025).

[4] The Superfund Amendments and Reauthorization Act (SARA). *US EPA*. Available at: https://www.epa.gov/superfund/superfund-amendments-and-reauthorization-act-sara (February 04, 2025).

[5] O vnesenii izmenenii v otdel'nye zakonodatel'nye akty Rossiiskoi Federatsii: Federal'nyi zakon ot 3 iyulya 2016 g. № 254-FZ [On making alterations into certain legal acts of the Russian Federation: The Federal Law issued on July 3, 2016 No. 254-FZ]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_200513/ (February 06, 2025) (in Russian).

The Federal Law "On Environmental Protection" regulates issues related to discovering, evaluating, accounting and eliminating brownfields[6]. The Federal Project titled Elimination of Hazardous Objects is being implemented in the country to resolve this long-term issue; it envisages profound analysis of each such object and assessment of its influence on environmental objects, people's lives and health[7]. Inclusion of effects produced by brownfields not only on the environment but also on people's lives and health is substantiated in the Project by multiple research works and convincing evidence [1, 5, 13, 14]. Following the results obtained by examining and assessing brownfields, their step-by-step elimination is expected considering ranks assigned to them according to their hazards and established priorities.

Results of health risk assessment are considered together with ecological criteria and this allows covering all aspects of negative outcomes appearing due to brownfields and making a well-grounded decision as regards priorities in allocating funds and implementing measures for elimination of such objects.

At present, the State Register of Brownfields contains data on more than 3.5 thousand of such objects; they are of various types and origins and have existed for different periods of time. Several objects are located in the Perm region. They are former industrial sites, deserted mines, ownerless disposal sites for solid and liquid wastes, buildings and constructions not in use and partially demolished and household waste landfills, which are no longer exploited[8].

The aim of this study was to assess and rank regional brownfields per their hazards for people's lives and health in order to establish the order for their elimination.

Materials and methods. The research objects were 29 brownfields located in the Perm region: 18 exhausted sections of a coalfield, 2 land spots polluted with oil products, 4 solid household and / or industrial waste landfills, 3 wood waste heaps, 1 ash heap, and 1 industrial sludge pit.

All brownfields located in the region were divided into the following types fixed in the Russian legislation: a) solid waste disposal sites; b) liquid chemical waste disposal sites; c) polluted areas.

Effects produced by the analyzed brownfields on people's lives and health were assessed in conformity with the Methodology for Assessing Effects of Brownfields on Citizens' Lives and Health approved by the Rospotrebnadzor's Order issued on November 27, 2023 No. 851[9].

Instruments described in the methodology are based on the fuzzy set theory and allow considering any sets of numeric and logical variables [15]. Each brownfield type was estimated using a set of indicators typical for such objects (not less than 40 indicators for each brownfield type). We considered those indicators that could both directly and indirectly shape the quality of the environment and, accordingly, affect human health (hazardous chemicals in wastes, protective barriers around a brownfield, proximity to drinking water sources, hazardous chemicals typical for a brownfield detected in ambient air, water, soils in residential areas, etc.)

Scales grading a hazard level for each indicator (from low to very high) were used to estimate influence exerted by each analyzed

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[6] Ob okhrane okruzhayushchei sredy: Federal'nyi zakon ot 10.01.2002 № 7-FZ (poslednyaya redaktsiya) [On Environmental Protection: the Federal Law issued on January 10, 2002 No. 7-FZ (the latest edition)]. *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_34823/ (February 06, 2025) (in Russian).

[7] General Provisions: the Statute on the Ministry of Natural Resources and Environment of the Russian Federation. *Ministry of Natural Resources and Environment of the Russian Federation*. Available at: https://www.mnr.gov.ru/en/ (February 06, 2025).

[8] O sostoyanii i ob okhrane okruzhayushchei sredy Permskogo kraya v 2023 godu [On the state and protection of the environment in the Perm region in 2023]: the State Report. Perm, Ministry of Natural Resources, Forestry and Ecology of the Perm region, 2023, 112 p. (in Russian).

[9] Metodika osushchestvleniya otsenki vozdeistviya ob"ektov nakoplennogo vreda okruzhayushchei srede na zhizn' i zdorov'e grazhdan [Methodology for Assessing Effects of Brownfields on Citizens' Lives and Health]. Moscow, Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2023, 57 p. (in Russian).

indicator on human health. Indicators were combined in groups and the weighting coefficient was established for each group taking a brownfield type into account (v_j): the general profile of a brownfield (v_j = 0.10÷0.15); climatic parameters (v_j = 0.10); spatial characteristics (v_j = 0.30÷0.40); geological and hydrological properties of a given area (v_j = 0.15÷0.35); indicators describing the quality of the environment in a given area (v_j = 0.10÷0.40).

The total health risk per all indicator groups (R) was calculated per the following formula:

$$R = \sum_j R_j v_j , \quad (1)$$

where R_j is the health risk caused by the j-th indicator group; v_j is the weighted contribution of the j-th indicator group to the total health risk.

The calculated risk level was matched with a relevant scale range, the score estimate of which is used in the overall brownfield assessment and its subsequent ranking (Table 1).

The first stage in assessing effect of brownfields on people's lives and health in the Perm region involved examining background materials (project documents, results of brownfield assessment performed by Rosprirodnadzor, etc.). Based on the initial data, programs of additional laboratory measurements were developed and implemented in order to estimate the quality of the environmental components in an area influenced by a brownfield and the closest residential area.

Points where instrumental measurements were taken were located at outer boundaries of brownfields and in the closest residential areas. All tests were conducted by the accredited test laboratory center of the Center for Hygiene and Epidemiology in the Perm region using only certified measuring techniques.

More than 100 laboratory tests were conducted at each point for instrumental research to measure chemical, microbiological, and radiological factors in order to cover all aspects of effects produced by brownfields on people's lives and health.

Upon completion of data analysis, the results were fed into program modules that implemented the mathematical apparatus of the approved methodology. Health risk levels and their criterion scores were calculated for each analyzed brownfield.

Results and discussion. The test results have revealed that practically all analyzed brownfields are unsafe for the environment and pose potential threats for people's lives and health. Thus, 19 brownfields out of analyzed 29 are located directly within settlements, starting from small urban ones (exhausted sections of coal-fields) to the regional center (solid household waste landfills). Some brownfields have been acting as pollution sources for a very long time, up to several decades. Thus, effusions of acidic mine waters have been polluting soils and water objects in

Table 1

Scale ranges for health risk categories and score estimate of health risk

Scale indicator	Health risk categories				
	Low	Moderate	Medium	High	Very high
Range	(0; 0.25]	(0.15; 0.45]	(0.35; 0.65]	(0.55; 0.85]	(0.75; 1.0]
Mean range value	0.125	0.300	0.500	0.700	0.875
Score estimate[10]	0	1	2	2.3	3

[10] O vedenii gosudarstvennogo reestra ob"ektov nakoplennogo vreda okruzhayushchei srede: Postanovlenie Pravitel'stva RF ot 23.12.2023 № 2268 (s izmeneniyami na 14 marta 2024 goda) [On keeping the State Register of Brownfields: the RF Government Order issued on December 23, 2023 No. 2268 (the latest edition as of March 14, 2024)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1304418172 (February 04, 2025) (in Russian).

neighboring areas for 24–60 years. For more than 20 years, wood waste heaps of closed pulp and paper productions and food processing plants have been the reason for chemicals penetrating water objects by migration of pollutants into subterranean and storm waters, ambient air, and soils. It should be noted that only one object (a sludge pit of a former chemical plant) out of 29 analyzed brownfields has a protective barrier for partially preventing and / or slowing down penetration of chemicals into the environment.

Masses and volumes of wastes accumulated due to former economic activities differ considerably, from 2 to 812 thousand tons and from 4 to 68 thousand m^3. Practically all brownfields contain chemicals able to produce carcinogenic, mutagenic, embryotoxic or reprotoxic effects.

Brownfields located close to water objects and / or agricultural lands are extremely hazardous as regards their potential effects on human health. Thus, 10 brownfields (34 % of all analyzed ones) are located in close proximity to water objects, less than 50 meters away from shore lines of rivers or ponds, including those used as drinking or household water sources or as recreational areas. One of such objects is located 5 meters away from water and in the second belt of drinking water intake created to supply water to a town with its population of approximately 60 thousand people.

The situation is aggravated further by small occurrence depth of subterranean waters; background data on bedrocks are available for some objects and according to them subterranean waters occur at a depth not more than 2 meters below the foundation of an object. This poses a threat that pollutants could penetrate the upper water-bearing horizon and spread over the whole area.

More than a half of all analyzed brownfields have agricultural lands in areas influenced by them. This creates a threat that certain chemicals, including mobile phases of metals, could migrate into plants used as raw materials for food products or forages.

Hazards and threats identified by analyzing background materials on the examined brownfields have been confirmed by instrumental measurements of the environment quality.

Chemical pollution of the environment is established as a main health risk factor in areas influenced by brownfields. Such pollution is especially typical for industrial brownfields. To illustrate the point, Table 2 provides the results obtained by instrumental tests of the chemical structure of soils in an area influenced by an ash heap of a former metallurgic plant (28 test sites and 2 background sites). The object is located 5 meters away from the shore line of a water reservoir (a pond in the Lysva River). The closest residential area is located 215 meters away from the ash heap. A gardening association is located 125 meters away from the brownfield boundary.

Obviously, soils in an area influenced by this brownfield are heavily polluted with metal compounds, including their mobile phases, oil products, and anion-active surfactants. Identified chemicals are hazardous since they can affect human health. Lead, cadmium, nickel, and arsenic compounds are established carcinogens. Concentrations of these chemicals identified in some soil samples taken in the nearest settlement are by many times higher than the background levels: lead, up to 18.5; nickel, up to 9.7; arsenic, up to 5.8; cobalt, up to 4.8 times. Compounds of mercury, a hazardous toxicant, have been established in concentrations up to 33.6 times higher than the background level.

Soil pollution near the water object leads to water pollution as well. Thus, safe standards have been found to be violated in the water from this pond located in the settlement per levels of lead, mercury, oil products, and other chemicals typical for the brownfield (up to 2 MPL).

Any violations of safe standards for chemical contents in ambient air have not been established in the area influenced by this brownfield; however, significant concentrations have been detected for such chemicals as nickel, benzo(a)pyrene, chromium, cobalt, lead, and zinc compounds, which allows

Table 2

Chemicals detected in soil in an area influenced by an ash heap of a former metallurgic plant and potential negative health effects

Indicator	Level, mg/kg			Potential negative health effects
	Mean value	Maximum	Permissible level (background)	
Oil products	741 ± 223	1480	140 ± 42	Carcinogenic effects, affects respiratory organs and the nervous system
Anion-active SAS	3.69 ± 1.23	6.0	2.70 ± 0.90	Affects the nervous system
Aluminum	7731 ± 2275	18766	5093 ± 1732	Affects the nervous system and the liver
Mercury	0.92 ± 0.48	3.02	0.09 ± 0.05	Affects the nervous system, development and kidneys
Copper	577 ± 143	1838	51 ± 16	Affects the cardiovascular system, nervous system and respiratory organs
Zinc	1399 ± 350	4408	142 ± 36	Affects the immune system and blood
Manganese	2922 ± 584	5042	994 ± 199	Affects the nervous system
Lead	484 ± 121	1091	59 ± 18	Carcinogen. Affects the nervous system, blood, development, endocrine system, etc.
Nickel	162 ± 41	330	34 ± 9	Carcinogen. Systemic harm
Cadmium	7.68 ± 2.62	21	3.8 ± 1.3	Carcinogen. Affects the kidneys
Cobalt	3.32 ± 1.37	14	2.9 ± 0.9	Carcinogen. Affects the endocrine system
Arsenic	1.15 ± 0.58	1.74	0.30 ± 0.15	Carcinogen. Affects development cardiovascular system, nervous system, etc.

assuming that people living in adjoining areas are exposed to heavy metals in various environmental objects.

High levels of soil pollution with heavy metals have also been found in an area influenced by a solid household waste landfill located in Perm (Table 3).

Soil pollution in the area influenced by this brownfield occurs due to absence of any geological-technical constructions (no barriers or waterproofing screens). Therefore, chemical concentrations established directly in the area influenced by the brownfield are above permissible levels as regards such chemicals as mercury (32.5 times higher), copper (8.32 times), lead (4.75 times), oil products (3.33 times), nickel (up to 2.45 times), and zinc (up to 1.29 times).

Significant chemical hazard posed by industrial brownfields is also confirmed by the data describing quality of environmental objects in an area influenced by a sludge pit for solid industrial wastes (Table 4).

Water objects in the region, which are located in areas influenced by various brownfields, are polluted with a whole set of common and specific chemicals in concentrations substantially higher than safe levels: magnesium, up to 190 MPL; hydroxybenzene, up to 160 MPL; manganese, up to 20.0 MPL; benzo(a)pyrene, up to 19.8 MPL; mercury, up to 19.8 MPL; lead, up to 14.9 MPL; chlorides, up to 2.73 MPL; iron, up to 8.33 MPL; ammonia, up to 11.50 MPL; cadmium, up to 4.80 MPL; sodium, up to 2.93 MPL; sulfates, up to 2.70 MPL; chromium, up to 2.16 MPL; formaldehyde, up to 1.12 MPL.

Safe standards for environmental objects have been established to be violated per microbiological parameters in areas influenced by brownfields with accumulated household or industrial wastes and / or biodegradable organic wastes. Thus, soils in areas where solid household waste landfills are located within settlements or in close proximity to them contain elevated levels of total coliforms, up to

Table 3

Quality of environmental objects in an area influence by unregulated dump

Indicator	Measuring units	Value		
		Mean	Maximum	Permissible (MPL / norm / background)
Oil products	Mg/kg	143 ± 35.8	200	60.0 ± 24.0
Copper	Mg/kg	205 ± 51.3	308	37.0 ± 11.0
Mercury	Mg/kg	0.036 ± 0.009	0.13	0.004 ± 0.001
Zinc	Mg/kg	50.3 ± 12.6	62	48.0 ± 14.0
Lead	Mg/kg	31.8 ± 8.0	48	10.1 ± 3.0
Nickel	Mg/kg	24.5 ± 6.1	49	20.0 ± 5.0

Table 4

Quality of environmental objects an area influenced by a sludge pit of a former chemical plant

Indicator	Measuring units	Value		
		Mean	Maximum	Permissible (MPL / norm / background)
Soil in an area influenced by a brownfield and located within the city boundary				
Oil products	Mg/kg	1017 ± 308	8040	86.7 ± 30.7
Nitrites	Mg/kg	0.271 ± 0.11	0.52	0.193 ± 0.08
ASAS	Mg/kg	108.92 ± 29.99	547	4.95 ± 1.50
Copper	Mg/kg	353 ± 68.5	893	2.23 ± 0.433
Chromium	Mg/kg	3.132 ± 0.782	6.6	1.563 ± 0.393
Vanadium	Mg/kg	70.0 ± 21.1	118	34.3 ± 12.67
Sulfates	Mg/kg	620.9 ± 155.2	2193	14.6 ± 3.65
Water in a surface water object within the city boundary (500 meters downstream form the brownfield) and at the point with its assumed highest influence				
Oil products	mg/dm^3	0.16 ± 0.040	0.27	0.05 ± 0.01
Nitrite-ion	mg/dm^3	0.202 ± 0.04	0.230	0.08 ± 0.02
Copper	mg/dm^3	0.052 ± 0.013	0.080	0.010 ± 0.002
Chromium	mg/dm^3	0.037 ± 0.010	0.072	0.020 ± 0.005
Vanadium	mg/dm^3	0.003 ± 0.001	0.015	0.001 ± 0.0003
Sulfates	mg/dm^3	861 ± 172	1479	100 ± 25

100 and higher CFU/g (the permissible level is 1–9 CFU/g); enterococci (fecal), up to 100 CFU/g (the permissible level is 1–9 CFU/g). Water in water objects for recreational use, which are located close to such brownfields, has been found to contain *Escherichia coli (E.coli)* in a concentration equal to 130 CFU/100 cm^3 (the permissible level is not higher than 100 CFU/100 cm^3); enterococci, up to 240 CFU/100 cm^3 (the permissible level is not higher than 10 CFU/100 cm^3).

Overall, analysis of background materials and results obtained by instrumental tests has made it possible to assess and rank 29 brownfields per potential health risks for the regional population (Table 5).

Four brownfields, which are located within urban settlements, have been ranked as 'high risk objects' (Table 6). They are characterized with considerable volumes of accumulated wastes, long existence as ‘ownerless objects’, and proximity to water objects used by people.

Three objects do not have banks, barriers or any other protective constructions, which could prevent hazardous chemicals from

Table 5

The results of assessing and ranking brownfields in the Perm region per health risks for the regional population

No.	Brownfield	Risk level (R)	Risk characteristic
1	Ash heap of a former metallurgic plant in water-protection area	0.75	High
2	Household and industrial waste landfill	0.65	High
3	Unregulated dump in Perm	0.64	High
4	Sludge pit of a former chemical plant	0.62	High
5	Wood waste heap of a liquidated pulp and paper production	0.57	Medium
6	Exhausted section of a coal field (mine pit)	0.57	Medium
7	Wood waste dump	0.53	Medium
8	Household waste landfill in Kungur, Perm region	0.52	Medium
9	Soils in a closed settlement polluted with oil products	0.52	Medium
10	Soli household waste landfill	0.52	Medium
11	Exhausted section of a coal field (mine passage)	0.51	Medium
12	Exhausted section of a coal field, mine	0.50	Medium
13	Exhausted section of a coal field, mine	0.49	Medium
14	Soils in a closed settlement polluted with oil products	0.49	Medium
15	Exhausted section of a coal field (mine passage)	0.49	Medium
16	Exhausted section of a coal field (mine passage)	0.49	Medium
17	Wood waste heap	0.48	Medium
18	Exhausted section of a coal field (mine pits)	0.46	Medium
19	Exhausted section of a coal field (pipe passage)	0.45	Medium
20	Exhausted section of a coal field (mine passage)	0.41	Medium
21	Exhausted section of a coal field (mine pit)	0.39	Moderate
22	Exhausted section of a coal field (mine passage)	0.37	Moderate
23	Exhausted section of a coal field (mine shaft)	0.37	Moderate
24	Exhausted section of a coal field (mine passage)	0.36	Moderate
25	Exhausted section of a coal field (well)	0.36	Moderate
26	Exhausted section of a coal field (mine passage)	0.34	Moderate
27	Exhausted section of a coal field (well)	0.33	Moderate
28	Exhausted section of a coal field (mine pit)	0.31	Moderate
29	Exhausted section of a coal field (well)	0.25	Moderate

Table 6

Basic characteristics of brownfields that create high risks for human health

Brownfield	Ash heap of a former metallurgic plant in water-protection area	Household and industrial waste landfill of a former chemical plant	Unregulated dump in Perm	Sludge pit of a former chemical plant
Existence, years	4	12	27	12
Waste volume, thousand m^3	461.29	22.650	177.14	24.411
Square, hectares	34.18	5.78	11.6	1.33
Located within a settlement	yes	yes	yes	yes
Distance from the closest water object, m	5	5	680	18
Chemicals with carcinogenic, embryotoxic, teratogenic and reprotoxic effects in wastes	yes	yes	yes	yes
Depth of subterranean water occurrence, m	1.2	1.0	1.6	0.5
Banks, barrier, derivation canals, etc.	no	no	no	yes
Exposed population, thousand people	60.3	151.3	1049.2	151.3

penetrating environmental objects or keep people away from their territory. Accordingly, these brownfields are sources of chemical dusts and vapors coming from the surface of the accumulated waste mass; they pollute surface and subterranean waters through pollution filtration and wash-out with storm or melted waters, spread of chemical and biological agents by wild animals, etc.

Highly hazardous chemicals are present in wastes accumulated at all these brownfields; these chemicals are identified in the nearest residential areas, sometimes in concentrations higher than the valid safe standards. This creates hazardous levels of exposure for people who reside permanently near the analyzed brownfields (see Tables 2–4).

These brownfields are subject to immediate elimination with subsequent redevelopment of destroyed and polluted soils until the land spots are in a condition allowing their full-fledge use for municipal and regional needs.

Medium and / or moderate risk objects located in the region are mostly small landfills, areas polluted with oil products, and exhausted sections of a former coal-field; they all are located in small settlements or near them. It is noteworthy that safe standards have not been established to be violated in residential areas influenced by many brownfields ranked as medium or moderate risk objects. At the same time, it is still advisable to eliminate them, redevelop soils and recover quality of environmental objects. The matter is even more important due to the fact that most brownfields of the formed coal-field are located in areas, which have high potential for tourism and are actively visited by people living in the Perm region and its guests [16].

Our results are fully consistent with findings reported in similar research works, both domestic and foreign ones. Studies that focus on decision-making as regards elimination of brownfields and subsequent use of redeveloped land spots emphasize the importance and advisability of comprehensive multifactorial analysis of the environment and population health in areas influenced by brownfields (our study has followed the same principle) [17–19]. Some studies confirm that the highest health hazards are posed by long-existing waste deposit sites of former economic activities performed by chemical, petrochemical, metallurgic productions and oil extraction enterprises [20–22]. Microbial pollution identified by examining ownerless landfills of household wastes or mixed household and industrial wastes in the Perm region is confirmed by studies accomplished at similar objects in other areas [23, 24].

It is noteworthy that the hygienic research society in general emphasizes that it is vital to eliminate negative effects produced by brownfields as completely and promptly as only possible, first of all, bearing minimization of health risks in mind [25–27].

Conclusions. Health risk assessment is a powerful instrument for identifying priorities to rank brownfields per their hazards and establishing the order and urgency of their liquidation. It is a mandatory element in brownfield assessment, which allows obtaining more objective results necessary for providing environmental and hygienic safety of the country population.

Out of 29 analyzed and assessed brownfields located in the Perm region, four (14 %) were ranked as 'high risk objects'. These objects are to be eliminated immediately since they all are located within urban settlements in close proximity to residential areas and water objects used by the regional population. Chemical pollution in soils and water objects, including carcinogens, mutagens, and reprotoxic chemicals, as well as microbial pollution of the environment are primary health risk factors.

Medium and moderate risk objects are mostly small landfills, soils polluted with oil products, and exhausted sections of former coal-fields located in small settlements or close to them; safe standards are not violated in residential areas influenced by such brownfields. These objects are to be eliminated according to approved schedules after all health hazards created by high risk brownfields have been eliminated.

It seems advisable to organize specialized medical and preventive aid to people who permanently reside in areas influenced by high risk brownfields for the whole period until these hazardous objects are eliminated and the quality of the environment is brought to conformity with safe standards in all areas previously influenced by such brownfields.

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Research article

THE CHANGES IN ANTHROPOMETRIC INDICES AND NUTRITIONAL STATUS AMONG PRESCHOOL CHILDREN IN A RURAL AREA OF THE RED RIVER DELTA, VIETNAM: A REPEATED CROSS-SECTIONAL STUDY OVER THREE YEARS

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A repeated cross-sectional assessment was conducted over three consecutive years to identify trends in anthropometric indices and nutritional status among preschool children in the Hung Ha district of Thai Binh province, Vietnam.

From 2021 to 2023, data were collected for three distinct samples with a total of 1002 children aged 24–72 months. For children younger than 60 months, the World Health Organization (WHO) 2006 criteria were used to determine the weight-for-age Z-score (WAZ), height-for-age Z-score (HAZ), BMI-for-age Z-score (BAZ), weight-for-height Z-score (WHZ). For children older than 60 age months, the 2007 WHO criteria were used to assess WAZ, HAZ, and BAZ. Significant improvements in weight, height, BMI, and anthropometric Z-scores were observed over the three-year period. While the rates of underweight and stunting declined, the prevalence of overweight and obesity rose significantly, indicating a double burden of malnutrition. This trend appears to originate from socioeconomic changes, increased caloric intake, and reduced physical activity.

The study underscores the need for comprehensive nutritional strategies to address both malnutrition forms, focusing on improving height for balanced and healthy growth among preschool children in rural areas of the Red River Delta.

Keywords: *anthropometric indices, nutritional status, preschool children, cross-sectional study, socioeconomic changes, healthy nutrition strategies, rural area.*

Anthropometric indices play an important role and are used as measures to assess children's physical growth and nutritional status (NS), providing insights into their health and overall development [1]. As the preschool age is crucial for growth and development and serves as the foundation for children's later progress, malnutrition in this early stage, whether undernutrition (underweight, stunted, and wasted) or overnutrition (overweight and obesity), detrimentally affects health and psychology in adulthood [2]. A number of studies have indicated that malnourished children are at a higher risk of diminished physical health, and even obesity in adulthood, while overweight or obese children are more susceptible to early-onset puberty, bone diseases, high blood pressure, metabolic disorders, cancers, and obesity as adults [3, 4]. Therefore, it is essential to assess changes in NS trends and children's anthropometric characteristics during the preschool years to develop effective nutritional strategies at family, school, and national levels.

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Vietnam currently suffers from the double burden of malnutrition, a common nutritional problem in developing countries with the coexistence of both overnutrition and undernutrition [5]. The Red River Delta of Vietnam is a densely populated region with diverse economic contributions from agriculture, industry, and services. However, a disparity in nutritional status between urban and rural children still persists, with a higher prevalence of underweight and stunting in rural areas [6–8]. Hung Ha is a rural district located in the northwest of Thai Binh province, part of the northern Red River Delta, comprising 33 communes and 2 towns. Its economy is largely driven by agriculture, industry, and handicrafts, with a total production value of about VND 23 trillion in 2023, marking a 6 % increase over 2022 (ranking 3rd among 8 districts and cities)[1].

To date, research on NS and anthropometric characteristics in Vietnamese children primarily focuses on central cities or ethnic minorities [9, 10], resulting in a paucity of data on rural areas or those with moderate economic development. Recently, the NS of first-grade students in the Kien Xuong district of Thai Binh province was reported by Pham Quoc Hung [11] but this remained a cross-sectional study on a small sample size. Another longitudinal study by Nguyen Thi Nhan also examined the NS of preschool children in the Vu Xuong district of Thai Binh province, but the changes were observed over only a three-month period [12]. Therefore, this study **aims** to examine the changing trends in anthropometric characteristics and NS of preschool children in Hung Ha district, Thai Binh province over three years (2021–2023) using a large sample size ranging from 24 to 72 age months. The findings of this study may serve as the basis for developing and implementing targeted interventions to enhance the optimal development of preschool children in rural areas of the Red River Delta.

Materials and methods. This repeated cross-sectional study was carried out over three consecutive years from 2021 to 2023 in order to assess trends in anthropometric indices and nutritional status (NS) among preschool children in Hung Ha district, Thai Binh province. The sampling method was cluster-based, representative, and random. Preschool children participating in the study were selected from 10 kindergartens in Hung Ha. All children from these schools were measured for height and weight on the 4th day of the 2nd week of December in 2021, 2022, and 2023, after obtaining written consent from parents or legal guardians.

Exclusion criteria included children with acute or chronic illnesses documented in medical records and under medical care at the time of collecting sample or those receiving treatment for lipid disorders or obesity. Children whose parents or legal guardians did not agree to participate were also excluded.

The anthropometric indices and NS of the children were analyzed and compared after randomly matching the data by age and sex, ensuring consistent sex ratios and age groups over the three years examined. After matching by sex and age, there was a total of 1002 children (aged 23.9–72.4 months, 54.5 % male) included in the final analysis.

Anthropometric measurements were conducted between 9:00 and 10:30 a.m. in a climate-controlled room. Children wore light clothing and were weighed and measured following standard procedures of the National Institute of Nutrition. Weight was measured using an electronic scale with a precision of 100 grams. Standing height was measured using a stadiometer with an accuracy of 0.1 cm.

For children younger than 60 months, the World Health Organization (WHO) 2006 criteria were used to determine the weight-for-age Z-score (WAZ), height-for-age Z-score (HAZ), BMI-for-age Z-score (BAZ), weight-for-height Z-score (WHZ) [13]. For children older than 60 age months, the 2007 WHO criteria were used to assess WAZ, HAZ, and BAZ [14]. These analyses were automatically computed by the WHO Anthro software (for children younger than 60 months) version 3.2.2 and AnthroPlus®

[1] The total production value of the whole district in 2023 is estimated to increase by 6.38 %. *Thaibinh Province Portal*, 2023. Available at: https://s.net.vn/kinh-te-hung-ha (April 12, 2024).

software (for children older than 60 months) version 1.0.4 (Geneva, Switzerland). Table 1 provides the cutoff points of anthropometric Z-scores for classification of children's nutritional status based on the WHO standards.

Statistical tests were conducted using SPSS version 16.0 (SPSS, Chicago, USA), and relevant graphs were generated using Excel. Quantitative variables were assessed for normality and expressed as mean ± standard deviation if they were normally distributed or median (25th – 75th percentile) if not. The Student's t-test was employed to compare the distribution of two normally distributed groups, and the Mann-Whitney U test was employed to compare the distribution of two non-normally distributed groups. Differences in proportions were analyzed using the Chi-square test or Fisher's exact test. A two-tailed p-value of less than 0.05 was considered statistically significant.

Results and discussion. ***Changes in anthropometric indices in preschool children from 2021 to 2023.*** Changes in weight, height, BMI, WAZ, HAZ, BAZ, and WHZ for male children over the three-year period from 2021 to 2023 are presented in Table 2 and Figure 1.

Table 1

Cut-offs for classification of nutritional status for preschool children according to WHO standards

Index	Value	Nutritional status
WAZ	< –3SD	Severe underweight
	< –2SD	Moderate underweight
	from –2SD to 2SD	Normal
	> 2SD	Overweight
	> 3SD	Obesity
HAZ	< –3SD	Severe stunting
	< –2SD	Moderate stunting
	from –2SD to 2SD	Normal
BAZ	< –3SD	Severe wasting
	< –2SD	Moderate wasting
	from –2SD to 2SD	Normal
	> 2SD	Overweight
	> 3SD	Obesity

Table 2

Changes in anthropometric indices among male preschoolers in Hung Ha from 2021 to 2023

Index	2021 (1)	2022 (2)	2023 (3)	$P_{(1)-(2)}$	$P_{(2)-(3)}$	$P_{(1)-(3)}$
Age (months)	48.93 (36.93–60.46)	48.58 (36.03–60.9)	49.45 (36.63–61.0)	0.979[b]	0.968[b]	0.938[b]
Weight (kg)	15.90 (13.50–18.0)	16.5 (14.0–19.0)	17.0 (15.0–19.5)	0.002[b]	0.297[b]	< 0.000[b]
Height (cm)	101.0 (93.0–106.0)	104.5 (97.0–110.0)	103.0 (98.0–110.0)	< 0.000[b]	0.430[b]	0.001[b]
BMI (kg/m²)	15.71 (14.71–16.9)	15.50 (14.41–16.91)	16.01 (15.03–17.46)	0.487[b]	0.011[b]	0.055[b]
WAZ	-0.25 ± 1.08	0.30 ± 1.03	0.40 ± 1.11	< 0.000[a]	0.360[a]	< 0.000[a]
HAZ	-0.69 ± 1.42	0.24 ± 0.99	0.06 ± 1.25	< 0.000[a]	0.120[a]	< 0.000[a]
WHZ	0.18 ± 1.08	0.14 ± 1.16	0.48 ± 1.25	0.762[a]	0.018[a]	0.031[a]
BAZ	0.27 ± 1.10	0.17 ± 1.29	0.52 ± 1.25	0.422[a]	0.009[a]	0.044[a]

Note: [a] Variables are expressed as mean ± standard deviation; *p*-values were obtained from Student's *t*-test; [b] Variables are expressed as median (25th–75th percentile); *p*-values were obtained from the Mann – Whitney *U*-test.

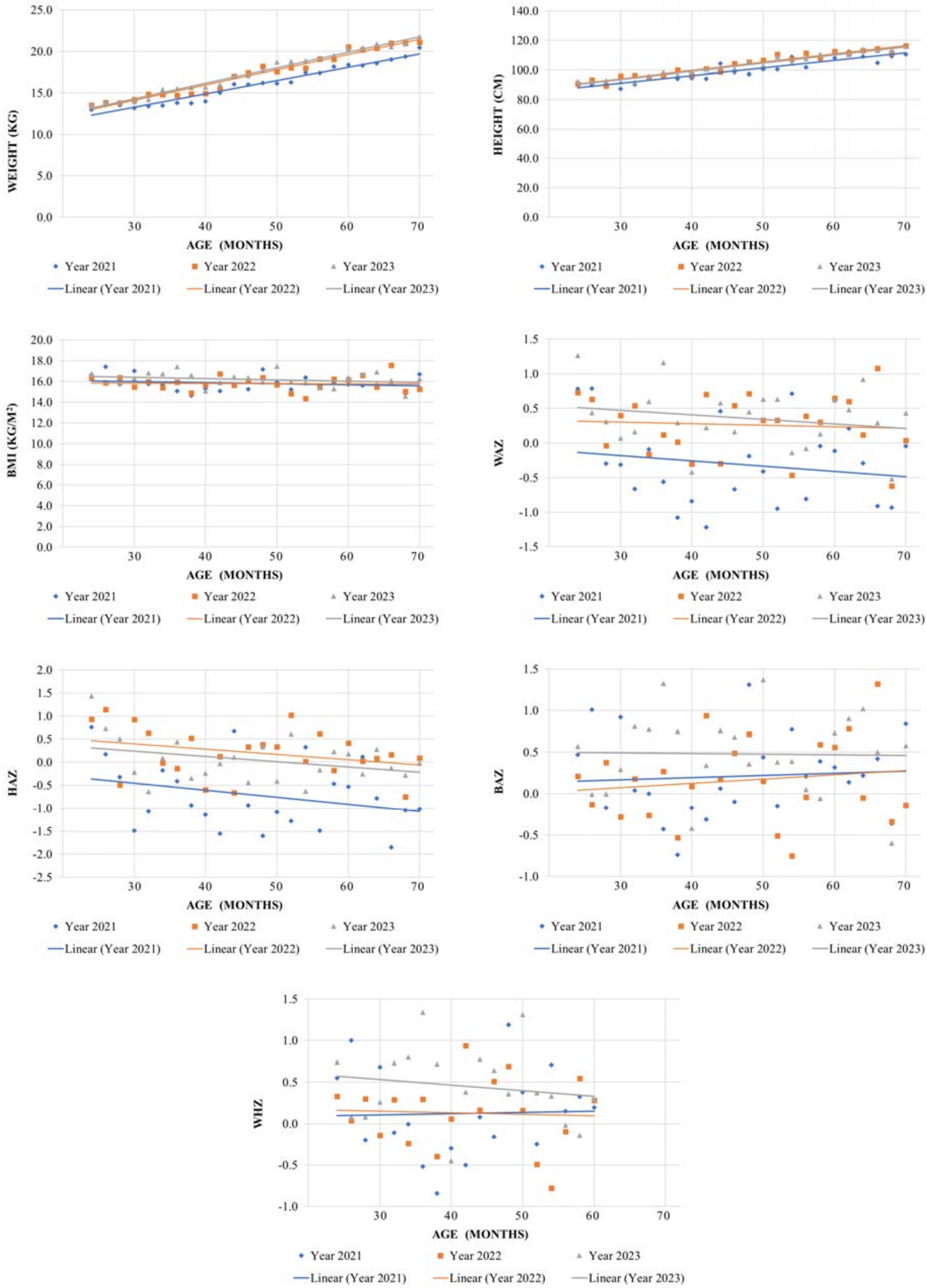

Figure 1. Changes in Weight, Height, BMI, WAZ, HAZ, BAZ, and WHZ by Age
in Male Preschool Children in three survey years

According to Table 2 and Figure 1, the weight, height, and WAZ of male preschoolers in Hung Ha district were higher in 2022 than in 2021 (16.5 kg vs. 15.9 kg; 104.5 cm vs. 101.0 cm; 0.3 SD vs. -0.25 SD, respectively) but no significant difference in these indices between 2022 and 2023 was observed ($P > 0.05$). In contrast, WHZ and BAZ were statistically higher in 2023 than in 2022 and 2021 ($P < 0.05$). For the HAZ, this index was found to be significantly different among three years examined ($P > 0.05$) with the highest value detected in 2022 (0.24 SD) and the lowest in 2021 (-0.69 SD).

The changes in weight, height, BMI, WAZ, HAZ, BAZ, and WHZ indices in female children over the three years from 2021 to 2023 are presented in Table 3 and Figure 2.

Similar to the male children, there were significant increases in weight, height, WAZ, and HAZ from 2021 to 2022 among female children ($P < 0.05$) but not between 2022 and 2023 ($P > 0.05$). By contrast, the WHZ index of female preschoolers was significantly higher in 2023 in comparison to both 2021 and 2022, at 0.55 SD versus 0.17 SD and 0.15 SD, respectively ($P < 0.05$). Notably, BMI and BAZ did not exhibit significant differences across the three years in the female group ($P < 0.05$).

Changes in nutritional status. The prevalence of nutritional status among preschool children, classified by WAZ, HAZ, and BAZ indices, in the three study years is presented in Figures 3, 4, and 5, respectively.

In the present study, there has been a notable increase in the anthropometric indices of preschool children in Hung Ha district from 2021 to 2023. Interestingly, the survey time coincides with the coronavirus disease 2019 (COVID) pandemic and post-COVID periods providing evidence of shifts in the nutritional status of children during and after the wave of COVID-19 in Vietnam.

For boys, the average weight and height, along with their WAZ and HAZ, were the lowest in 2021. These measures showed a significant increase in 2022 and remained stable in 2023 indicating sustained improvement over the initial survey. The proportional growth in weight and height of boys from 2021 to 2022 resulted in no significant year-to-year differences in WHZ and BAZ. However, these two indices exhibited a significant increase from 2022 to 2023 suggesting that weight growth had surpassed height growth during the latter period. This trend can be visualized through the linear regression analyses of WHZ and BAZ depicted in Figure 1. When comparing the changes in weight, height, and BMI by age with the WHO sex-specific growth reference curves [13, 14], the data for 2021 showed that the height growth of preschool boys was still approaching below the Z-score = 0 curve, while the growth in weight and BMI generally fell within the Z-score = 0 threshold. By the years 2022 and 2023, all these curves have

Table 3

Changes in anthropometric indices of female preschool children in Hung Ha from 2021 to 2023

Index	2021 (1)	2022 (2)	2023 (3)	$P_{(1)\text{-}(2)}$	$P_{(2)\text{-}(3)}$	$P_{(1)\text{-}(3)}$
Age (months)	48.83 (36.13–60.68)	49.11 (36.13–60.5)	48.82 (35.37–61.05)	0.969^b	0.931^b	0.899^b
Weight (kg)	15.0 (13.1–16.8)	15.5 (14.0–19.0)	16.5 (15.0–18.35)	0.001^b	0.134^b	< 0.000^b
Height (cm)	97.0 (93.0–105.0)	103.0 (95.0–109.0)	103.0 (96.5–108.5)	< 0.000^b	0.982^b	< 0.000^b
BMI (kg/m²)	15.46 (14.51–16.40)	15.47 (14.39–16.81)	15.70 (14.70–16.93)	0.973^b	0.141^b	0.109^b
WAZ	-0.40 ± 1.06	0.17 ± 0.97	0.33 ± 1.08	< 0.000^a	0.176^a	< 0.000^a
HAZ	-0.80 ± 1.43	0.12 ± 1.10	0.11 ± 1.29	< 0.000^a	0.934	< 0.000^a
WHZ	0.17 ± 1.14	0.15 ± 1.25	0.55 ± 1.21	0.930	0.018	0.016
BAZ	0.14 ± 1.11	0.11 ± 1.26	0.37 ± 1.24	0.823	0.063	0.081

Note: **^{a}** Variables are expressed as mean ± standard deviation; *p*-values were obtained from Student's *t*-test; **^{b}** Variables are expressed as median (25th–75th percentile); *p*-values were obtained from the Mann – Whitney *U*-test.

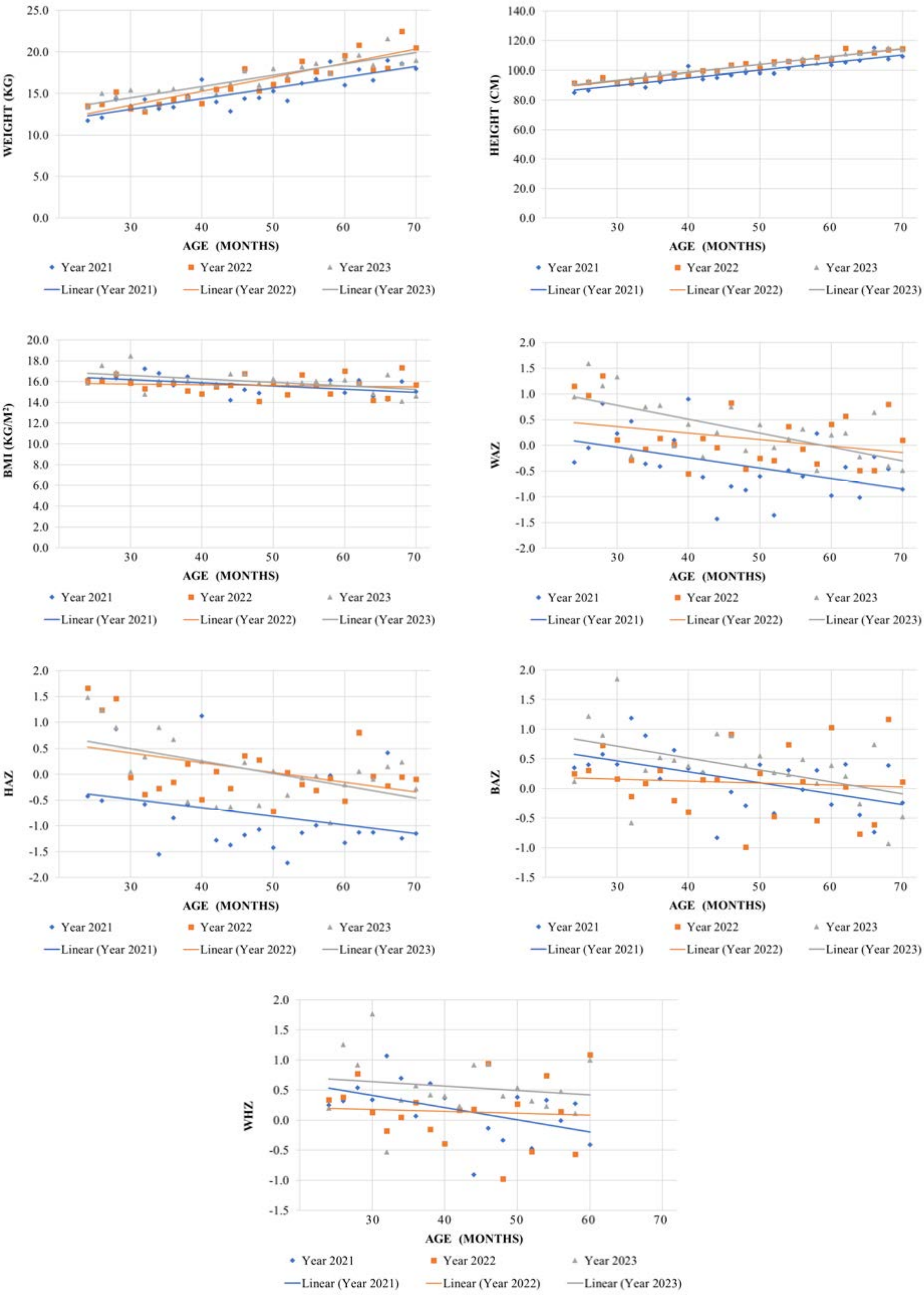

Figure 2. Changes in weight, height, BMI, WAZ, HAZ, BAZ, and WHZ by age in female children in three survey years

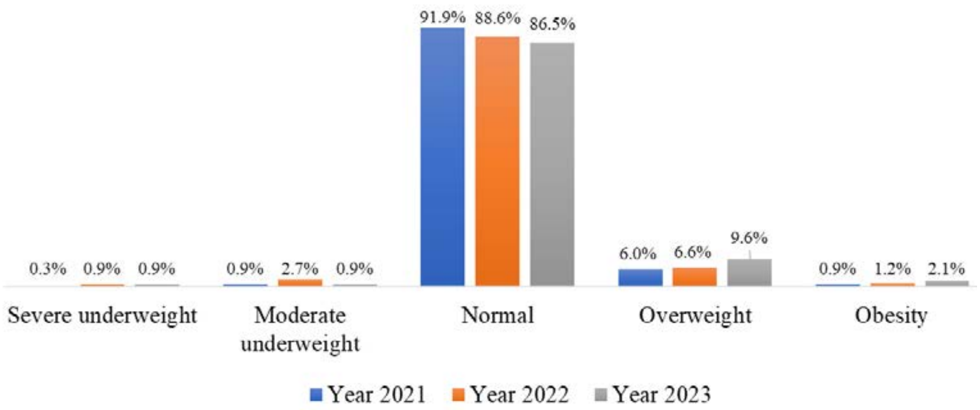

Figure 3. Nutritional status of children classified by WAZ

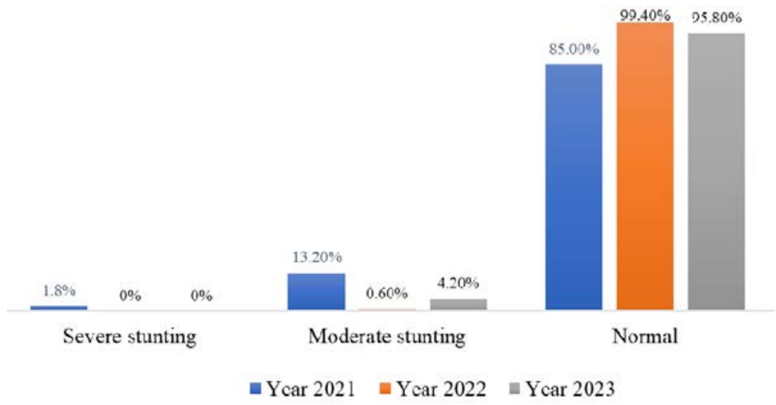

Figure 4. Nutritional status of children classified by HAZ

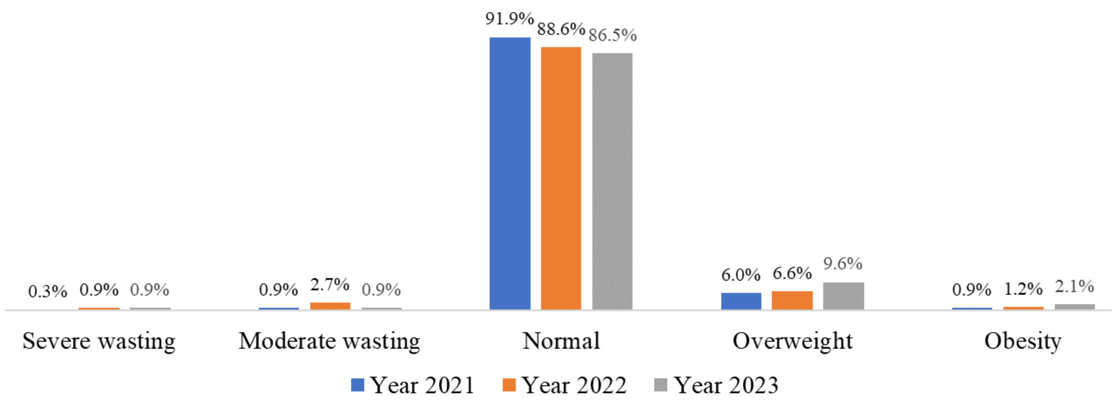

Figure 5. Nutritional status of children classified by BAZ

reached and even surpassed the Z-score = 0 threshold, reflecting an overall enhancement in growth patterns.

For girls, a significant increase in HAZ and BAZ in 2022 compared to 2021 resulted from corresponding improvements in height and weight of children during the same period. Although there were no statistical differences in BMI and BAZ over the three examined years, the notably higher WHZ value year to year indicated a similar trend where weight growth exceeded height growth, albeit less pronounced than in boys. This phenomenon can be explained by the fact that boys eat fast foods and consume sugar-sweetened drinks more often than girls leading to a higher caloric intake [15, 16]. When changes in weight, height, and BMI of female children by age (Figure 2) were compared to WHO growth standards, it was found that curves of height growth and weight growth in 2021 were still approaching below the Z-score = 0 curve, but by 2022 and 2023, all three curves reached or even surpassed the Z-score = 0 threshold [13, 14]. These findings suggest a consistent improvement in the care and nutritional practices for preschool girls in the region. Thus, over the three consecutive years of assessment for both sexes, there was a consistent trend of growth in both weight and height. However, weight growth was more pronounced compared to improvements in children's height, which may reflect the early impact of the nutrition transition resulting from increased caloric intake in their diet [17].

Regarding nutritional status, stunting was the most prevalent form of malnutrition in 2021 (15.5 %) and 2023 (4.2 %), whereas wasting was the most common form in 2022 (3.6 %). Among the three years of assessment, malnutrition rates varied inconsistently across forms. While underweight and stunting rates in 2022 decreased compared to 2021 but rose again in 2023, the wasting rate in 2022 (3.6 %) was higher than in 2021 (1.6 %) and 2023 (1.8 %). This result possibly arises from the interruption of schooling in Vietnamese children during the COVID-19 pandemic. Since all kindergartens were closed in late 2021 and 2022 to implement the social distancing directive, children had to stay at home for a long time and thus did not have any chance to lose weight due to various factors including incorrect diets, increased screen time, decreased physical activity, family and individual stress [18]. During this period of lockdown imposed by the outbreak, many Vietnamese parents were under the misconception that feeding their children more would make them healthy, boost their immunity, and reduce the impact of the disease, thus focusing on providing their children with high-energy meals. As a result, children were less likely to suffer from undernutrition but were at risk of overweight and obesity. In line with this hypothesis, studies in several populations have reported an increase in weight gain among children and adolescents during the COVID-19 pandemic compared with the rate before the pandemic [19–21]. In addition, as the stunting rate in children is assessed based on the height-for-age Z-score, which reflects long-term nutritional deficits, the high prevalence of stunting in this study indicates that children's growth remains affected by socioeconomic constraints; therefore, chronic malnutrition has cumulative effects on this growth[2]. The consistently low wasting rate, in contrast, does not reflect an improvement in socioeconomic conditions or long-term nutritional changes, since this form of malnutrition is assessed based on BAZ, which represents short-term, acute nutritional deficiencies[2].

In contrast to the decrease in the rate of child malnutrition, this study demonstrates a continuous upward trend in the rates of overweight and obesity among preschool children in Thai Binh in recent years. In 2023, overweight and obesity rates classified by BAZ were 9.6 % and 2.1 %, respectively, significantly higher than the corresponding rates in both 2022 and 2021 ($P < 0.05$). According to another study on preschool children of Thai Binh province, the prevalence of underweight stunting, wasting, overweight/obesity in children under 5 of was 12.8 %, 24.3 %, 3.1 %, and 2.5 %, respectively [12]. Compared with our results, the malnutrition rates of children from 2021 to 2023 have decreased remarkably in all three forms, but overweight and obesity rates have also increased. While in 2021 and 2022, the increased rate of overweight and obesity could partly be explained by a sedentary lifestyle and changes in food habits during the COVID-19 pandemic [18], these forms of overnutrition continued to rise in 2023 despite schools reopened and chil-

[2] Sommerfelt A.E., Stewart M.K. Children's nutritional status. Maryland, USA, Macro International Publ., 1994, 47 p.

dren no longer being limited in their play and interaction spaces at this time. This phenomenon can be ascribed to a combination of reasons, in which increased consumption of processed foods, along with the habit of using electronic devices for entertainment (which indirectly reduces physical activity), has contributed largely to the increased risk of obesity in this age group. As indicated by previous studies, Vietnamese children nowadays, particularly in Delta Red River regions, have been affected by the obesogenic environment, which promotes high-energy food consumption while reducing physical activity, thereby increasing sedentary behaviors [22]. In addition, the recent changes in children's nutritional status also resulted from the active implementation of malnutrition prevention programs as well as the improvement of socioeconomic conditions enabling children to be better nourished than before [10].

The present study has some strong points. It is the first to analyze the trends in anthropometric changes in Vietnamese preschool children in a rural area over three consecutive years, a period with numerous changes from both socioeconomic conditions and the influence of the COVID-19 pandemic. As each survey period involves a new sample, the study design avoids bias that might result from participants dropping out in longitudinal studies, and the results are more generalizable to represent the entire population. Despite that, the inability to track changes within individual children over time is a major limitation of this study. Longitudinal studies that follow children over time in order to elucidate the trajectory of growth patterns and the impact of various interventions therefore are suggested.

Thus, this study reaffirms that Vietnamese rural areas continue to bear the double burden of malnutrition. Although there were significant improvements in child nutrition and care, the growing rates of overweight and obesity are alarming. Insights from the present study underscore the need for policy makers to revise current nutritional guidelines and promote community-specific health programs aimed at eradicating malnutrition in all its forms. Nutritional intervention programs for young children must prioritize enhancing height and reducing stunting, which remains a critical issue in child nutrition in Vietnam.

Conclusion. Data from the three-year survey revealed significant improvements in weight, height, WAZ, and HAZ among Vietnamese rural preschool children in 2022 compared to 2021. In boys, there were also significant increases in BMI, BAZ, and WHZ indices in 2023 than in 2022. Regarding nutritional status, stunting remained the most prevalent form of malnutrition among preschool children. From 2021 to 2023, undernutrition rates changed inconsistently across all forms, while rates of overweight and obesity exhibited a constant increase. These changes likely reflect progress in child nutrition and care practices as well as the influence of the COVID-19 pandemic. Nutritional policies, particularly those focused on the prevention of stunting and overnutrition should be developed and implemented to ensure the healthy development of children.

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Research article

ASSESSMENT OF HEALTH RISKS BY WORKING POPULATION AS A FACTOR IN CHOOSING A STRATEGY FOR SELF-PRESERVATION

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The article has aimed to identify and classify behavioral risk-associated strategies of self-preservation among adult working population in urban areas in Russia, perception of health risks taken into account. The research object is represented by people aged 18–68 years who live in three Russian cities with their population beyond 1 million. The empirical basis of the study is quantitative (the method was formalized questionnaire; n = 300) and qualitative data (the method was in-depth interview; n = 17), which have been collected and analyzed within the framework of a mixed methodology per the "additional coverage" type.

Four groups of health risk factors have been studied: living conditions, sanitary and epidemiological, social and natural ones. Health risks have been subjectively assessed by the respondents as a combination of likelihood of negative events and their severity (each indicator was estimated with the range between 0 and 1). Social risk factors (criminal and illegal actions of other people, traffic accidents, terrorist attacks and military actions) have been revealed to be perceived by Russians as the most hazardous to health. Sanitary-epidemiological risks are ranked the second per their significance.

The study identifies specific types of individual self-preservation based on the intention either to reduce risk or avoid it and on the nature of actions (active or passive): acting, avoiding, waiting and adapting. Quantitative data have shown the share of "active" is significantly lower among Russians than that of "passive" (on average 25 % versus 75 %). Passive behavior is caused not only by a low level of knowledge about risks and ways to minimize them but also by Russians not being interested in solving these issues, the desire to shift responsibility for risk management to others (even if they distrust their strengths and capabilities).

It seems advisable to develop and implement a strategy aimed at preventing and controlling health risks, monitoring of subjective risk perception and using its results to raise people's awareness about potential hazards. Rospotrebnadzor, within implementing its functions and powers, should provide comprehensive communication about sanitary-epidemiological and other health risks, group and individual ways and methods to minimize them; this communication should be widely available and easily understood per both its form and contents. This will make for correct choice on self-preservation strategies and, consequently, health promotion among the country population.

Keywords: *health risk, risk assessment, risk perception, living conditions, sanitary and epidemiological factors, social factors, natural factors, risk management strategies.*

Health risk assessment and management is a key trend in healthcare science and policy and in providing sanitary-epidemiological safety of the country population [1]. Health risk identification makes it possible not only to capture potential threats but also to get an insight into their realization as well as possible ways to minimize them. Risk perception and adequate risk assessment create social attitudes associated with individual health-related decisions and specific health-protective behaviors [2, 3].

In the current socioeconomic conditions, special attention is paid to health and self-protective behavior of the employable population. This is extremely relevant considering the actual strategic goals and tasks set in the Russian Federation within the state demographic and economic strategies [4, 5]. Literature analysis established that the major focus of

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attention in studies devoted to health risks for workers was on occupational factors (especially unsafe working conditions, including occupational hazards and hard work)[1] [6–8], environmental pollution [9, 10]; psychological and social factors able to induce stress and emotional strain [11–13]. Some studies investigate such behavioral (internal) health risk factors as smoking, alcohol use, low physical activity, social and psychological issues, and neglect of periodical medical check-ups [14–16]. In other studies, special emphasis is placed on the 'background' for formation of health risks for workers including sanitary-hygienic and socioeconomic conditions as well as the current state of health typical for residents of a given region [17, 18].

Overall, multiple studies give evidence that health of working population is influenced not only by working conditions but also by many other routine factors and threats, which should be given more attention and thought. By now, a certain ground has been created for getting an insight into a complicated picture of working population's health being determined by environmental conditions, housing, a possibility to catch a communicable disease and some other threats. Preservation of the country labor resources requires considerable efforts aimed at mitigating and minimizing health risks. However, it is important to understand that risk minimization is possible only if we consider both its objective (that is, actually considered and calculable risks) and subjective (that is, risk perception and assessment by specific people) components.

The objective component in health risk assessment is based on establishing likelihood of negative consequences; it reflects actual phenomena, processes and aspects of people' life activities [19]. The subjective component in risk assessment, which is in the main focus of the present article, is based on a social attitude influencing estimations of possible losses or benefits and combining monitoring of likelihood of a negative event and severity of its consequences in human mind [20]. In Russian and foreign practice, the level of risk acceptability is, as a rule, determined as low, not higher than a habitual level typical for everyday life. A moderate risk is also determined, which is above the low risk but is not within the critical range; a high level risk is a risk that requires special attention and immediate action. Likelihood of a negative effect can be 'very low' meaning that this event is practically sure to never happen; 'low' (not above the habitual level) meaning that an event is typical and rarely happens; 'medium / moderate' is above the low level but is not within the critical range (approximately 50 %); 'high' meaning that the event is very likely to happen; 'extremely high' meaning the event is almost surely to happen [1, 5, 19].

When people do not wish to bear with risk, they activate their behavioral resources by asking for help from relevant authorities and other responsible persons in places of residence, using personal protection (both physical things such as face masks and actions such as closing windows and doors). In case of emergency, people are often ready to migrate from a habitual environment into a new, more favorable one [21]. However, the cognitive and behavioral components might have no connections. The foregoing study that focused on investigating risk perception by industrial workers found either no or very weak relationship between high subjective hazard assessment and adherence to self-protective behaviors [21]. People from the analyzed group were shown to overestimate influence of environmental and occupational factors but to underestimate significance of their individual behaviors. Multiplicity of daily routine contexts associated with both personal traits and sociocultural factors creates differences in approaches to overcoming potential health threats.

Individual strategies for health risk management that can be found in research literature are quite diverse. Experts in psychology

[1] Koshurnikova N.A., Nifatov A.P. Rak legkogo u rabotnikov plutonievogo proizvodstva [Lung cancer in workers of plutonium production]. *Radiatsiya i risk (Byulleten' NRER)*, 1995, no. 5, pp. 123–128 (in Russian).

describe strategies based on the emotional component, which is an individual's mental state in case of a risk (threat or danger). It can be adequate (corresponding to a situation), alerting (danger is exaggerated), ignoring (danger is underestimated) and uncertain (involving various actions) [22]. Sociologists investigate individual strategies for health risk management through specific behaviors. Such behavioral practices can mostly be located within the continuum from responsible self-protective behavior to risky one. Thus, a Russian study focused on industrial workers and used quantitative indicators that described specific health-related behaviors (diet, smoking, alcohol use, medical and physical activity). As a result, it established three specific behavior types with various levels of risks involved, namely, low, medium, and high [23]. Another Russian study was accomplished on a sample made of employable people and considered the same behaviors; as a result, five health-related behavioral models were outlined: highly interested, moderately interested, inconsistent, passive, and destructive [24].

However, certain limitations appear when self-protective strategies are investigated only through implementation of individual health-protecting strategies. Individuals are assumed to determine their health behavior relaying on the 'risk – effect' relationship. At the same time, this relationship cannot be obvious in all cases, especially when environmental factors are involved, and not for all individuals; therefore, implementation of specific behaviors does not always mean an effective decrease in risk burden [25]. To avoid this limitation, foreign experts suggest two opposite health-related strategies based on risk assessment: risk minimization and risk avoidance [26].

It is important to remember that there are different strategies aimed at mitigating health risks separately for different environmental risk factors. In a situation when epidemiological threats are serious, just as it was during the COVID-19 pandemic, individuals implemented one of three strategies to mitigate risks of infection: 1) maximum protection strategy (following most recommendations); 2) dominant protection strategy (following basic recommendations); 3) mixed strategy (following some recommendations and simultaneous risky behaviors) [27]. In case of health risks, which are associated with criminal and illegal actions taken by others, several strategies can be outlined including avoidance (creation of a protected space), negotiations (interaction with an aggressive environment using verbal visual-emotional forms), and actions (attack, force interaction with an aggressive environment) [28]. Other strategies are usually pursued in a situation when a health risk is associated with a terrorist threat: looking for information, alertness, and habituation [29].

Therefore, since any state is interested in protecting and improving health of its employable population, a necessity arises to investigate various health risks and relevant behavioral risk-associated strategies, which can be useful for developing adequate healthcare policies.

In this study, we aimed to analyze subjective risk assessment by working population in Russia as regards various health factors and examine people's behavior concerning health risks.

Materials and methods. The empirical study was conducted using a mixed methodology, which involves collecting and analyzing data following two sociological traditions (qualitative and quantitative). The methods were integrated as per 'additional coverage' type (quant + qual) [30].

Quantitative data were obtained by using a formalized survey conducted in 2024 in a sample made of employed people aged between 18 and 65 years (*n* = 300). The survey took place in three large cities in Russia: Perm, Nizhniy Novgorod, and Novosibirsk. The preliminary stage in data analysis involved weighing the samples per the 'sex' parameter (weighing was based on the men-to-women ratio in Russian cities). The subsequent analysis was performed taking the weight coefficients into account. The sample structure is provided in Table 1.

Table 1

The structure of the analyzed sample

Parameter		Number (people)	Proportion (%)
Sex	Men	138	46
	Women	162	54
Education	Secondary school	13	5
	Vocational or unfinished higher education	60	20
	Higher	225	75
Income level*	Low	126	43
	Medium	142	49
	High	24	8
Having a partner	Yes	212	71
	No	87	29
Having children younger than 16 years	Yes	127	42
	No	173	58

Note: *The income level was measured by subjective estimates using the following question: 'Please state, which description suits your financial position the most'. Low level corresponded to the following answers: sometimes I don't have enough money to buy food / I have enough money to buy food but clothing is less affordable / I can buy food or clothing but buying some durable things (furniture, electronics, or household appliances) is an issue. Medium income is when people can afford durable goods but have no money for expensive purchases (apartment, car, etc.). High income means a person can buy some expensive things (apartment, car, etc.).

Official employment in leading branches of the economy was the basic criterion in selecting the study participants; their occupations included those with high work intensity. The study sample included heads of companies or structural divisions (21 %); specialists (59 %); support, technical and servicing staff (13 %); private entrepreneurs, self-employed and freelancers (7 %). The sample was made up of people involved in material production (light and heavy industry, 15 %; construction, 7 %) and in social and cultural activities (including education and science, 26 %; public authorities and law enforcement agencies, 6 %). Most respondents said they had full-time job and a permanent workplace (76 %); still, some worked remotely (12 %), in shifts (2 %) or had to constantly travel for work (5 %).

Health risks for the employed respondents were assessed using the following formula:

$$R = p \cdot g,$$

where R is the level of the subjectively perceived risk, p is likelihood of negative health outcomes upon exposure to a certain risk factor, g is severity of health harm (severity of negative health outcomes) due to impacts exerted by a certain risk factor. Perceived likelihood and severity were measured using the following questions: *'On the scale from 1 to 10, where 1 is the lowest score and 10 is the highest score, please estimate the following: 1) How likely is [a certain risk factor] to affect your health? 2) How severe can health outcomes be for you upon exposure to [a certain risk factor]?'*. Several risk factors were proposed to be estimated by the respondents including 1) ambient air; 2) consumed foods; 3) consumed water; 4) housing conditions; 5) working conditions; 6) weather phenomena and natural disasters; 7) poisonous plants or hazardous animal, fish, and insect species; 8) other people's criminal and illegal actions; 9) terrorist attacks and hostilities; 10) traffic accidents. For further analysis, all scores were transferred to the range between 0 and 1.

Self-protective strategies were established based on a certain risk-related behavior. The inventory had a question (*Do you take any action to mitigate negative influence [of a certain risk factor] on your health?)*, which helped divide the respondents into those who took some actions to minimize a certain health risk and those who didn't do anything. In addition, instruments eligible for quantitative research made it possible to assess specific actions aimed at risk management as well as reasons for inactivity.

Quantitative data were analyzed using the SPSS Statistics 21.0 software package. The analysis involved using one-dimensional (descriptive statistics, odds ratio calculation and correlation analysis) and multidimensional methods (factor analysis).

Qualitative data were represented by transcripts of in-depth interviews (n = 17), which were conducted with residents of the abovementioned cities in Russia in 2024. The interview findings were used to supplement quantitative data and get a better insight into self-protective behaviors as regards variable health risks. The research guide included some open questions concerning risk perception and risk-related behaviors such as *'What risk factors for your health can you name?'; 'What do you think is the most serious threat for your health at the moment?'; 'What factors affect your health above all?'; 'What do you do to a) protect your health, b) feel safe, c) minimize health risks etc.?'*. The open and axial coding method was employed to analyze the transcripts.

Results. Following the questioning results, an inverse pyramid was created to show significance that variable health risk factors had in the employed respondents' perception (Figure 1). Among all analyzed factors, the most hazardous ones included 1) other people's criminal and illegal actions (mentioned by 67 % of the respondents), 2) traffic accidents (63 %), 3) terrorist attacks and hostilities (60 %). That was also confirmed by the interviews: *'Primarily, above all, this is about physical safety, no external threats such as an attack, roughly speaking, a threat of physical violence for me and my family … impossibility or unwillingness to be exposed to any physical impact, either a fight, a traffic accident … or a catastrophe' (male, 35 years old, Nizhniy Novgorod).* Housing conditions were the last thing that concerned the respondents as regards their health since this factor was mentioned by only 10 % of all the participants.

Based on odds ratio calculation, some sociodemographic peculiarities were identified as regards how health risks were perceived by the respondents.

Thus, women considered several health risks factors more likely to affect them authentically more frequently than men; these factors included terrorist attacks and hostilities (OR = 2.055 with 95 % CI: 1.285–3.285), weather phenomena and natural disasters (OR = 2.540 with 95 % CI: 1.449–4.454),

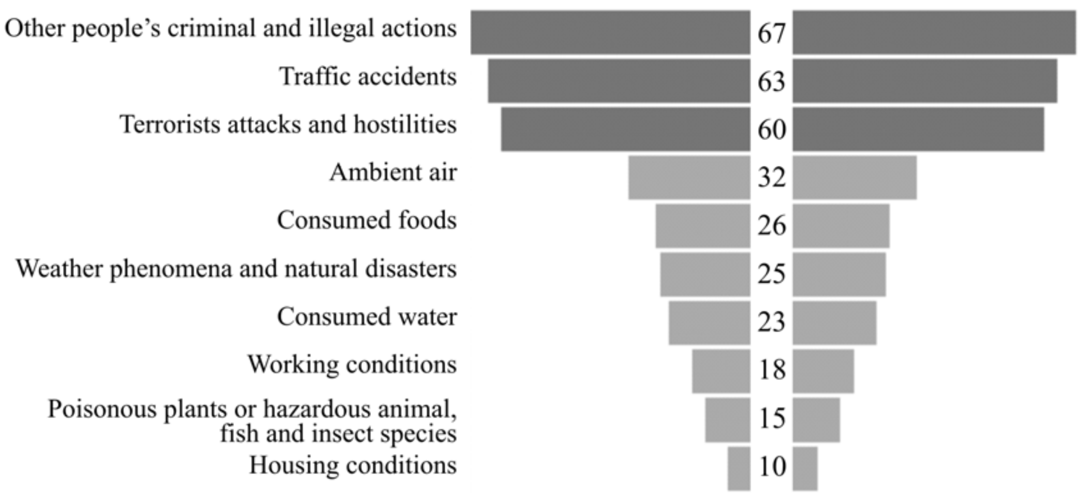

Figure 1. The inverse pyramid to show significance of variable risk factors as perceived by employed Russians (% of the respondents who mentioned the factor)

poisonous plants or hazardous animal, fish and insect species (*OR* = 3.067 with 95 % CI: 1.489–6.318). Having a higher education was associated with higher likelihood of estimating consumed foods as a health hazard (*OR* = 2.145 with 95 % CI: 1.085–4.240).

Traffic accidents were perceived as a health risk factor more frequently by Russians with higher incomes (*OR* = 1.652 with 95 % CI: 1.022–2.669) and those who were married, either officially or unofficially (*OR* = 1.847 with 95 % CI: 1.110–3.075). Notably, perception of a health risk was not age-specific according to the correlation analysis; still, some interviewed people mentioned something like *'fears come with age'*.

The foregoing risk factors were classified into groups by factor analysis (explanatory power of the model was 56 % at $p < 0.001$; the Kaiser–Meyer–Olkin (KMO) test was 0.7 confirming the sample being suitable for factor analysis). The first group can be denoted as sanitary-epidemiological health risk factors, which include quality of ambient air, foods, and water. The second group comprised living conditions, that is, housing and working conditions. The third group included social risk factors associated with existence of an individual within a given society such as other people's criminal and illegal actions, terrorist attacks and hostilities, and traffic accidents. These three groups correspond to principles applied to define a factor type within the health risk analysis methodology. Natural risk factors, namely weather phenomena and natural disasters, poisonous plants or hazardous animal, fish and insect species were assigned into the fourth group.

A worker's category (per the position) was established to be associated with selecting a group of health risk factors by using the chi-square correlation coefficient. The association was obvious for the sanitary-epidemiological risk factors (*Cramer's V* = 0.247 for ambient air at $p < 0.001$; foods, *Cramer's V* = 0.254 at $p < 0.001$; water, *Cramer's V* = 0.254 at $p < 0.001$). Low- and middle-position workers were established to deem such factors as a health threat authentically more frequently than executives.

When it comes down to perceived likelihood of negative health outcomes upon exposure to the analyzed risk factors, estimated mean likelihood was considerably higher for the social health risk factors (traffic accidents, 0.69; terrorist attacks and hostilities, 0.68; other people's criminal and illegal actions. 0.66); the lowest values were obtained for the natural factors (weather phenomena and natural disasters, 0.54). Mean perceived severity of health harm turned out to be higher than mean perceived likelihood of negative health outcomes. In general, the following regularity can be traced: the higher likelihood is the higher severity is. Housing conditions are the only exclusion since, in the respondents' opinion, perceived severity of negative health outcomes due to poor housing conditions (0.55) is lower than their likelihood (0.62).

Various sociodemographic characteristics may act as predictors of 'likelihood' and 'severity'. For example, women considered several factors to more likely affect their health including ambient air pollution (Pearson's $r = 0.272$ at $p < 0.001$), water pollution (*Pearson's* $r = 0.272$ at $p < 0.001$), contacts with hazardous plants or animals (*Pearson's* $r = -0.414$ at $p < 0.001$). An association between sex and 'severity' was also traced for such factors as housing conditions (*Pearson's* $r = 0.470$ at $p < 0.001$).

It is interesting that age turned out to be significant only for water quality (*Pearson's* $r = 0.340$ at $p < 0.001$ for the association with likelihood; *Pearson's* $r = 0.322$ at $p < 0.001$ for the association with severity). Financial position also had some influence on how the respondents assessed likelihood of negative health outcomes as regards such social factors as other people's criminal and illegal actions (*Spearmen's* $\rho = -0.226$ at $p < 0.001$) and traffic accidents (*Spearmen's* $\rho = -0.186$ at $p < 0.001$). Marital status, namely, having a partner, determined assessment of likelihood as regards housing conditions (*Pearson's* $r = -0.430$ at $p < 0.001$) and working conditions (*Pearson's* $r = -0.382$ at $p < 0.001$).

Subjective risk assessment based on the product of 'likelihood' and 'severity' was interpreted in this study judging from risk

Severity \ Likelihood	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1
0.1	0.01	0.02	0.03	0.04	0.05	0.06	0.07	0.08	0.09	0.1
0.2	0.02	0.04	0.06	0.08	0.1	0.12	0.14	0.16	0.18	0.2
0.3	0.03	0.06	0.09	0.12	0.15	0.18	0.21	0.24	0.27	0.3
0.4	0.04	0.08	0.12	0.16	0.2	0.24	0.28	0.32	0.36	0.4
0.5	0.05	0.1	0.15	0.2	0.25	0.3	0.35	0.4	0.45	0.5
0.6	0.06	0.12	0.18	0.24	0.3	0.36	0.42	0.48	0.54	0.6
0.7	0.07	0.14	0.21	0.28	0.35	0.42	0.49	0.56	0.63	0.7
0.8	0.08	0.16	0.24	0.32	0.4	0.48	0.56	0.64	0.72	0.8
0.9	0.09	0.18	0.27	0.36	0.45	0.54	0.63	0.72	0.81	0.9
1	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1

Interpretation:

- High risk
- Alerting risk
- Permissible (acceptable) risk
- Minimal risk

Figure 2. Subjective risk assessment and risk acceptability level

acceptability for a person. Acceptability was established based on the following scale: minimal risk (0.01–0.09), permissible risk (0.1–0.29), alerting risk (0.3–0.59) and high risk (0.6–1.0). To visualize the assessment results, we created a contingency table with the aim to establish individual risk values and levels of its acceptability (Figure 2).

In this study, averaged values of subjective risk perceptions were established among employed Russians; Table 2 provides the results. Social factors were considered to have the highest risk level since their values were within the 0.56–0.58 range (high risks were mentioned by 44–48 % of the respondents). Housing and working conditions had almost acceptable risk level for the respondents (0.39) Ambiguous (that is, uneven) risk assessment was discovered for sanitary-epidemiological and natural factors, especially when the assessment was sex-specific (validity of differences was confirmed by the Kruskal – Wallis test at $p < 0.001$). Although women considered poisonous plants or hazardous animal, fish and insect species a serious health threat more often than men (21 % against 8 %), men thought the health risk posed by this factor to be twice as high (0.77 against 0.39). In contrast to men, women gave higher estimates to health risks associated with drinking water (0.5 against 0.34). Russians who were employed in the tertiary sector tended to give higher estimates to risks associated with weather effects on health against those employed in material production (30 % against 11 %; *Spearmen's* ρ = 0.303 at $p < 0.001$).

The analysis established that although subjective risk perception could be considered a factor influencing a choice on a risk-related behavior, it was not either necessary or sufficient. The correlation analysis results found no direct significant correlation between risk assessment and actions taken to minimize it. Within the discourse about forming a self-protective behavior, the respondents named feeling stable as another significant condition for choosing a strategy, which was achieved due to having relevant information about a health risk as well as due to conditions able to create a safe environment: "*Today, my work plan is clear and I do not have any overdue tasks. In general, everything is fine in our city, public transport works, Yandex cards too, the school is open. Overall, I do not feel any threats…" (a woman, 38 years old, Nizhnii Novgorod).* When being in uncertainty, without any knowledge, and having to assess risk uncontrollability, people demonstrate only the

Table 2

Health risk assessment by employed Russians

Groups of risk factors		Mean risk level			Risk acceptability level (% of the respondents)			
		Total	Men	Women	High	Alerting	Permissible	Minimal
Social	Other people's criminal and illegal actions	0.56	0.56	0.55	44.4	34.4	16.1	4.8
	Traffic accidents	0.58	0.59	0.58	48.3	38.1	13.4	0.5
	Terrorist attacks and hostilities	0.58	0.57	0.59	48.5	28.9	19.6	3.4
Sanitary-epidemiological	Ambient air	0.41	0.35	0.45	23.4	37.1	35.1	4.4
	Consumed foods	0.45	0.46	0.44	31.0	34.2	28.7	6.1
	Consumed water	0.44	0.34	0.5	36.5	24.2	23.3	16
Living conditions	Working conditions	0.39	0.40	0.39	29.1	24.7	34.5	11.8
	Housing conditions	0.39	0.29	0.46	22.0	33.2	30.7	14.1
Natural	Weather phenomena and natural disasters	0.38	0.38	0.38	21.2	28.3	41.3	9.5
	Poisonous plants or hazardous animal, fish and insect species	0.48	0.77	0.39	39.7	23.3	25	12

emotional component and fail to mention the behavioral one: "*I explain that your house can fall down even if you're at home…? That is, nothing depends on you in this case. You are crossing the street when the light is green… but nobody can expect a psycho who is breaking the rules by going at the red light and can hit you. I can't help feeling alert… I feel like this all the time…" (a woman aged 46 years, Perm). "This is probably uncertainty. Because you don't know what can harm you, what roof an ice block or snow is going to fall down on your head…" (a man, 52 years old, Perm).*

In general, we can speak about active and passive behaviors as regards health risks. Active behaviors are based on a respondent having conscious interactions with a risky environment and taking relevant actions aimed at managing risks. Not many respondents showed themselves to adhere to such strategies, namely, one quarter on average. The proportion of active people was mostly within the range between 7 and 26 %. The respondents turned out to be active mostly as regards social risk factors, namely, traffic accidents (55 % of the respondents who selected the factor took relevant actions to mitigate its negative influence on their health); other people's criminal and illegal actions (47 % of the respondents). The respondents took the least significant actions as regards sanitary-epidemiological and natural risks, which is consistent with their low levels in people's perception (see Table 2).

The results obtained by analyzing qualitative data showed that directions and intensity of actions aimed at managing risk was determined by different intentions. In one case, a person wanted to mitigate a risk *("…as for personal safety: as it seems now … complicated in general, it is vary unsafe to take a walk, for example, at night, so, I think some self-defense means are necessary" as stated by a woman aged 20 years, Novosibirsk)*. Notably, this intention to mitigate a risk may be associated with not only one's own health protection but also with protecting other people's health: "*You go out and check everything … Switch off electricity, when going out. It is also about safety, and not only yours but your neighbors as well. We live in apartment buildings and you have to think about others, not only about yourself (a woman, 24 years old, Perm)*. In other case, a person's behavior might be aimed at avoiding risks: *"Just as any other, I'm afraid of … drunk and aggressive people …, it's better to avoid them … let the police deal with them" (a man, aged 31 years, Perm).*

Actions aimed at managing various health risks were factored on the basis of the respondents' answers. Based on that, taken actions can be generalized and placed in the continuum depending on their intensity: 1) interacting actively with a risky environment (adherence to safety rules), 2) creating a safe space (use of specific protection means and examining information about health risks and ways to minimize them), and 3) deliberately avoiding a potentially risky environment.

Active interaction with a risky environment is predominantly observed as regards health risks associated with housing and working conditions. The informants stated in the interview: "*Adherence to some basic safety household rules such as switching off the stove, gas, never put a hairdryer next to the bathtub, turn off water" (a woman, 18 years old, Perm).* This behavior turned out to be the most common since almost all respondents who took actions to minimize such risks mentioned keeping an eye on the state of the electrical household appliances, water and gas supply systems (96 %); they also adhered to safety rules of using gas, water and electricity (100 %) and to safety rules at their workplace (92 %). This conclusion can explain why housing conditions were considered the least hazardous for health among all analyzed risk factors (see Figure 1).

Deliberate avoidance of a potentially risky environment was mostly used by the respondents as regards natural risk factors. Most respondents who took actions to minimize such risks stated that they tended to avoid places where a natural disaster was likely to occur (100 %) and potentially hazardous animals or plants (89 %). Only one third of the respondents in this group mentioned having specific skills necessary to manage such risks.

As for social and sanitary-epidemiological risk factors, the respondents preferred not only to interact actively with the environment but also to create a safe space. Thus, the respondents stated that they studied (knew) how to behave safely in the street and in public places (91 % among those who took actions concerning social risk factors), safety rules in case of a terrorist attack or hostilities (93 %) and traffic safety rules (96 %). At the same time, they tried to adhere to safety rules when consuming foods and water; for example, 95 % minded quality of food products and 88 % consumed only bottled or boiled water for drinking.

Passive behavior is to a great extent manifested through unconscious adherence to self-preservation instincts and habitual behavioral patterns without considering or regardless of subjective risk perception. It is caused by several reasons, the most obvious one being lack of relevant knowledge, skills and (or) resources for minimizing various risks as mentioned by 30 to 88 % of the respondents in the 'passive' group. According to the questioning, Russians predominantly need knowledge and resources for securing life and health safety from negative influence exerted by ambient air pollution, terrorist attacks and hostilities (more than 80 % of the respondents mentioned that). Interestingly, during the interview, the informants tended to more often mention lack of knowledge among other people and not themselves: *"Children must be taught; everybody must be taught how to cross the street correctly […] because neither drivers nor pedestrians know how to behave in traffic" (a woman, 42 years old, Novosibirsk).*

The second reason, also not the second in significance, is excluding oneself as a subject from health risk management and placing the responsibility on other subjects in a risky space, in particular, public authorities or other authorized services. On average, 60 % of the 'passive' respondents stated that. Largely, people tend to consider weather phenomena or natural disasters (mentioned by 91 % of the respondents), terrorist attacks or hostilities (89 %) and ambient air pollution (72 %) to be 'uncontrollable' factors. In the block named 'other', the respondents additionally stated that *"there are services to deal with it"; "how to make our district safe if we do not have a police officer or post here…?"; "this depends on the state".* Expecting some help from institutionalized services is also traced in the answers: *"I think it's only logical and honest to thank our special services for that, who are responsible for protecting people's safety and providing peace…, who protect us from all these disasters: that's the first. Secondly, I simply try not to think about it" (a man, aged 35 years, Nizhnii Novgorod).* At the same time, as opposed to a wish to get some help, some signs of mistrust in these subjects and doubts that they are competent enough can also be seen (*"Many people become top managers or supervisors without relevant skills, I think. It's very bad" (a man, 44 years old, Nizhnii Novgorod)).*

The third reason is lack of interest in resolving issues associated with health risk assessment and mitigation. Health risks caused by consumed foods are the least concerning for Russians as they were mentioned by 61 % of the respondents in this respect; however, the proportion of those who mentioned other risk factors is between 10 and 40 %. On one hand, this lack of interest can be explained by the existing system of values. In the survey, the respondents gave some additional comments under the heading 'other' such as *'there are much more interesting things to do at the moment'; 'because I don't have enough time to pay any attention to this aspect'*. On the other hand, this absence of involvement in health risk management can be associated with deliberate disregard of information about realized risks *("At least, I try to protect myself from some strong negative moral feelings as regards safety" (a man, 31 years old, Perm); I have no wish to turn on TV and watch any news; it's better to have some general idea of what's going on, without any details… it's better to live without knowing" (a woman, 18 years old, Nizhnii Novgorod)).*

In addition to the foregoing reasons, we should consider poor awareness about health risks among the population; that is, people are not always aware what negative influence may be exerted on their health by risk factors. Therefore, they do not take any actions (*"I think it's quite possible that I simply don't know anything about that. And if I don't know about that, then it's not discussed properly in the society. Not enough information is provided [about health risks]" (man, 23 years old, Perm)).* For example, the following comments were given in the survey under the heading 'other': *"I don't think about it"; "everything is fine by me"; "it does not interfere with my life"; "I hope this will not happen [a negative effect]"*.

To generalize the results obtained by the quantitative and qualitative study, we can propose the following types of individual self-protecting strategies depending on the intention (risk mitigation or risk avoidance) and actions (active or passive) taken by a person concerning health risks (Table 3). These self-protective strategies can be complementary and used depending on a situation and personal traits.

Table 3

Types of individual self-protecting strategies concerning health risks

Intention / Actions	Active	Passive
Risk mitigation	Acting	Waiting
Risk avoidance	Avoiding	Adapting

1) 'Acting' people understand and accept the fact that health risks exist based on subjective risk perception; they take conscious highly intensive actions to minimize likelihood of negative health outcomes due to effects produced by a given factor (for example, follows the safety rules) and if a health risk has been realized, they try to minimize severity of health harm. Here's an example of such behavior from the interview: *"Yes, to a certain extent, I understand, I know what's going to happen tomorrow, which means I can influence this or that situation and what happens to me" (a woman, aged 27 years, Nizhnii Novgorod).*

2) 'Avoiding' people also understand and accept that risks exist but their subjective risk perception can overestimate actual risk levels and thereby activate the emotional component. This leads to refusal from any interactions with a risky environment. Actions within this behavioral type are aimed at avoiding any risky space as much possible (*"It is necessary to follow various safety precautions so that any extraordinary situation is prevented. For example, if an elevator is creaking, I won't take it" (a man, aged 32 years, Perm)).*

3) 'Waiting' people hope that health risks will remain unrealized (that is, their perception underestimates actual risk levels). This behavioral type is primarily manifested through following habitual self-protective behavior patterns but also involves thinking over necessary actions as regards potential risks (*"Water starts to become a concern, I'm thinking about buying some bottled one … Well, only thoughts so far, no actions have been taken" (a man, 44 years old, Nizhnii Novgorod).* For this behavioral type, a realized risk is mitigated not due to any taken actions but by delegating the responsibility for risk management to other people: *"First of all, you should wait for something bad to happen; secondly, you should understand that in case of emergency there are people and means and you can get any necessary help" (a woman, 38 years old, Nizhnii Novgorod).*

4) And the last type is 'adapting' people. In other words, they pursue the passive adaptation strategy by denying / ignoring any information about risk realization or by trying to minimize these risks in their perception without taking any specific actions concerning them: *"I have been watching some videos… one of my favorites is 'Stop it' … so that I could stop frightening myself, feeling scared, thinking the world is a dangerous place and threats are waiting for me at every corner. The idea is to stop doing it, to start living here and now, being exactly where I am at the moment…" (a woman, 68 years old, Nizhnii Novgorod).* A good example of such behavior is speaking about one's wish to live in a safe environment without any actions to achieve it: *"Given this situation with the ongoing war, I'd like to live in peace and not think about what is going to happen tomorrow. I wish all people around me to be kind and trustworthy, unable to betray or deceive. I wish to be protected and to have someone to rely on and to live in comfort" (a woman, aged 34 years, Perm).*

Discussion. According to our findings, social risk factors are the most hazardous for health. Averaged subjective levels of perception of risks associated with a person's existence in the society are within the 0.56–0.58, the maximum level being equal to 1.0. Experts in the sphere point out that a specific risky essence typical for these factors is created by constant social changes, which cannot be controlled by a person [31]. In addition, Russians doubt that other subjects involved in a risky space can mitigate such risks, which is opposite to the position that individual risk management is determined by trust in a social system [32].

Medical and social studies employ the theory of planned behavior to explain risk-related behaviors. This theory considers subjective risk assessment to be the basic self-protection factor [33]. However, the quantitative data obtained in this study did not establish any direct significant correlation between risk perception and actions taken to mitigate it. Several necessary sections in this correlation were identified based on the qualitative data: 1) sufficient awareness about risk factors and ways to manage them; 2) sufficient level of perceptible risk control; 3) trust in other subjects involved in a risky space. Findings reported in other studies confirm the significance of the foregoing factors for selecting a risk management strategy [34–36].

An empirically fixed preference in taking passive, and not active, actions aimed at managing risks can be associated with the fact that people do not consider themselves responsible for their own health and life safety; therefore, they rely on instructions and actions issued and taken by other competent authorities [37]. Active strategies imply that people should act on their own. This includes obtaining relevant knowledge about health risks since high awareness not only promotes actions aimed at mitigating risks but also makes it possible to keep a stable mental state, that is, without any anxieties about health risks [38]. Such reasons as poor literacy and awareness about risk factors and ways to manage them reduce a person's ability to actively participate in risk mitigation and this is consistent with our findings.

Within the self-protective behavior context, not only actions are to be considered but the intention as well. People have been established to take actions either to mitigate or avoid risks. And here risk avoidance, on one hand, can be an active action, which involves choosing an option how to avoid a risky space, that is, situations or places, which can be potentially hazardous for health. On the other hand, avoidance can be passive, in other words, inactive, when risks are mitigated and neutralized only in a person's mind without any actual effects on a risky environment. Researchers call the second avoidance type 'passive adaptation', which is largely manifested as a consequence of existing lack of trust in subjects responsible for making risk-related decisions [39].

Conclusion. Duality of the components that constitute self-protective strategies is manifested upon exposure to health risks. Both active and passive behavior can be adopted when such strategies are implemented. The highest health risk as subjectively perceived by employed people is associated with social risk factors determined by a person's existence within the society. This leads to active behavior, which is typical for a smaller proportion of Russians. Passive behavior is determined by lack of necessary knowledge, skills and resources and is implemented in a situation when a person perceives a risk as unmanageable and is not interested in its mitigation.

Formation of self-protective behavior triggers the necessity to feel stability in people's subjective perception. The emotional component, which arises under uncertainty and exposure to uncontrollable risks, leads to inactivity in most cases. Within this context, human adaptation resources become a significant factor that promotes manifestations of social skills and mutual support upon exposures to risks.

Given all the above-stated, the following actions can be recommended: 1) to develop a strategy aimed at preventing and controlling health risks, including monitoring of subjective risk perception and using its results to raise people's awareness about potential hazards; 2) to create conditions for active interaction between subjects involved in a risky space, which emphasizes the importance of such social institutions as education, healthcare and local communities in creating a safety culture as well as people's trust in them. These recommendations highlight the significance of mutual responsibility for safety where team efforts can substantially enhance the level of security for the population. This can be achieved through creating public initiatives and programs promoting cooperation between various social groups.

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Research article

FREQUENCY OF CO-INFECTION WITH UROGENITAL CHLAMYDIAL INFECTION AND OTHER SEXUALLY TRANSMITTED INFECTIONS AND ASSESSMENT OF ASSOCIATED RISK FACTORS

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Chlamydia trachomatis is one of the most common sexually transmitted infection (STI) pathogens worldwide. Co-infection with multiple STI pathogens increases the risk of complications and the spread of infections necessitating research of risk factors for effective prevention and control.

We analyzed 1,201 medical histories of patients who sought treatment at a specialized dermatovenereological center between 2005 and 2022. Logistic regression was used to assess the independent influence of each analyzed factor.

Co-infection with multiple pathogens was detected in 7.8 % of patients, more frequently among women (68.1 %) and individuals aged 18–29 years (71.3 %). The main co-infections in patients with urogenital chlamydial infection were anogenital (venereal) warts (80.9 %), anogenital herpes infection (20.2 %), and gonococcal infection (14.8 %). Logistic analysis revealed that the likelihood of co-infection was higher among women (OR = 4.84), minors (OR = 3.26), individuals aged 18–29 years (OR = 1.97), those with regular sexual activity (OR = 1.56), and those not in a marital relationship (OR = 2.72).

This study identified factors associated with co-infection with multiple STI pathogens in patients with chlamydial infection, including female sex, age 18–29 years, being unmarried, and having regular sexual activity. The results emphasize the need for early screening for chlamydial infection and other STIs, as well as preventive measures for high-risk groups.

Keywords: *Chlamydia trachomatis, sexually transmitted infections (STIs), co-infection, risk factors, epidemiology, urogenital chlamydial infection, incidence, risk assessment.*

Genitourinary chlamydial infection (caused by *Chlamydia trachomatis* (*C. trachomatis*)) is the most common sexually transmitted infection (STI) worldwide. In 2020, WHO estimated nearly 129 million new cases of C. trachomatis infection emphasizing the issue being truly global [1]. In the Russian Federation, official incidence of the infection amounted to 17.1 cases per 100,000 people in 2023 [2]. However, its actual prevalence can

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be considerably higher due to predominantly asymptomatic disease course, drawbacks of early diagnostics and screening as well as differences in systems for epidemiological surveillance. As reported in epidemiological studies, which have been conducted on samples made of people from various population groups, prevalence of the disease is estimated to vary between 3.8 and 7.1 % in the country, which is comparable with findings reported in European and North American studies [3–7].

Despite the overall decline in the incidence of chlamydial infection in Russia from 2005 to 2022, a reverse trend has been identified in Moscow: the incidence grew from 10 to 14 per 100,000 people between 2018 and 2022[1]. This growth is rather alerting since the infection can induce severe reproductive complications including pelvic inflammatory diseases and infertility as well as promote susceptibility to HIV infection and other STI [8–10].

The high percentage of asymptomatic disease cases creates a significant difficulty in controlling genitourinary chlamydial infection; this makes it harder to perform timely diagnostics and treatment [11, 12]. Genitourinary chlamydial infection (GCI) is predominantly detected in young people, which makes this age group a primary target of relevant prevention and treatment [13–15].

Infection with *Chlamydia trachomatis* simultaneously with other sexually transmitted pathogens considerably increases risks of complications such as pelvic inflammatory diseases, infertility, and ectopic pregnancy [16]. Moreover, co-infection increases risks of getting infected with other STI due to a greater viral load and mucosa lesions, which create favorable conditions for pathogen penetration [17, 18]. For example, co-infection with *Neisseria gonorrhoeae* or simple herpes virus can aggravate the clinical course of genitourinary chlamydial infection and lead to more severe clinical manifestations [19]. These data emphasize the necessity to examine risk factors and peculiarities of co-infection with several pathogens in order to develop more effective prevention and treatment strategies.

In this study, we aimed to identify frequency and risk factors of *C. trachomatis* co-infection with other STI pathogens in patients who applied for treatment to specialized dermatological-venerologic clinics.

Materials and methods. An unselected study sample was made of 1201 medical histories of patients who voluntarily underwent clinical tests to identify STI with subsequent treatment of genitourinary chlamydial infection (GCI) (ICD-10 code A56.0-8) of various localizations at the State Scientific Center of Dermatovenerology and Cosmetology of the RF Ministry of Health between 2005 and 2022.

A case-control study was selected as a method for investigating what factors could influence risks of getting infected with chlamydia and other STI pathogens. Independent effects produced by each analyzed factor were investigated by using logistic regression; to get more precise results, weighted logistic regression (where weight given to variables when examining factors influencing co-infection was equal to 11.78). Co-infection with other sexually transmitted infections (STI) was selected as a dependent variable.

Selection criteria were met for 1201 patients who applied to the clinical and diagnostic center of the State Scientific Center of Dermatovenerology and Cosmetology. The patients were divided into two groups. The control included 1107 patients (92.17 %; 95 % CI: 90.55–93.59 %) with diagnosed genitouri-

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nary chlamydial infection (A56.0-8); the main group was made of 94 patients (7.83 %; 95 % CI: 6.4–9.45 %) with diagnosed chlamydial infection together with other STI (A60; A63; A59; A54; A51).

We analyzed the following variables: sex, age, STI in medical history, chlamydial infection in medical history, complications (for diagnosed A56.1 per ICD-10), marital status, age of the first sexual contact, regularity of sexual contacts, the number of sexual partners, surgery on the genitourinary system in medical history, chicken pox in medical history.

Statistical analysis, creation of graphs, tables and diagrams as well as analysis of the study results were accomplished with Microsoft Excel 2010 and IBM SPSS Statistics 22 software packages. Significance in the case-control study and logistic regression was estimated using the Chi-square test (χ^2) and Fischer's exact test for small samples. The Wald test was employed to calculate confidence intervals.

Results and discussion. One thousand two hundred and one patients with genitourinary chlamydial infection (GCI) were almost evenly distributed per sex: 634 (52.75 %) men and 568 (47.25 %) women. Young patients (aged 18–29 years) prevailed in the groups; minors accounted for 7.2 %. Sexually transmitted infections (STI) appeared in patients' medical history in 23.1 % of the cases and re-infection with chlamydia was detected in 8.9 % of the patients.

Genitourinary chlamydial infection (GCI) combined with other STI was established in 94 patients (7.82 %; 95 % CI: 6.3–9.3). GCI was the most frequent together with anogenital (venereal) warts, 80.9 % (74 patients); genital herpes, 20.2 % (19 patients); gonococcal infection, 14.8 % (14 Patients). GCI combined with two other STI was established in 18.1 % (17 patients); three other STI, 1.06 % (1 patient). Co-infections were more frequent among women (11.3 % (of all women); 95 % CI: 8.9–14.1, against 4.7 % (of all men); 95 % CI: 3.3–6.6 among men). The average age of patients with co-infection was 24.5 (16 to 55, the median age was 24 years). The lowest medium age was established among patients with anogenital warts, 21.75 years (16 to 34, the median age was 19 years) (Table 1).

Factors that increased risk of co-infection with chlamydial infection and other STI pathogens included female sex (*OR* = 2.6; 95 % CI: 1.6–4.0), age between 18 and 29 years (*OR* = 1.8; 95 % CI: 1.1–3.1), being single (*OR* = 2.9; 95 % CI: 1.5–6.2), chicken pox in medical history (*OR* = 2.04; 95 % CI: 1.5–3.9). Other analyzed indicators did not have any statistical significance (Table 2).

Independent influence exerted by each analyzed factor was examined by using logistic regression. It should be noted that only those patients, for whom all factors included in the analysis are known, can be considered in a logistic regression model. To get more authentic results, we selected only those factors for our analysis, which allowed minimal reduction in the number of patients in both groups (Figure 1).

The results obtained by logistic regression analysis showed that female sex and being single were two independent factors, which increased the risk of co-infection with several STI by 4.88 (95 % CI: 1.9–12.4) times and 3.12 (95 % CI: 1.1–9.3) times accordingly.

The results obtained by weighted logistic regression established an association between co-infection with several STI and regular sexual contacts (*OR* = 1.56 (95 % CI: 1.14–2.14)), being a minor (*OR* = 3.26 (95 % CI: 2.0–5.29)), age between 18 and 29 years (*OR* = 1.97 (95 % CI: 1.39–2.79)), female sex (*OR* = 4.84 (95 % CI: 3.47–6.74)) and being single (*OR* = 2.72 (95 % CI: 1.83–4.06)) (Figure 2).

The analysis established that the risk of ci-infection simultaneously with *Chlamydia trachomatis* and other STI pathogens was higher for women, patients aged between 18 and 29 years and single (not married) patients. Higher odds ratio for women can be caused by their greater readiness to undergo a preventive medical check-up even if they do not have any complaints concerning the genitourinary system functioning or when planning

Table 1

Profile of patients with genitourinary chlamydial infection

	Cases (percentage [95 % CI])		
	Co-infection with other STI	Without co-infection	Total
Total	94 (7.8 % [6.3–9.3])	1107 (92.2 % [90.7–93.7])	1201 (100 % [100–100])
Sex			
Male	30 (31.9 % [22.5–41.3])	604 (54.6 % [51.6–57.5])	634 (52.8 % [50–55.6])
Female	64 (68.1 % [58.7–77.5])	503 (45.4 % [42.5–48.4])	567 (47.2 % [44.4–50])
Age			
Minors	6 (6.4 % [1.4–11.3])	81 (7.3 % [5.8–8.9])	87 (7.2 % [5.8–8.7])
between 18 and 29	67 (71.3 % [62.1–80.4])	652 (58.9 % [56–61.8])	719 (59.9 % [57.1–62.6])
Older than 30	21 (22.3 % [13.9–30.8])	374 (33.8 % [31–36.6])	395 (32.9 % [30.2–35.5])
Chicken pox in medical history			
Yes	27 (28.7 % [19.6–37.9])	159 (14.4 % [12.3–16.4])	186 (15.5 % [13.4–17.5])
No	67 (71.3 % [62.1–80.4])	948 (85.6 % [83.6–87.7])	1015 (84.5 % [82.5–86.6])
STI in medical history			
Yes	24 (25.5 % [16.7–34.3])	254 (22.9 % [20.5–25.4])	278 (23.1 % [20.8–25.5])
No	70 (74.5 % [65.7–83.3])	853 (77.1 % [74.6–79.5])	923 (76.9 % [74.5–79.2])
Chlamydial infection in medical history			
Yes	5 (5.3 % [0.8–9.9])	102 (9.2 % [7.5–10.9])	107 (8.9 % [7.3–10.5])
No	89 (94.7 % [90.1–99.2])	1005 (90.8 % [89.1–92.5])	1094 (91.1 % [89.5–92.7])
Complications			
Yes	3 (3.2 % [-0.4–6.7])	30 (2.7 % [1.8–3.7])	33 (2.7 % [1.8–3.7])
No	91 (96.8 % [93.3–100.4])	1077 (97.3 % [96.3–98.2])	1168 (97.3 % [96.3–98.2])
Marital status			
Data not available	20 (21.3 % [13–29.6])	354 (32 % [29.2–34.7])	374 (31.1 % [28.5–33.8])
Married	56 (59.6 % [49.7–69.5])	369 (33.3 % [30.6–36.1])	425 (35.4 % [32.7–38.1])
Single	18 (19.1 % [11.2–27.1])	384 (34.7 % [31.9–37.5])	402 (33.5 % [30.8–36.1])
Age of the first sexual contact			
Data not available	49 (52.1 % [42–62.2])	833 (75.2 % [72.7–77.8])	882 (73.4 % [70.9–75.9])
Younger than 18 years	34 (36.2 % [26.5–45.9])	203 (18.3 % [16.1–20.6])	237 (19.7 % [17.5–22])
Older than 18 years	11 (11.7 % [5.2–18.2])	71 (6.4 % [5–7.9])	82 (6.8 % [5.4–8.3])
Regular sexual contacts			
Data not available	55 (58.5 % [48.6–68.5])	563 (50.9 % [47.9–53.8])	618 (51.5 % [48.6–54.3])
Yes	27 (28.7 % [19.6–37.9])	352 (31.8 % [29.1–34.5])	379 (31.6 % [28.9–34.2])
No	12 (12.8 % [6–19.5])	192 (17.3 % [15.1–19.6])	204 (17 % [14.9–19.1])
The number of sexual partners over the whole life time			
Data not available	76 (80.9 % [72.9–88.8])	1015 (91.7 % [90.1–93.3])	1091 (90.8 % [89.2–92.5])
More than 2	13 (13.8 % [6.9–20.8])	56 (5.1 % [3.8–6.3])	69 (5.7 % [4.4–7.1])
2 or less	5 (5.3 % [0.8–9.9])	36 (3.3 % [2.2–4.3])	41 (3.4 % [2.4–4.4])
Surgery on the genitourinary system			
Data not available	41 (43.6 % [33.6–53.6])	442 (39.9 % [37–42.8])	483 (40.2 % [37.4–43])
Yes	3 (3.2 % [-0.4–6.7])	42 (3.8 % [2.7–4.9])	45 (3.7 % [2.7–4.8])
No	50 (53.2 % [43.1–63.3])	623 (56.3 % [53.4–59.2])	673 (56 % [53.2–58.8])

a pregnancy. Age between 18 and 29 years and extra-marital sexual contacts are likely to be associated with frequent change of sexual partners, neglected barrier contraception, low vigilance and low readiness to have any check-up for having a STI and consequently, a higher risk of co-infection with several such diseases simultaneously.

Chicken pox in medical history was associated with an elevated risk of co-infection with chlamydial infection together with other STI. However, a significant association between chicken pox in medical history and risks of co-infection was established only in the case-control study. It did not persist when logistic regression was used. This may indicate

Table 2

Factors associated with risks of co-infection with chlamydial infection and other STI pathogens, the case-control study

Indicator	Odds Ratio [95 % CI]	*p* value
Female sex	2.55 [1.635–4.042]	0.00001303
Age younger than 18 years	1.319 [0.516–3.372]	0.3572
Age between 18 and 29 years	1.829 [1.114–3.094]	0.008917
Being single	2.887 [1.469–6.232]	0.001137
Chicken pox in medical history	2.04 [1.471–3.846]	0.0001101
Complications	1.184 [0.354–3.953]	0.4851
STI in medical history	1.151 [0.6982–1.853]	0.284
Chlamydial infection in medical history	0.5538 [0.1946–1.305]	0.1017
The first sexual contact prior to 18 years of age	1.081 [0.5278–2.334]	0.4173
More than 2 sexual partners over the whole life time	1.664 [0.5566–5.595]	0.1812
Regular sexual contacts	1.227 [0.6142–2.561]	0.2836
Surgery on the genitourinary system in medical history	0.8901 [0.2119–2.691]	0.4539

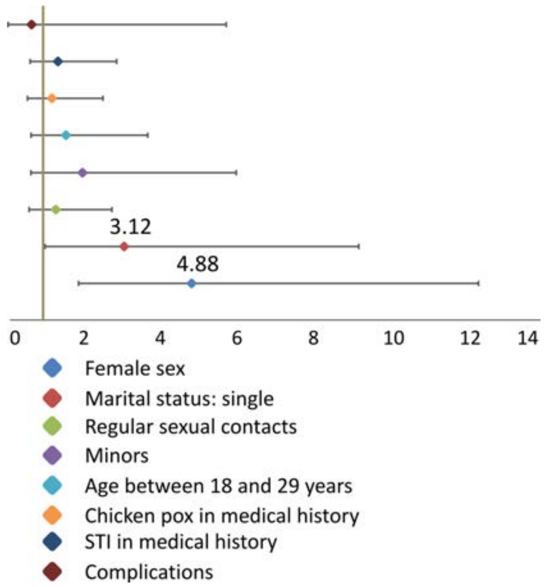

Figure 1. Logistic regression showing risk factors that influence risk of co-infection simultaneously with GCI and other STI (R^2 = 0.1 (Hosmer & Lemeshow); 0.48 (Cox & Snell); 0.121 (Nagelkerke); Chi-square – 26.792; $p < 0.001$)

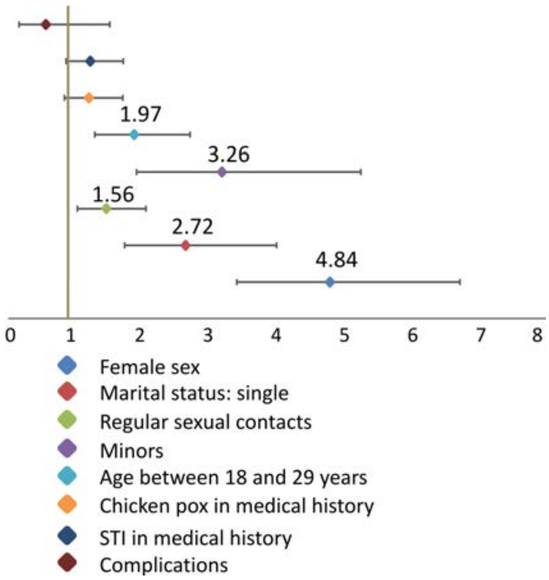

Figure 2. Logistic regression with weighted risk factors influencing the risk of co-infection simultaneously with GCI and other STI (R^2 = 0.17 (Hosmer & Lemeshow); 0.179 (Cox & Snell); 0.239 (Nagelkerke); Chi-square – 187.539; $p < 0.001$)

either certain effects produced by confounders, which were not considered, or the applied model being not being powerful enough to reveal weaker associations. Therefore, the results require further analysis involving additional variables and a larger sample.

Logistic regression analysis found an association between co-infection with several STI, female sex and being single. Although the model is significant, the codetermination coefficients (R^2) show that it explains only a small part of the analyzed variation. This indicates there might be other significant risk factors, which were not included in the analysis.

To achieve make our analysis and study more precise, weighted logistic regression was employed; this made it possible to consider impacts exerted by different factors more profoundly. This approach confirmed the results obtained by the case-control study and revealed additional significant associations: regular sexual contacts (*OR* = 1.56) and being a minor (*OR* = 3.26) turned out to be associated with elevated risks of co-infection with several STI pathogens. Minor patients face a considerably higher risk of co-infection as compared with people aged between 18 and 29 years. This difference may be due to anatomic and physiological peculiarities of the genital organs as well as low awareness, tendency to neglect barrier contraception (largely due to difficulty in buying relevant means). Another reason might be difficulties in performing STI prevention check-ups when it concerns young patients (both psychological and financial), which make young people more susceptible to sexually transmitted infections. Use of weighted logistic regression raised the explanatory capability of the model considerably, which is confirmed by the determination coefficients growing up to R^2 = 0.179 (Cox & Snell) and R^2 = 0.239 (Nagelkerke). High statistical significance of the model is confirmed by the Chie-square test results (χ^2 = 187.539; p < 0.001). These data give evidence that the model is reliable and capable of adequately describe relationships between key risk factors and likelihood of co-infection.

Conclusions. Co-infection with other STI pathogens was established in 7.8 % of the analyzed patients with genitourinary chlamydial infection; more frequently, it occurred together with anogenital (venereal) warts (80.9 %), anogenital herpes (20.2 %) and gonococcal infection (14.8 %).

Female sex, age between 18 and 29 years, being a minor, regular sexual contacts and being single are key independent risk factors of co-infection with simultaneously *C. trachomatis* and other STI pathogens.

Our findings give evidence of the necessity to intensify prevention aimed at reducing levels of co-infection with several STI pathogens. Given that women and young people are the most susceptible population groups, prevention programs should include some educational initiatives targeted at them. Such activities should be aimed at promoting barrier contraception and safe sex concepts (having one regular sexual partner, both partners having regular check-ups to identify STI) [20]. It is also important to develop a system for early testing and preventive check-ups and to implement programs for raising awareness and motivation of both partners to have an examination and, if necessary, treatment. This will help effectively break the chain of infection transmission.

A complex approach based on the findings reported in this study can make for reduction in incidence, prevention of complication and protection of reproductive health.

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Research article

OBESITY AND METABOLIC SYNDROME ASSOCIATED WITH COMBINED LOW-DOSE EXPOSURE TO DISRUPTOR METALS AND CHLORINATED ORGANIC COMPOUNDS IN DRINKING WATER

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The aim of the study was to examine peculiarities of obesity development under combined exposure to disruptor metals and chlorinated organic compounds among population and in an experimental study upon exposure to doses not exceeding the maximum permissible levels.

Clustering was carried out according to indicators of total and primary obesity (E66) incidence among population of the Orenburg region in several age groups: 0–14 years, 15–17 years, 18 years and older, as well as among the total population. Hygienic assessment of drinking water taken from the centralized water supply system was performed on the territory of the selected clusters to identify levels of disruptor metals and chlorinated organic compounds and to check their conformity with the requirements fixed in the SanPiN 1.2.3685-21. Spearman's rank correlation analysis was carried out.

The experimental study was conducted on male rats; in its course, the experimental group was given drinking water containing iron and 2,4-DA in concentrations corresponding to 0.5 MPC. Upon completion of the experiment, relevant indicators were measured in the lab animals including body weight, epididymal fat mass, and levels of the following hormones: insulin, leptin, T3, and T4.

Clustering of municipalities revealed areas with high obesity prevalence among local population including areas with a 2.2-fold higher level of obesity among children aged 0–14 years, 3-fold among children aged 15–17 years and 1.8–1.9 times higher prevalence among adults against the reference areas and regional averages.

The results of the model experiment revealed 20 % growth in body weight and 8 % growth in adipose tissue mass in the experimental group of lab animals. The level of insulin increased by 23 % and leptin by 1.2 times while the levels of T3 and T4 decreased by 27 % and 44 %, respectively.

There are differences in indicators and statistically significant correlations indicating the need to further investigate cause-and-effect relations between obesity and effects produced by disruptors.

Keywords: *metabolic syndrome, low doses, disruptor, 2,4-D, 2,4-dichlorophenoxyacetic acid ammonium salt, microelements, obesity, drinking water, iron.*

The Healthcare National Project outlines the key tasks in consolidating efforts made by the state and the society and aimed at improving health of both adult and child population of the country. The project goals can be achieved only by implementing the Strategy for National Safety in the sphere of sanitary-epidemiological wellbeing combined with

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relevant activities aimed at promoting healthy lifestyles.

Issues related to healthy lifestyle promotion remain especially relevant at the moment since they have direct effects on health and physical development, especially when it comes down to children. In 2018, several goals were set within the National Project to optimize environmental conditions and improve population health measures. Since then, they have been achieved according to schedules and quite effectively. Nevertheless, physical development of the country population cannot be considered satisfactory since the proportion of people with overweight and obesity has been growing. This makes the highlighted issue a priority one [1, 2].

Thus, the WHO estimations show that the proportion of global population with overweight has tripled since the middle of 1970ties. This is also typical for the Russian Federation as a whole. Thus, a study performed by an expert team revealed that people with overweight accounted to 20–55 % in the country population and an ascending trend was identified for overweight prevalence among children. In 2023, the number of overweight and obese children tripled against 2013 [3]. The proportion of overweight children is growing faster against the same indicator in adult population [3–5].

This existing negative trend established within the Population Health Improvement Observation Program is typical for the Orenburg region as well. Thus, according to monitoring results obtained by Rospotrebnadzor within the Demography National Project, more than 20 % of people in the age group younger than 18 years were obese or overweight [1].

In addition to carbohydrate and lipid metabolic disorders, obesity involves disrupted metabolism of chemical elements, iron being one of them [6, 7]. Effects produced by iron on body tissues involve damage to the lipid bilayer in cell membranes by free radicals. The liver, pancreas and adipose tissue are primary targets upon iron exposure; given that, realization of biological effects produced by iron on the body seems quite significant in pathogenesis of obesity and metabolic syndrome [8–10].

Long-term research has established that endocrine disorders develop not only due to unhealthy lifestyle and diets but also due to exposures to endocrine disruptors, primarily, chlorinated organic compounds and metals. Their destructive properties have been shown to become evident even upon exposures to their permissible levels [11–15]. Chlorinated organic compounds occur in drinking water due to water treatment and human-induced pollution in surface water bodies and underground water sources. Apart from human-induced pollution, metal occurrence in drinking water is directly linked to biogeochemical structures of soil and adjoining rocks [16, 17].

A growing number of people with endocrine disorders involving metabolic syndrome and obesity calls for well-planned investigations aimed at establishing cause-effect relations together with assessing contributions made by risk factors of the foregoing disorders. Results obtained by clinical studies and experiments [18] clearly indicate that iron and chlorinated organic compounds affect adipose tissue functioning. Despite that, a role played by combined exposure to these disruptors in doses within established safe ranges in pathogenesis of obesity and metabolic syndrome has not been examined sufficiently so far.

The aim of this study was to perform hygienic assessment of obesity prevalence among population associated with exposure to metals and chlorinated organic compounds in water from centralized water supply and in an animal experiment simulating exposure to doses not exceeding the maximum permissible levels.

Materials and methods. To achieve the study aim, pathology as per the disease class E66 (obesity) was analyzed by using data provided by the Healthcare Information Analytical Center (41 settlements and districts; 2013–2021). Areas in the region with high proportion of obese people were established by using clusterization, a statistical method for arranging proper groups of attributes. To make these groups, the following attributes were employed: total obesity incidence (age groups: between 0 and 14 years; between 15 and 17 years; 18 years and older).

Hygienic assessment of drinking water in the analyzed areas relied on sanitary-hygienic analysis aimed at checking conformity with the SanPiN 1.2.3685-21 Hygienic Standards and Requirements to Providing Safety and (or) Harmlessness of Environmental Factors for People[1].

An experiment on assessing metabolic disorders in animals (56 male Wistar rats) was conducted to confirm results obtained by field investigation.

Requirements stipulated by the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Strasburg, France, 1986) were met in the accomplished experiment. At the start of experimental research, all animals were divided into the test and control groups; animals' weight was 165 ± 5 grams. Animals in the test group were given drinking water with iron and 2,4-DA in concentrations equal to 0.5 MPL. The experiment lasted for 135 days. The animals were euthanized by decapitation and blood serum was analyzed to check levels of triiodothyronine (T3), thyroxine (T4), insulin and leptin using Roche test systems (Switzerland) and a Cobas e 411 device.

All obtained data were analyzed using Microsoft Excel and Statistica V.10. All analyzed attributes were tested to prove their conformity to the Shapiro – Wilk normality test; therefore, the results were given as simple mean (*M*) and standard error of mean (*m*). Statistical validity was determined per parametric Student's t-test. Correlations (direction and intensity) between the analyzed attributes were established by Spearman's correlation analysis (Spearman's rank correlation coefficient R). Significance P-test was established by using Fischer's exact test.

Results and discussion. Over the analyzed period, obesity was established to be more prevalent among adolescents aged 15–17 years in the Orenburg region (54.68 ± 1.048 cases per 1000 people) than among children younger than 14 years (24.49 ± 0.976 cases per 1000 people). Over the analyzed period, obesity incidence was the highest in 2020 in the Orenburg region and then declined in 2021 from 52.9 ± 1.519 down to 36.68 ± 1.406 cases per 1000 people (Figure 1), which was due to limited numbers of examined patients during the pandemic and valid epidemic restrictions. An authentic 2-2.5 times increase in the number of overweight and obese people was established in the Orenburg region. It is noteworthy that the growth was the highest in the age group of 15–17 years.

Municipal districts and settlements in the region were combined into three clusters by statistical data clustering. The first cluster (the observation areas including such towns as Novotroitsk, Buzuluk, Abdulino, Gai, Buguruslan, Mednogorsk and such districts as Oktyabrskii, Grachevskii, Asekeevskii, and Severnyi) had the highest obesity prevalence and primary obesity incidence reached 35.5 ± 0.15 cases per 1000 people among children aged 0–14 years. It is 2.1 times higher than primary obesity incidence among people living in the areas included in the second cluster (the reference areas (16 ± 0.12 cases per 1000 people)) and also 1.5 times higher than the regional average (24.4 ± 0.09 cases per 1000 people). Obesity and overweight reached 97.8 ± 0.18 cases per 1000 people among adolescents aged 15–17 years in the observation areas; this was 3 times as high as in the reference areas (35.2 ± 0.14 cases per 1000 people) and 1.9 times higher than the regional average (54.71 ± 0.11 cases per 1000 people). In the first cluster (the observation areas), obesity prevalence among adults (32.7 ± 0.19 cases per 1000 people) was 1.8 times higher than in

[1] SanPiN 1.2.3685-21. Gigienicheskie normativy i trebovaniya k obespecheniyu bezopasnosti i (ili) bezvrednosti dlya cheloveka faktorov sredy obitaniya; utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha Rossiiskoi Federatsii ot 28 yanvarya 2021 goda № 2 (s izmeneniyami na 30 dekabrya 2022 goda) [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 (last altered as of December 30, 2022)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573500115 (April 13, 2024) (in Russian).

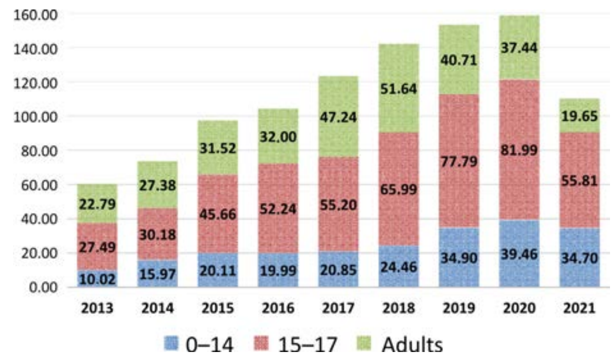

Figure 1. Primary obesity incidence among the Orenburg region population (cases per 1000 people)

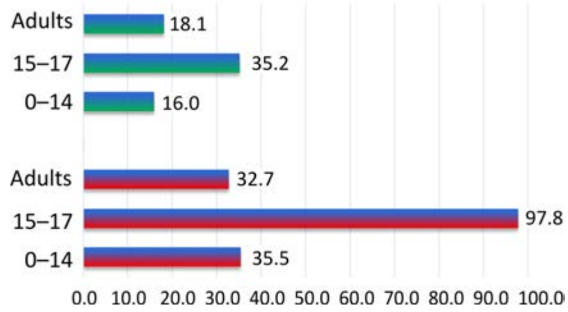

Figure 2. Primary obesity incidence among the population in the observation and reference areas (cases per 1000 people)

the second one (the reference areas (18.1 ± 0.14 cases per 1000 people)) and 1.9 times higher than the regional average (34.5 ± 0.12 cases per 1000 people) (Figure 2). Therefore, obesity prevalence tends to be 1.5–2 times higher than the regional average in all age groups in the areas in the Orenburg region included in the first cluster and labeled as observation areas. This requires an additional and more profound investigation aimed at establishing cause-effect relations of frequent obesity among the population in these areas (Figure 3).

The third cluster included areas without any significant differences in obesity prevalence as compared to the regional average.

The next stage in this research involved estimating levels of metals and chlorinated organic compounds in drinking water in the analyzed areas. The analysis did not establish any violations of maximum permissible levels (MPL) for the analyzed metals, which could be considered endocrine disruptors. Nevertheless, levels of iron (0.70 ± 0.11 MPL), manganese (0.49 ± 0.11 MPL), lead (0.39 ± 0.05 MPL), chromium (0.23 ± 0.03 MPL), nickel (0.36 ± ± 0.04 MPL) and cadmium (0.28 ± 0.07 MPL) in drinking water were significantly ($p \leq 0.05$) 1.4–2.5 times higher in the areas in the first cluster with the highest obesity prevalence among population than in the reference areas. The coefficient for the total disruptor metal contamination in water from centralized water supply was shown to be twice as high in the observation areas and equal to 2.74 ± 0.97 (Table 1).

Analysis of possible correlations between obesity incidence among the total population and levels of disruptor metals established positive correlations between them; significant ($p \leq 0.05$) weak correlations were established for levels of iron, manganese, lead, chromium, and nickel as well as with the total disruptor metal contamination in drinking water (Table 1).

The accomplished analysis did not establish any violations of maximum permissible levels as regards analyzed chlorinated organic compounds, which could be considered endocrine disruptors. Nevertheless, levels of 2,4-D (0.037 ± 0.006 MPL), benzene (0.171 ± 0.066 MPL), chloroform (0.090 ± 0.012 MPL), tetrachloromethane (0.216 ± 0.048 MPL), 1,2-dichloroethane (0.134 ± 0.032 MPL), bromoform (0.027 ± 0.001 MPL), and DDT (0.0004 ± 0.0002 MPL) in drinking water were significantly ($p \leq 0.05$) 1.4–2.5 times higher in the areas in the first cluster with the highest obesity prevalence among population than in the reference areas. The coefficient for the total contents of chlorinated organic compounds did not exceed safe ranges; nevertheless, it was 1.5 times higher in the observation areas and equaled 0.926 ± 0.042 (Table 2).

The Spearman's correlation method established positive correlations between obesity prevalence in the population and levels of chlorinated organic compounds in drinking water; significant correlations were established for 2,4-D, benzene, chloroform, DDT and the coefficient for the total contamination with chlorinated organic compounds (COCs) in water from centralized water supply (Table 2).

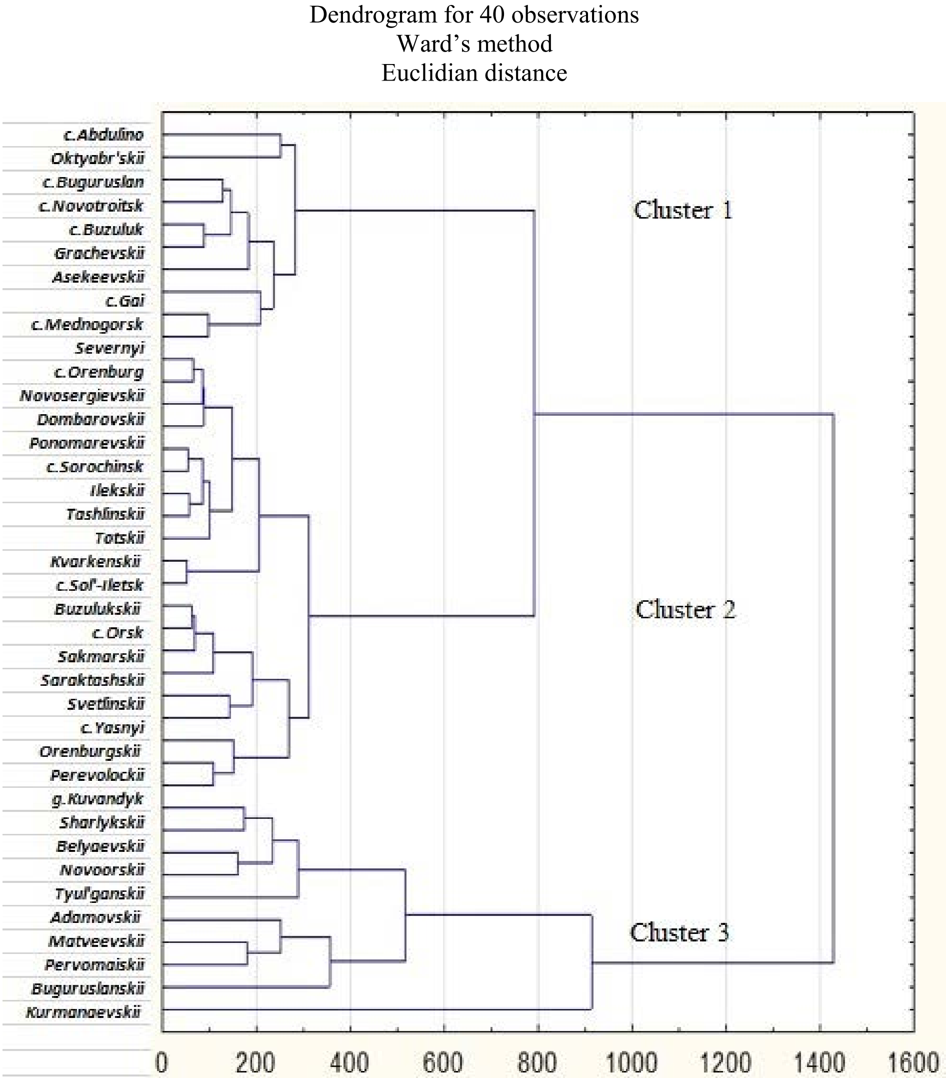

Figure 3. Three clusters of the areas in the Orenburg region per obesity incidence

Table 1

Levels of disruptor metals in water from centralized water supply ($M \pm m$, % of MPL)

Metal	Observation areas	Reference areas	Spearman's R (correlation between obesity incidence and levels of disruptor metals)
Chromium	0.229 ± 0.024*	0.109 ± 0.028	0.12*
Iron	0.69 ± 0.109*	0.386 ± 0.08	0.21*
Copper	0.039 ± 0.008	0.038 ± 0.007	0.05
Manganese	0.485 ± 0.108*	0.149 ± 0.029	0.18*
Aluminum	0.119 ± 0.068	0.109 ± 0.0289	0.01
Lead	0.39 ± 0.05*	0.195 ± 0.049	0.22*
Molybdenum	0.018 ± 0.0008	0.0198 ± 0.007	0.05
Cadmium	0.278 ± 0.068*	0.198 ± 0.0567	0.09
Nickel	0.356 ± 0.038*	0.218 ± 0.039	0.11*
Selenium	0.007 ± 0.009	0.038 ± 0.008	0.03
Mercury	0.046 ± 0.017	0.068 ± 0.017	0.08
Zinc	0.048 ± 0.028*	0.029 ± 0.009	0.02
Total contamination (*Me*)	2.736 ± 0.968*	1.576 ± 0.808	0.28

Note: * difference from the reference areas is valid, $p \leq 0.05$.

Table 2

Levels of chlorinated organic compounds in water from centralized water supply
($M \pm m$, % of MPL)

Chlorinated organic compounds	Observation areas	Reference areas	Spearman's *R* (correlation between obesity incidence and levels of chlorinated organic compounds)
2,4-D	0.037 ± 0.006*	0.020 ± 0.005	0.19*
Trichloroethylene	0.013 ± 0.003	0.011 ± 0.002	0.11
Tetrachloromethane	0.216 ± 0.048*	0.142 ± 0.026	0.05
Bromdichloromethane	0.123 ± 0.005	0.108 ± 0.055	0.05
Chloroform	0.090 ± 0.012*	0.062 ± 0.036	0.17*
DDT	0.0004 ± 0.0002*	0.0002 ± 0.0001	0.08*
Benzene	0.171 ± 0.066*	0.094 ± 0.037	0.17*
Dibromchloromethane	0.097 ± 0.008	0.073 ± 0.030	0.05
1,2-Dichloroethane	0.134 ± 0.032*	0.109 ± 0.022	0.05
Bromoform	0.027 ± 0.001*	0.011 ± 0.005	0.08
Tetrachloroethylene	0.018 ± 0.004	0.022 ± 0.007	0.09
Total contamination (COCs)	0.926 ± 0.042*	0.652 ± 0.023	0.21*

Note: * difference from the reference areas is valid, $p \leq 0.05$.

The experiment accomplished within the present study involved simulating combined exposure to iron and 2,4-Dichlorophenoxyacetic acid in small below-threshold doses and its effects on obesity and metabolic syndrome development. The experiment results gave grounds for extrapolation of potential effects on human health. This research approach is significant for getting an insight into pathways of such diseases and for developing effective measures to prevent them (Table 3).

Relying on the experiment results, we can conclude that a 20 % growth in body weight was established in animals exposed to low doses of 2,4-D herbicide and iron in drinking water against the controls. Body weight of animals exposed to 2,4-D in drinking water in levels equal to 0.5 MPL grew considerably by 13 % against the controls. Moreover, epididymal fat mass was 8 % higher in animals from the second group against the controls on the 135th day in the experiment.

Repeated exposure to a mix of 2,4-D and iron in low doses in drinking water resulted in insulin levels growing by 23 % in the exposed animals against the controls. It is noteworthy that oral iron intake led to a significant 1.5 times decrease in insulin levels against the unexposed group. A combination of 2,4-Dichlorophenoxyacetic acid and iron led to 1.2 times higher leptin levels against the controls. Repeated intake of this herbicide and iron with drinking water resulted in marked hyperinsulinemia and hyperleptinemia in the experimental animals.

Table 3

Indicators of metabolism regulators under chronic exposure to 2,4-D and Fe^{2+} mixture ($M \pm m$)

Indicators	Day	Group 1 – control (n = 28)	Group 2 – 2,4-D (n = 28)	Group 3 – Fe^{2+} (n = 28)	Group 4 –2,4-D and Fe^{2+} mixture (n = 28)
Body weight, grams	135	331.5 ± 5.32	374.00 ± 6.10*	351.45 ± 9.35	396.2 ± 6.21*
Epididymal fat mass, grams	135	6.61 ± 0.31	6.81 ± 0.26	5.86 ± 0.43	7.11 ± 0.43
Insulin, µIU/ml	135	10.13 ± 0.56	9.11 ± 0.31	8.17 ± 0.23*	12.41 ± 0.23*
Leptin, pg/ml	135	244.00 ± 38.56	264.00 ± 53.16	260.00 ± 34.67	308.00 ± 81.74
T3, pmol/l	135	5.62 ± 0.32	4.37 ± 0.35*	6.22 ± 0.40	4.11 ± 0.08*
T4, pmol/l	135	31.23 ± 0.28	17.40 ± 0.88*	20.10 ± 1.50*	17.42 ± 0.18*

Note: * means authentic differences against the controls, $p \leq 0.05$.

Analysis of the experimental data provided in Table 3 makes it possible to conclude that intake of drinking water with 2,4-D and Fe^{2+} resulted in a considerable decrease in circulating levels of triiodothyronine (T3), by 27 %, and thyroxin (T4), by 44 %, in the experimental animals' serum. This should be taken into account since lower levels of these hormones can have negative effects on metabolic processes in the body. In addition to that, an authentic decrease in T3 and T4 levels, by 22 % and 45 % respectively, was found in the animals from the second group against the control. T4 serum levels went down by 36 % in the animals exposed to iron in drinking water against the unexposed ones.

Intake of drinking water that contains a mixture of 2,4-D (agricultural pesticide) and iron salt (Fe^{2+}), even in levels below safe standards, had more marked effects on the analyzed indicators in the experimental animals. The experiment results indicate that it is important to not only assess exotoxins and their levels separately but also consider their combinations when analyzing exposure to environmental pollution. This combination of environmental factors has shown certain metabolic activity in model experiments.

Our experiment results showed that a combination of two chemicals in low doses, 2,4-D and iron, in drinking water induced negative changes in the experimental animals' bodies. These changes were manifested as growing body weight and accumulation of fat depots. According to literature, 2,4-D as an adverse chemical can promote obesity and metabolic syndrome by influencing the hormonal balance [19]. Therefore, we can assume that changes observed in the 'Organic and Inorganic Disruptors' system can result in increased accumulation of fat tissue in animals.

Iron intake in doses equal to 0.5 MPL can activate free radical oxidation and fat depot formation. The latest research has established that fat tissue is a key target of metabolic effects produced by iron on the carbohydrate and lipid metabolism. Experiments on mice gave evidence that excessive iron in food stimulated iron accumulation in fat depots and promoted insulin resistance [20]. Iron accumulation in liver cells leads to higher insulin levels due to hepatocytes losing their sensitivity to the hormone [21]. Induced hyperinsulinemia in the experimental animals was another significant result of the accomplished experiment. This disorder is a sign of insulin resistance, which is often accompanied with obesity [22].

The experiment data indicate that occurrence of 2,4-Dichlorophenoxyacetic acid and iron in drinking water in levels within safe ranges has a significant impact on the analyzed indicators. This means that metals and chlorinated organic compounds are possibly involved in obesity and metabolic syndrome development through influencing relevant pathological pathways, oxidative stress included [21]. These results emphasize the importance of drinking water quality control and the necessity to conform to maximum permissible levels established for such chemicals in order to prevent negative health outcomes. This also confirms the necessity to conduct further investigations aimed at full disclosure of pathways, through which these chemicals affect development of the analyzed pathologies. In is important to consider these factors when developing environmental and water protection policies aimed at providing the population with safe drinking water and protecting people's health.

Summary and conclusions. Structural-dynamic analysis of obesity incidence in the Orenburg region population gives evidence of a serious challenge for the healthcare system in the region. Our findings indicate that obesity prevalence is higher than both the average level identified in the Volga Federal District and the national average as well. Cluster analysis identified areas with the highest obesity incidence in the Orenburg region. These areas should be given special attention since obesity incidence in them is 1.5–2 times higher than the regional average among both children and adults. This means it is necessary to take relevant measures aimed at fighting obesity in the Orenburg region. Obviously, the current approaches are not effective and require improvement. Possible solutions include conducting prevention campaigns and educational work, developing individual programs for losing weight and organizing physical activity as well as creating specialized centers for fighting obesity. It is noteworthy that reduction in obesity incidence in the Orenburg region has positive influence on population health since obesity is a well-known risk factor of such serious diseases as diabetes mellitus, cardiovascular pathologies and some cancers.

Therefore, it is necessary to take action to reduce obesity incidence in the Orenburg region and to improve people's health. This should become a priority task for local authorities, healthcare experts and the society in general.

Levels of metal disruptors and chlorinated organic compounds in drinking water were established to be within their safe ranges in all analyzed areas. Nevertheless, levels of chemicals were 1.5–2 times higher in drinking water in the observation areas against the reference ones. The correlation analysis was then conducted for further investigation of effects produced by the 'Organic and Inorganic Disruptors' system on health. It established a significant positive weak and very weak correlation between obesity incidence and levels of the analyzed endocrine disruptors in drinking water. This allowed us to plan and conduct the animal experiment on rats to investigate effects produced by the analyzed disruptors on indicators that describe fat metabolism and metabolic syndrome development.

The results obtained by the modeling animal experiment showed that oral intake of 2,4-D and iron in low doses had an obesogenic effect, which was caused by promotion of free radical oxidation. These changes in animals can be caused by weaker activity of thyroid hormones induced by low-dose exposure to 2,4-D; they can also result from developing insulin resistance.

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Research article

COMPARATIVE ASSESSMENT OF ISOLATED INFLUENCE EXERTED BY PHYSICAL AND CHEMICAL FACTORS ON RELATIVE TELOMERE LENGTH OF LABORATORY ANIMALS IN A MODEL EXPERIMENT

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Assessment of effects produced by physical and chemical occupational factors on changes in the relative telomere length (RTL) in workers is a promising trend in contemporary research. It can be used as a marker of not only ageing but also intensity of oxidative stress and chronic inflammation. Simulation of such effects in experiments on laboratory ICR mice and Wistar rats enriches our knowledge on the subject.

In this study, we were interested in performing comparative assessment of isolated effects produced by physical and chemical factors on the relative telomere length of laboratory animals in a model experiment. The study involved using laboratory animals (mice, n = 65; rats, n = 65) divided into the experiment (total vibration, noise and a mixture of aromatic hydrocarbons) and the control groups. Animals in the control group were intact. Exposure to chemical and physical factors was simulated in a model animal experiment. The relative telomere length was established using the quantitative real-time polymerase chain reaction. The experimental data were analyzed by non-parametric analysis techniques in Statistica 10 software package. Intergroup differences were estimated using the Mann – Whitney test. Critical significance in testing of statistical hypotheses was taken below 0.05.

Physical and chemical factors had the greatest influence on RLT shortening in the experimental animals relative to the control (intact animals). This indicates activation of the accelerated ageing pathways and growing risks of diseases associated with these exposures. The fastest RLT shortening rates were established upon exposure to total vibration and the chemical factor in mice after 30 days in the experiment; rats, after 60 days. The maximum growth in RLT shortening upon exposure to noise was established in mice after 60 days in the experiment; rats, after 180 days. Differences in RLT in comparison with its initial value were lost in mice on the 90th day in the experiment and in rats on the 180th day of the modeled chemical and physical exposure, which may be interpreted as overall ageing of the experiment animals.

RLT shortening in biological objects upon long-term exposure to adverse chemical and physical factors gives evidence of accelerated ageing of the biological systems in the body and can create elevated risks of cardiovascular and aging-associated diseases.

Keywords: *occupational factors, periodic effects, physical exposure, chemical exposure, mice, rats, relative telomere length, comparative assessment, comparability of the results, accelerated ageing, risks.*

Assessment of effects produced by physical and chemical occupational factors on changes in the relative telomere length (RTL) in workers is a promising trend in contemporary research. It can be used as a marker of not only ageing but also intensity of oxidative stress and chronic inflammation. Simulation of such effects in experiments on laboratory ICR mice and Wistar rats enriches our knowledge on the subject [1].

Chronic effects produced by physical [2] and chemical [3] occupational factors (stressors) [4] on employable population can lead to health impairments, increase risks of

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various diseases [5] and trigger accelerated ageing [6, 7].

Long-term exposure to various stressors can induce accelerated biological ageing (reduced leucocyte telomere length) and chronic hyperactivation of the body's physiological stress systems [8]. Combined exposure to physical and chemical stressors, both at workplace and at home, also promotes prevalence of occupational diseases and accelerated ageing [9].

A study by L.Y. Hao et al., 2005, established that the progressive worsening of disease was directly associated with decreasing telomere length, which was manifested by stem cell failure [10]. This is also confirmed by findings reported in some other studies; thus, M. Shoeb et al., 2021, found that accelerated ageing and incidence were closely related to telomere length [11]. Several foreign studies accomplished by leading experts (H. Li et al., 2021; B. Celtikci et al., 2021) reported that reduced RTL was a biomarker of human ageing and was associated with developing age-related renal diseases [12]; it also increased the risk of diseases associated with weaker cell proliferation and tissue degeneration [13]. However, at present biomedical studies with their focus on investigating isolated periodical impacts exerted by physical and chemical factors on changes in RTL commonly rely on using model experimental animals, such as ICR mice and Wistar rats [14, 15]. This helps investigate processes and pathways of accelerated ageing.

The aim of this study was to perform comparative assessment of isolated effects produced by physical and chemical factors on the relative telomere length of laboratory animals in a model experiment.

Materials and methods. The study involved using laboratory animals, ICR mice (n = 65) and Wistar rats (n = 65) for 90 and 180 days accordingly considering the recommendations stipulated in European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes[1] and Guide for the Care and Use of Laboratory Animals (Washington, 2011)[2].

According to the experiment design, the animals were divided into four groups; each group included the equal number of animals. The first group (n = 15 + 15) was the control one (animals not exposed to any physical or chemical occupational factors).

The second animal group (n = 15 + 15) was exposed to vibration similar to technological one typical for stationary workplaces[3]: vibration acceleration levels in octave bands with center frequencies were 1–63 Hz, OX – 57.3–100.2; OY – 51.4–101.5; OZ – 62.5–103.6 dB; equivalent adjusted vibration acceleration level was as follows, dB: OX – 98.6; OY – 99.9; OZ – 102.1; the exposure lasted for 0.5 hour every day.

The third animal group (n = 15 + 15) was exposed to noise at the level of 81.5–85.3 dBA in a noise chamber for 0.5 hours every day. The fourth animal group (n = 15 + 15) was exposed to a chemical mixture of hydrocarbons, 200 liter volume, in an inhalation exposure chamber: dimethyl benzene (a mixture of 2-, 3-, 4-isomers), 225 mg/m^3; benzine fuel sol-

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[1] European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes ETS N 123 (Strasburg, March 18, 1986). *GARANT: information and legal support*. Available at: https://base.garant.ru/4090914/?ysclid=lx32x1xmrq588324754 (December 12, 2024).

[2] National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals. Guide for the Care and Use of Laboratory Animals, 8[th] ed. Washington (DC), National Academies Press Publ., 2011. DOI: 10.17226/12910

[3] SanPiN 1.2.3685-21. Gigienicheskie normativy i trebovaniya k obespecheniyu bezopasnosti i (ili) bezvrednosti dlya cheloveka faktorov sredy obitaniya (s izmeneniyami na 30 dekabrya 2022 goda), utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha Rossiiskoi Federatsii ot 28 yanvarya 2021 goda № 2 [Hygienic standards and requirements to providing safety and (or) harmlessness of environmental factors for people (last amended as of December 30, 2022), approved by the Order of the RF Chief Sanitary Inspector on January 28, 2021 No. 2]. *KODEKS: electronic fund for legal and reference documentation*. Table 5.4. Available at: https://docs.cntd.ru/document/573500115 (December 12, 2024) (in Russian).

vent, 225 mg/m^3; methyl benzene, 450 mg/m^3; propane-2-on, 1200 mg/m^3 in a concentration equal to 1.5 MPL for 0.5 hour daily.

To perform a background analysis, control groups were made of five animals each (*n* = 5 + 5), which were kept separately from the rest.

RTL was established on the Day 0, 30 (60), 60 (120) and 90 (180) in the experiment. DNA was extracted from biological samples of transversal striated muscle fiber of the animal thigh by phenol-chloroform extraction[4] using quantitative real-time PCR based on the methodology developed by R.S. Lee et al. [16] and modified by V.N. Maksimov [17]. DNA concentration was measured with an Epoch microplate spectrophotometer (BioTek Instruments, USA).

The albumin gene was taken as a single-copy reference gene. Separate quantitative reactions for telomeres and the albumin gene were set in pair 96 well plates in identical positions. Each plate included a series of DNA dilutions (0.5; 1.0; 2.0; 5.0; 10; 20 and 30 ng), which were used to create a calibration curve and quantitative estimation of each sample.

A reaction mixture for the telomere analysis contained the following reagents: 270 nM tel1b primer (5′ ACACTAAGGT-TTGGGTTTGG-GTTTGGGTTT-GGGTTAGTGT 3′); 900 nM tel2b primer (5′ TGTTAGGTAT-CCCTAT CCCT-ATCCCTATCC-CTATCCCTAACA-3′); 0,2X SYBR Green I; 5 mM DTT (dithiothreitol); 1 % DMSO (dimethyl sulfoxide); 0.2 mM of each dNTP; 1.5 mM MgCl2; 1.25 units of DNA polymerase in the total volume of 15 µl of the PCR buffer. The PCR cycles were as follows: 10 minutes at 95 °C, then 25 cycles as 15 seconds at 95 °C, 30 seconds at 54 °C, and 90 seconds at 72 °C. A reaction mixture for the albumin gene analysis contained the following reagents: 300 nM Albd primer (5′ GCTGACT GCT-GTACAAAACA-AGAG-3′), Albr primer (5′ TGACTATCAG-CATAAGTGTT-ACTA-3′), 0.2X SYBR Green I; 5 mM DTT (dithiothreitol); 1 % DMSO (dimethyl sulfoxide); 0.2 mM of each dNTP; 1.5 mM MgCl2; 1.25 units of DNA polymerase in the total volume of 15 µl of the PCR buffer. The PCR cycles were as follows: 3 minutes at 95 °C, then 35 cycles as 15 seconds at 95 °C, 20 seconds at 58 °C, and 20 seconds at 72 °C. Both reactions were set on a QuantStudio 5 amplifier (Thermo Fisher Scientific, USA). The quality control was performed and the T / S (telomeres to the single copy gene) ratio was calculated. If sample amplification curves had standard deviation > 0.5 in three replicas, than this sample was excluded from further analysis [18].

Experimental data were statistically analyzed using non-parametric analysis methods in the Statistica 10 software. Intergroup differences were estimated using the Mann – Whitney test. Critical significance in statistical hypothesis testing was taken at the level below 0.05.

Results and discussion. The experiment on Wistar rats continued our previous experiments on ICR mice [18], which made it possible to compare repeatedly obtained experimental data basing on biomechanical simulation. Analysis of RTL in muscle thigh tissue samples in the experimental groups revealed a significant association between RTL and age during the 90 days of observation for ICR mice and 180 days of observation for Wistar rats. RTL differences were also established between the experimental group and the control. For example, RTL turned out to be reduced in control ICR mice on Day 90 in the experiment (0.33 [0.32; 0.35] relative units) against Day 0 (0.84 [0.81; 0.93] relative units). In control Wistar rats, a similar result was obtained as regards RTL reduction (Table) on Day 180 (1.52 [1.48; 1.61] relative units) against Day 0 (2.38 [1.92; 2.41] relative units).

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[4] Smith K., Kalko S., Cantor Ch. Pul's-elektroforez i metody raboty s bol'shimi molekulami DNK [Pulsed-field gel electrophoresis of large DNA molecules]. In book: *Analiz genoma [Genome analysis]*. Moscow, Mir Publ., 1990, pp. 58–94 (in Russian).

Table

Comparative results obtained for isolated effects produced by occupational factors on RTL of ICR mice [18] and Wistar rats in model experiment, *Me* [*LQ*; *HQ*]

Group	*n*	Day 30	*n*	Day 60	*n*	Day 90	*n*	Day 60	*n*	Day 120	*n*	Day 180
	RTL of ICR mice [18]						*RTL of Wistar rats*					
Group 1 (control)	5	0.79 [0.73; 0.81]	5	0.62 [0.55; 0.76]	5	0.33 [0.32; 0.35]*	5	1.84 [1.82; 2.38]	5	1.79 [1.66; 2.22]	5	1.52 [1.48; 1.61]*
Group 2 (vibration)	5	0.61 [0.61; 0.66]	5	0.47 [0.38; 0.55]*,#	5	0.29 [0.28; 0.32]*,#	5	1.79 [1.72; 2.31]	5	1.11 [0.98; 1.27]*,#	5	0.69 [0.62; 0.82]*,#
Group 3 (noise)	5	0.61 [0.61; 0.66]	5	0.47 [0.38; 0.55]*,#	5	0.29 [0.28; 0.32]*,#	5	1.72 [1.51; 1.79]	5	1.47 [0.96; 1.49]*,#	5	0.83 [0.77; 0.93]*,#
Group 4 (chemicals)	5	0.56 [0.56; 0.69]*	5	0.37 [0.28; 0.41]*	5	0.25 [0.25; 0.35]*	5	1.51 [1.39; 1.57]*	5	1.03 [1.01; 1.13]*	5	0.67 [0.67; 0.82]*

Note: Table provides significant ($p < 0.05$) differences from the respective indicators: * – on Day 0, # – against the control; table also contains the results obtained in our previous study focused on RTL of ICR mice [18].

Comparative assessment of isolated impacts exerted by physical factors on mice RTL (Group 2 and 3) revealed a significant RTL reduction on Day 60 (Group 2 and Group 3 (0.47 [0.38; 0.33] relative units) and Day 90 (Group 2 and Group 3 (0.29 [0.28; 0.32] relative units) against the control on Day 60 (0.62 [0.55; 0.76]) and Day 90 (0.33 [0.32; 0.35]). A similar picture involving RTL reduction was observed for the experimental Wistar rats exposed to the selected physical factors on Day 120 in Group 2 (exposed to vibration (1.11 [0.98; 1.27] relative units) and Group 3 (exposed to noise (1.47 [0.96; 1.49] relative units)) and on Day 180 (Group 2 (0.69 [0.62; 0.82] relative units) and Group 3 (0.83 [0.77; 0.93] relative units)) against the control on Day 120 (1.79 [1.66; 2.22]) and Day 180 (1.52 [1.48; 1.61]). The analyzed physical factors affected the central nervous system (CNS) and cerebellum functioning, which led to RTL reduction and accelerated ageing of the biological systems in the experimental animals (on Day 60 and 90 in mice; on Day 120 and 180 in rats) against the control.

Exposure to a mixture of toxicants resulted in a considerable RTL reduction in the mice and rats from the chemically exposed groups against the control and those groups exposed to isolated impacts of the analyzed physical factors (see Table). In the experimental mice, RTL reduction occurred on Day 30 (0.56 [0.56; 0.69]) and only grew later on Day 60 (0.37 [0.28; 0.41]) and 90 (0.25 [0.25; 0.35]) against the control on Day 30 (0.79 [0.73; 0.81]), Day 60 (0.62 [0.55; 0.76]) and Day 90 (0.33 [0.32; 0.35]) [18]. Similarly, reduced RTL was established in the experimental rats (see Table) starting from Day 60, 1.51 [1.39; 1.57], against the control (1.84 [1.82; 2.38]); Day 120, 1.03 [1.01; 1.13], against the control (1.79 [1.66; 2.22]); and Day 180, 0.67 [0.67; 0.82], against the control (1.52 [1.48; 1.61]). Exposure to the 4-component mixture of hydrocarbons affected the alveolar-capillary lung membrane and the olfactory bulb and had negative effects on the CNS together with RTL reduction and accelerated ageing in the experimental mice and rats from the exposed groups against the control.

The results obtained by the previous experiments performed on ICR mice (Figure) [18] turned out to be quite comparable with experimental data repeatedly obtained in the experiment on Wistar rats (% of the RTL value on Day 0).

The greatest RTL reduction rates upon chemical exposure were established in the experimental mice after Day 30 in the experiment; the rats, day 60 in the experiment. RTL reduced most considerably upon exposure to vibration and noise on Day 60 in the experimental mice and Day 120 in the experimental rats. Differences in RTL against its initial level (% of the RTL value on Day 0) were lost in the experimental mice on Day 90 in the experiment and in the rats on Day 180 upon exposure to the analyzed physical and chemical

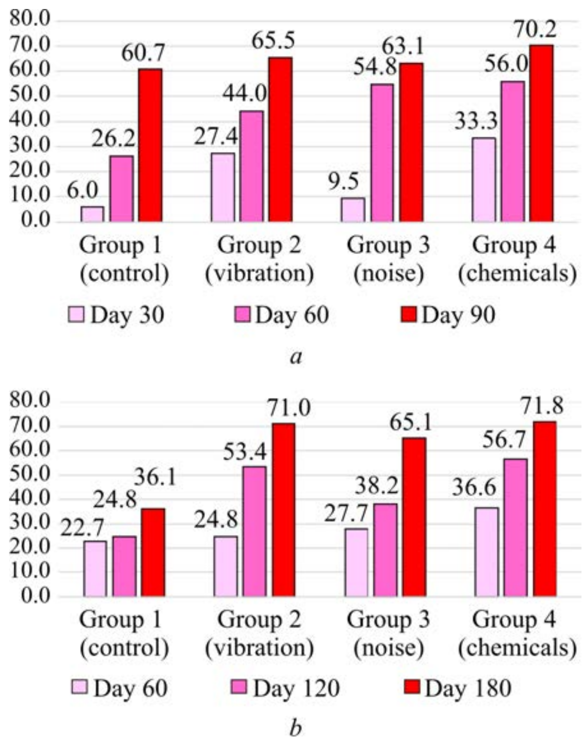

Figure. Changes in RTL (*a*) in ICR mice [18] and (*b*) Wistar rats upon periodic isolated exposure to physical and chemical factors

factors. This may be interpreted as overall ageing of the animals and elevated risks of chronic non-communicable diseases (as a percentage of their initial level on Day 0).

Available literature does not contain any publications, which allow us to fully estimate isolated effects produced by physical and chemical factors on RTL of Wistar rats in dynamics. The only exclusion was our own experimental study performed on ICR mice [18] and few works by various researchers (J. Lin et al., 2012; D. Stefler et al., 2018; D.D. Karimov et al., 2021), which reported a negative role played by exposure to stress [19] on RTL reduction [20] and developing cellular ageing in industrial workers [21]; this had a direct negative effect on life quality and life expectancy. Given that, we conducted several subchronic and chronic experiments to obtain comparable data about effects produced by periodical physical and chemical exposures (at the level of 1.5 MPL) on different animal species (mice and rats). This made it possible to get more profound knowledge of how to establish health risks and processes of accelerated ageing in biological systems of warm-blooded organisms.

Conclusion. The following conclusions can be drawn basing on the accomplished experimental studies. Telomeres protect the ends of chromosomes and play the key role in maintaining the genome stability and regulating cellular ageing. Our findings can be considered as a confirmation of the hypothesis that RTL reduction in biological objects upon long-term occupational physical and chemical exposure gives evidence of premature cellular ageing. This conclusion is consistent with findings reported in previous studies about the telomere length being a marker of risks of age-related diseases and occupational diseases, including cardiovascular ones (infarctions and strokes) [22]. In addition, isolated periodical exposure to physical and chemical factors (at the level of 1.5 MPL) in a chronic experiment on animal models induced RTL reduction [19], weakened motion, emotional and exploratory activity [1] as well as provoked morphological changes in two and more internal organs (biomarker of accelerated ageing) in animal models. Vascular changes were the most pronounced on Day 180 in the experiment but some initial manifestations occurred on Day 60 and 120 [23], which may indicate that ageing of biological systems was triggered and life expectancy of such animals can be affected.

The greatest effect that promoted RTL reduction in the experimental animals was produced by long-term chemical and vibration exposure in comparison with the control group (the intact animals).

At the initial stage, the smallest effect on RTL in the experimental mice and rats was produced by exposure to noise; later on, noise exposure continued to have the minimal effect on RTL in both species. These manifestations may imply that initially noise does not affect DNA considerably and does not induce the same levels of oxidative stress as total vibration and exposure to a mixture of hydrocarbons. However, despite its less considerable influence, long-term noise exposure can also trigger pathology of many organs and systems

[23] and have negative consequences for health of the whole body [24].

Changes in RTL were the most pronounced in the ICR mice on Day 90 in the experiment and in the Wistar rats on Day 180 upon periodical isolated exposure to the analyzed chemical and physical factors. This term can be recalculated for humans (1.3 weeks of a mouse's life are equal to one human year; 1 week of a rat's life is equal to one human year) and the result may indicate that negative outcomes of occupational exposures appear starting from 10–15 years of work. It should be noted that initial RTL reduction [18] and changes in animals' internal organs start developing when work records reach 5–9 years [23].

RTL reduction in biological objects upon long-term physical and chemical exposures indicates accelerated ageing of the biological systems in the body and may increase risks of cardiovascular and age-related diseases. Some experimental results give evidence of accelerated cellular ageing in the test groups against the control, which is also confirmed by appearing angiopathies in internal organs [23], weaker orientation and exploratory behavior and overall signs of accelerate ageing in experimental animals [1].

Our study emphasizes how important it is to reduce risks of accelerated (cellular) ageing, cardiovascular diseases (infarctions and strokes) in biological objects upon long-term adverse exposure to physical and chemical factors (at the level of 1.5 MPL). Our findings give evidence of the necessity to conduct hygienic control and qualitative hygienic assessment of working conditions at workplaces; to minimize physical and chemical exposures for workers by implementing additional preventive measures, breaks, use of necessary personal protective equipment (protection for eyes, skin and respiratory organs including ear-plugs, gas masks, respirators, goggles, and gloves) and protective clothing and footwear; to conduct ultrasound examinations during mass health examinations aimed at early diagnostics of diseases in workers exposed to occupational adverse factors in order to achieve career longevity.

In future, we plan to have a more profound investigation of pathways through which the above mentioned factors influence telomere length and processes of accelerated ageing of the biological systems in the body.

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Competing interests. The authors declare no competing interests.

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Research article

NOVEL BIOMARKERS FOR CARDIOVASCULAR RISK PREDICTION AMONG PROFESSIONAL DIVERS

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The study relevance is associated with remote negative effects produced by diving on health and related to high fatality rates. Research on cardiovascular risk assessment (CVRA) in divers is scarce. We aimed to evaluate the accuracy of some novel biomarkers versus an established cardiovascular risk estimator in CVRA among professional divers.

A comparative cross-sectional study was conducted on a total of 50 professional divers and an equal number of marine seafarers. Participants were clinically evaluated and subjected to electrocardiography (ECG), basic biochemical analyses, and assessment of some trace metals and oxidative stress biomarkers (OSBMs). Optimal, 10 years, and lifetime CVR was assessed by the Atherosclerotic Cardiovascular Disease (ASCVD) risk estimator. A predictive model for CVR among professional divers was built by testing the performance of some novel biomarkers versus the ASCVD risk estimator.

According to our findings, the professional divers and seafarers showed increased 10 years and lifetime CVD risk compared to the optimal, although the divers were at a higher risk and showed noticeable electrophysiological changes. A proposed model comprising significant CVR predictors and elements of the ASCVD risk estimator improved its performance in CVRA. Corrected QT wave interval was accurate in CVD risk definition and stratification in divers and seafarers (AUC (95 % CI) = 0.692 (0.584–0.800), sensitivity = 60.0 %, specificity = 84.0 %, PPV = 78.9, NPV = 67.7, $p < 0.001$).

Therefore, the CVD risk in divers is quite high and including CVRA in their periodic examinations is crucial. Adding selected biomarkers, particularly ECG changes and some OSBMs with elements of the ASCVD risk estimator improves its accuracy in CVRA.

Keywords: *risk factors, cardiovascular risk estimators, biomarkers, ECG changes, occupational diseases, oxidative stress biomarkers, professional diving.*

Professional divers' tasks expose them to hydrostatic and hyperbaric environments that involve many stresses [1]. This increase in stress levels is multifactorial and could be potentially harmful to the cardiovascular system [2]. Indeed, the unique underwater environment and increased physical efforts, changing hemodynamics (blood pressure and heart rate) and mental stresses during scuba diving are followed by a rise in the production of free radicals, increased oxidative stress (OS) and disturbed trace metal levels that all add to the deleterious effects on the cardiovascular system [3–5]. In addition, water immersion adds thermal stress, which may influence redistribution of the blood flow and volume overload to the compromised heart.

Cardiovascular associated events have been contributing to most of diving-related

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fatalities [6]. Accordingly, cardiovascular risk assessment during fitness evaluation is crucial for identification of patients with high risk of cardiovascular diseases (CVD). Conventional risk assessment tools are commonly utilized either by risk prediction models, risk charts or cardiac stress testing[1]. These decision tools allow early intervention by their users to recommend changes in patients' lifestyles and/or medications. Also, it helps control modifiable CVR factors such as smoking, dyslipidemia, hypertension, diabetes, and obesity [7]. Using cardiovascular risk (CVR) formulae at a population level can be beneficial in surveillance of CVD incidence rates and facilitates target public health interventions [7].

During any enforcement of preventive measures, a global risk approach leads to more accurate estimation of risk and guidance of the clinical primary prevention efforts. Global risk of coronary heart disease (CHD) is defined per calculating the absolute risk of having a CHD event (e.g., death, myocardial infarction) over a certain period. The calculation is based on an empiric equation that combines major risk factors, such as blood pressure and cholesterol levels. The atherosclerosis and cardiovascular diseases (ASCVD) risk estimator depends mainly on the traditional risk factors assessments [8]. It is currently replacing the known Framingham risk score of cardiovascular risk [9]. From the clinical and prevention perspective, there is a demand to improve risk estimation and stratification with robust biomarkers that provide long-term discriminative information better than those available for estimating CVR factors [10]. For instance, the prevalence of some cardiovascular symptoms and diseases may be higher in male former divers than in the general population. Further exploration of novel biomarkers and the recent analytical methods have been mentioned and recommended in many studies [11, 12].

On the other hand, electrocardiogram has been commonly used to determine individuals at high risk of cardiovascular disease. It also predicts those at high risk for certain specific diseases and coronary heart diseases[2]. Professional divers create adaptations to the underwater environmental changes including the myocardium, which may be associated with electrocardiographic (ECG) changes. Pathological ECG findings may offer important clues about structural abnormalities of the heart, that have been identified as possible causes of sudden death in divers [13].

In this context, we proceeded in this study to evaluate some novel biomarkers in CVR assessment among professional divers. This was achieved through investigating conventional as well as novel CVR biomarkers; assessing the validity of ASCVDR estimator and its relation to other biomarkers; and finding the best predictive model for CVR assessment among professional divers.

Materials and methods. The full description of the study population is found in a previous work by our group [14]. Briefly, we conducted a comparative cross-sectional study between June 2017 and May 2018 at the General Naval Hospital in Alexandria. A total of 100 subjects were recruited and assigned into two equal groups (a study group of professional divers (n = 50) and a group of seafarers sharing similar maritime environment except for diving (n = 50)). We used a predesigned interviewing questionnaire to collect background information on divers' sociodemographic data; physical activity and exercise; lifestyle; type of occupational activities; the number of immersions over the last year both as a leisure and occupational activity; average

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[1] Harding D.E. Head Off Stress. Beyond the bottom line. London, Shollond Trust Publ., 2009, 336 p.

[2] Kannel W.B., McGee D., Gordon T. A general cardiovascular risk profile: the Framingham Study. *Am. J. Cardiol.*, 1976, vol. 38, no. 1, pp. 46–51. DOI: 10.1016/0002-9149(76)90061-8

and maximum immersion depth and duration; family and individual medical history stating the existing health issues to exclude concomitant diseases.

The study was approved by the institutional review board and the Ethics Committee of the High Institute of Public Health Alexandria University. The research was conducted in accordance with the ethical guidelines of Helsinki's Declaration (2013). Data sheets were coded with numbers to maintain the anonymity and confidentiality of patient's data.

This article does not contain any studies with animals performed by any of the authors.

We informed the enrolled participants about the aims and concerns of the study and how it will add to better understanding of the disease etiology and triggering factors. The participants appreciated the outlined study aims and tasks and were highly motivated to be included in the cohort for long-term clinical observation. However, we did not involve the participants in the study design, or conduct, or dissemination plans of our research. All the laboratory and clinical data were reported to the participants, and we discussed the study findings in a simple language.

All participants signed an informed written consent after explaining the aim and concerns of the study.

All participants were interviewed to get a clear picture of occupational and common diseases and were clinically evaluated for anthropometric measurements and complete general and heart examination. All divers and marine seafarers were subjected to a 12 leads electrocardiography (ECG) to record Rate/min, QRS complex (msec), P-R interval (msec), QT wave (msec), R-R minimum and R-R maximum which is the measurement of the long lead II during deep inspiration and the Sokolov of the precordial chest leads. We used the equation developed by Chenoweth et al., to calculate the corrected QT wave interval [15]:

The corrected QT =
= QT Interval / sqr (RR Interval)

Basic biochemical analyses, assessment of some trace metals (Cu+, Fe+, and Zn+) and oxidative stress biomarkers (malonic dialdehyde (MDA), total antioxidant status (TAS), glutathione-S-transferase (GST), glutathione (GSH), glutathione-reductase (GR), glutathione peroxidase (GPx), superoxide dismutase (SOD) and catalase (CAT)) were done according to the standard procedures.

Cardiovascular risk assessment (CVRA) was done using the ASCVDR estimator Plus developed by the American College of Cardiology (ACC) and American Heart Association (AHA). The ASCVDR estimator Plus calculates the CVR by using the following data: age, sex, race, SBP, DBP, TC (mg/dl), HDL-C(mg/dl), LDL-C(mg/dl), smoking, history of DM, treatment of hypertension, use of statin, and use of aspirin. It estimates the 10 years risk, the life time risk and mentions the optimal risk value for comparison. It could be also used to compare the risk during the follow up of an individual according to the intervention done [16].

Data was revised and fed to computer software (IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp)). The Kolmogorov - Smirnov test was used to verify the normality of distribution. Qualitative data were described using number and percent. Quantitative data that was described using range (minimum and maximum), mean, standard deviation (SD), median and interquartile range (IQR). Significance of the obtained results was judged at the 5 % level. Chi-square test was used for categorical variables, to compare between different groups. Correction of chi-square was done using the Fischer's exact test (FET) when more than 20 % of the cells have expected count less than 5. Student's t-test was used to compare normally distributed quantitative variables between two studied groups. For abnormally distributed quantitative variables, Mann – Whitney U-test was used to compare between the two studied groups. Pearson coefficient was used to correlate between two normally distributed quantitative variables. To compare between two time periods, Wilcoxon signed ranks test was used for abnormally distributed quantitative variables. Univariate and multivariate binary logistic regression analyses were run to detect the most independent factors/predictors of lifetime, 10 years, and optimal CVD risk. A multivariate binary logistic regression model was built to infer the predicting value, it was used to draw the Receiver Operator Characteristic (ROC) curve and define the area under the curve (AUC). *P* value < 0.05 was set as a level of significance.

Results and discussion. The comparison of the ASCVD risk score between the two studied groups showed that the mean lifetime and the 10 years CVD risk were higher in the professional divers than the controls (46.36 ± 8.75 and 3.62 ± 2.29, $p = 0.081$ vs 40.72 ± 13.99 and 2.68 ± 2.09, $p = 0.009$ respectively). On the other hand, the mean optimal CVR score did not differ significantly between the two groups (0.63 ± 0.27 vs 0.68 ± 0.49 respectively; $p = 0.637$). The 10 years CVD risk was higher than optimal risk with a % change of 74.01 ± 20.35 for the diver and 66.89 ± 17.70 for the marine seafarers (Table 1).

The ROC curve in Figure 1 was built to select the best biomarkers in predicting the optimal, 10 years and lifetime CVD risks. The AUC for the different CVD risks was low (AUC = 0.523, 0.543, and 0.548, respectively $p > 0.05$).

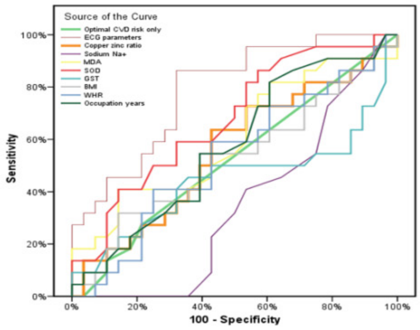
Consistently, ECG changes and serum SOD enzyme level were significant predictors of the optimal, 10 years and lifetime CVD risks as inferred by ASCVD risk estimator ($p < 0.05$). The other tested parameters including BMI, WHtR, serum Na+, serum Cu/Zn ratio, GST, MDA as well as the duration of employment showed poor performance in predicting the CVD risk ($p > 0.05$).

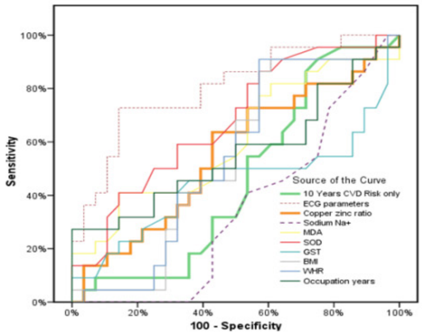
Table 1

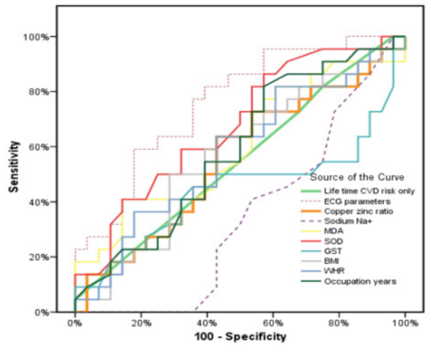
Atherosclerosis Cardiovascular Diseases (ASCVD) risk scores among the enrolled divers and marine seafarers

Cardiovascular Disease Risk (Mean ± *SD*)	Divers (*n* = 50)	Marine seafarers (*n* = 50)	Significance	Validity of differences (*p*)
Lifetime CVD risk	46.36 ± 8.75	40.72 ± 13.99	$t = 2.417^*$	0.018*
10 years CVD risk	3.62 ± 2.29	2.68 ± 2.09	$U = 872.0^*$	0.009*
Optimal CVD risk	0.63 ± 0.27	0.68 ± 0.49	$U = 1196.5$	0.637
Difference	2.99 ± 2.17	2.01 ± 1.74	$U = 885.5^*$	0.012*
% Changes	74.01 ± 20.35	66.89 ± 17.70	$U = 850.0^*$	0.006*
CVD risk (Mean ± *SD*)	Optimal CVD risk	10 years CVD risk		
Divers (*n* = 50)	0.63 ± 0.27	3.62 ± 2.29	$Z = 6.155^*$	< 0.001*
Difference	2.99 ± 2.17			
% Changes	74.01 ± 20.35			
Marine seafarers (*n* = 50)	0.68 ± 0.49	2.68 ± 2.09	6.155*	< 0.001*
Difference	2.01 ± 1.74			
% Changes	66.89 ± 17.70			

Note: CVD is cardiovascular diseases; *t* – Student's *t*-test; *U* – Mann – Whitney test; *Z* – Wilcoxon signed ranks test; *p* value for comparing between optimal CVD Risk and 10 Years CVD Risk in each group; * – statistically significant at $p \leq 0.05$.







		CVD Risk					
		AUC	p-value	Sensitivity (%)	Specificity (%)	PPV	NPV
Optimal CVD Risk~	Optimal CVD risk only	0.523	0.784	27.27	78.57	50.0	57.9
	ECG parameters	0.795	<0.001*	77.27	75.0	70.8	80.8
	Copper zinc ratio	0.555	0.506	63.64	57.1	53.8	66.7
	Sodium Na^+	0.654	0.063	90.91	42.9	55.6	85.7
	MDA	0.605	0.207	40.91	85.7	69.2	64.9
	SOD	0.677	0.033*	86.36	42.9	54.3	80.0
	GST	0.555	0.506	45.45	85.7	71.4	66.7
	BMI	0.528	0.740	54.55	60.7	52.2	63.0
	WHR	0.531	0.710	59.09	57.1	52.0	64.0
	Duration of employment	0.571	0.390	54.55	60.7	52.2	63.0
10 Years CVD Risk~	10 Years CVD Risk only	0.543	0.605	68.18	42.9	48.4	63.2
	ECG parameters	0.787	0.001*	77.27	75.0	70.8	80.8
	Copper zinc ratio	0.555	0.506	63.64	57.1	53.8	66.7
	Sodium Na^+	0.654	0.063	90.91	42.9	55.6	85.7
	MDA	0.605	0.207	40.91	85.7	69.2	64.9
	SOD	0.677	0.033*	86.36	42.9	54.3	80.0
	GST	0.555	0.506	45.45	85.7	71.4	66.7
	BMI	0.539	0.639	68.18	50.0	51.7	66.7
	WHR	0.544	0.598	63.64	50.0	50.0	63.6
	Duration of employment	0.558	0.482	59.09	50.0	48.1	60.9
Life time CVD risk~	Life time CVD risk only	0.548	0.564	4.60	100.0	100.0	57.1
	ECG parameters	0.786	0.001*	72.7	71.4	66.7	76.9
	Copper zinc ratio	0.555	0.506	63.6	57.1	53.8	66.7
	Sodium Na^+	0.654	0.063	90.9	42.9	55.6	85.7
	MDA	0.605	0.207	40.9	85.7	69.2	64.9
	SOD	0.677	0.033*	86.4	42.9	54.3	80.0
	GST	0.555	0.506	45.5	85.7	71.4	66.7
	BMI	0.573	0.379	54.6	60.7	52.2	63.0
	WHR	0.580	0.338	50.0	57.1	47.8	59.3
	Duration of employment	0.588	0.287	54.6	40.6	52.2	63.0

Figure 1. Performance of different biomarkers in predicting the optimal, lifetime, and the 10 years CVD risks among the enrolled divers

Predictors of lifetime and 10 years CVD risks among the studied divers and seafarers. In univariate analysis, history of smoking, disturbed levels of OSBMs (GH, GR, GPx, CAT and SOD), high plasma Cu+ and ECG changes reflecting LVH (S1/2+R5/6) were significantly associated with lifetime and 10 years CVD risk among the studied divers and seafarers. However, in our logistic regression model, history of smoking was the single predictor retained in the equation.

Likewise, none of the variables found associated with prolonged corrected QT interval, namely the WHR, BMI, duration of employment, history of smoking, disturbed levels of OSBMs (MDA, TAS, GSH, GR, CAT and SOD), varied trace metal levels (Fe+, Cu+ and Zn+) and some ECG changes (P-R interval, QRS complex, R-R SD and LVH (S1/2+R5/6)), appeared significant in our logistic regression model (Table 2).

Table 2

Predictors of lifetime CVD risk, 10 years CVD risk and prolonged corrected QT interval among the studied divers and marine seafarers

Parameter	Lifetime CVD risk				10 Years CVD Risk				Corrected QT Interval			
	Univariate analysis		#Multivariate analysis		Univariate analysis		#Multivariate analysis		Univariate analysis		#Multivariate analysis	
	(n = 100)		(n = 100)		(n = 100)		(n = 100)		(n = 100)		(n = 100)	
	OR (95 % CI)	p	OR (95 % CI)	p	OR (95 % CI)	p	OR (95 % CI)	p	OR (95 % CI)	p	OR (95 % CI)	p
Duration of employment	1.023 (0.973–1.077)	0.373			1.061 (1.006–1.118)	0.030*	1.02 (0.95–1.10)	0.510	1.003 (0.954–1.056)	0.895		
Smoking	40.86 (10.92–152.85)	<0.001*	64.25 (13.73–300.2)	<0.001*	10.31 (4.08–26.07)	<0.001*	20.24 (5.31–77.17)	<0.001*	1.440 (0.640–3.241)	0.378		
Systolic blood pressure	1.015 (0.988–1.042)	0.284			1.031 (1.003–1.061)	0.032*	1.04 (0.99–1.07)	0.054	1.028 (0.999–1.058)	0.056		
Diastolic blood pressure	1.002 (0.962–1.043)	0.937			1.022 (0.981–1.065)	0.292			1.015 (0.974–1.059)	0.473		
Waist / height ratio	0.025 (0.000–9.156)	0.221			0.34 (0.001–106.25)	0.715			0.001 (0.000–0.747)	0.040*	0.03 (0.001–118.19)	0.405
BMI (kg/m^2)	0.922 (0.839–1.013)	0.09			0.969 (0.885–1.061)	0.494			0.904 (0.818–1.000)	0.049*		
Glucose (mg %)	0.980 (0.958–1.003)	0.084			0.989 (0.970–1.009)	0.279			0.988 (0.966–1.010)	0.292		
Triglycerides (mg/dl)	1.015 (0.998–1.032)	0.075			1.009 (0.994–1.025)	0.249			0.991 (0.975–1.007)	0.26		
Cholesterol (mg/dl)	1.019 (0.995–1.044)	0.123			1.018 (0.995–1.042)	0.122			0.997 (0.977–1.018)	0.804		
HDL (mg/dl)	1.025 (0.933–1.125)	0.609			0.956 (0.871–1.049)	0.341			1.030 (0.937–1.133)	0.537		
LDL (mg/dl)	1.016 (0.990–1.042)	0.233			1.022 (0.996–1.049)	0.105			0.998 (0.975–1.021)	0.849		
MDA (µl)	1.070 (0.985–1.163)	0.110			1.133 (1.039–1.235)	0.005*	0.94 (0.80–1.11)	0.490	1.189 (1.084–1.304)	<0.001*	1.11 (0.97–1.30)	0.127
TAS	0.554 (0.255–1.205)	0.136			0.591 (0.274–1.275)	0.180			0.295 (0.123–0.708)	0.006*	0.59 (0.16–2.16)	0.425
GST (µm/dl)	0.941 (0.815–1.086)	0.408			0.832 (0.714–0.970)	0.019*	0.88 (0.65–1.18)	0.400	0.775 (0.650–0.925)	0.005*	1.09 (0.81 –1.47)	0.566
GSH (U/ml)	0.915 (0.852–0.983)	0.015*	0.93 (0.78–1.10)	0.373	0.900 (0.837–0.968)	0.004*	0.99 (0.86–1.15)	0.931	0.829 (0.760–0.904)	<0.001*	0.87 (0.76–1.01)	0.061
GR	0.929 (0.880–0.980)	0.007*	0.97 (0.87–1.08)	0.532	0.907 (0.857–0.960)	0.001*	0.94 (0.84–1.05)	0.275	0.915 (0.864–0.970)	0.003*	1.08 (0.97–1.21)	0.183
GPx (U/ml)	0.010 (0.000–0.314)	0.009*	0.37 (0.001–178.6)	0.754	0.005 (0.000–0.178)	0.004*	0.15 (0.001–49.12)	0.518	0.037 (0.001–1.327)	0.071		
SOD (U/ml)	0.991 (0.984–0.997)	0.007*	1.01 (0.10–1.02)	0.163	0.989 (0.982–0.996)	0.002*	1.01 (0.99–1.03)	0.308	0.983 (0.974–0.991)	<0.001*	0.99 (0.98–1.01)	0.347
CAT	0.993 (0.989–0.998)	0.003*	0.99 (0.99–1.01)	0.427	0.992 (0.988–0.997)	0.001*	0.99 (0.99–1.01)	0.663	0.991 (0.986–0.996)	0.001*	0.99 (0.99–1.01)	0.589
Fe^+ (µm/dl)	1.006 (0.997–1.015)	0.193			1.009 (0.999–1.018)	0.071			1.019 (1.008–1.030)	0.001*	1.01 (0.99–1.03)	0.092
Cu^+ (µm/dl)	1.006 (1.001–1.010)	0. 010*	1.01 (0.997–1.01)	0.186	1.008 (1.004–1.013)	0.001*	1.01 (0.99–1.02)	0.067	1.007 (1.002–1.011)	0.002*	0.99 (0.99–1.00)	0.212
Zn^+ (µm/dl)	0.996 (0.982–1.010)	0.566			0.991 (0.977–1.004)	0.183			0.981 (0.966–0.996)	0.014*	0.99 (0.97–1.02)	0.691
Ca^+ (mmol/l)	1.015 (0.504–2.042)	0.968			1.180 (0.591–2.358)	0.639			1.348 (0.658–2.762)	0.415		

End of the Table 2

Parameter	Lifetime CVD risk				10 Years CVD Risk				Corrected QT Interval			
	Univariate analysis (n = 100)		#Multivariate analysis (n = 100)		Univariate analysis (n = 100)		#Multivariate analysis (n = 100)		Univariate analysis (n = 100)		#Multivariate analysis (n = 100)	
	OR (95 % CI)	p	OR (95 % CI)	p	OR (95 % CI)	p	OR (95 % CI)	p	OR (95 % CI)	p	OR (95 % CI)	p
K^+ (mmol/l)	1.396 (0.464–4.200)	0.553			0.876 (0.296–2.596)	0.812			0.955 (0.313–2.921)	0.936		
Na^+(mmol/l)	1.004 (0.905–1.115)	0.933			1.017 (0.917–1.127)	0.752			0.946 (0.850–1.054)	0.316		
Na^+/K^+ ratio	0.958 (0.841–1.092)	0.524			1.017 (0.894–1.157)	0.798			0.987 (0.864–1.127)	0.846		
Urea (mg/dl)	0.956 (0.876–1.044)	0.317			0.964 (0.884–1.051)	0.405			0.973 (0.889–1.064)	0.546		
Creatinine (mg/dl)	0.136 (0.004–4.671)	0.269			0.618 (0.019–19.715)	0.785			0.586 (0.016–20.97)	0.770		
Uric acid (mg/dl)	1.366 (0.888–2.103)	0.156			1.280 (0.842–1.946)	0.249			1.105 (0.724–1.688)	0.644		
AST (mg/dl)	0.975 (0.922–1.032)	0.385			0.960 (0.908–1.016)	0.155			1.013 (0.957–1.072)	0.661		
ALT (mg/dl)	0.970 (0.919–1.024)	0.274			0.948 (0.896–1.004)	0.069			1.027 (0.973–1.085)	0.335		
Bilirubin (mg/dl)	0.113 (0.004–2.849)	0.186			0.214 (0.009–5.089)	0.340			0.129 (0.005–3.603)	0.228		
Rhythm	1.049 (0.399–2.759)	0.922			1.120 (0.426–2.942)	0.819						
Rate/min	0.994 (0.969–1.019)	0.613			0.994 (0.970–1.018)	0.624			0.995 (0.971–1.020)	0.703		
Axis	1.203 (0.631–2.292)	0.575			1.640 (0.843–3.192)	0.145			1.411 (0.756–2.633)	0.280		
P wave	1.470 (0.810–2.667)	0.205			1.281 (0.733–2.236)	0.384			1.487 (0.854–2.590)	0.161		
P-R interval (msec)	1.006 (0.992–1.021)	0.392			1.011 (0.997–1.026)	0.121			1.018 (1.003–1.033)	0.019*	1.00 (0.98–1.02)	0.824
QRS complex (msec)	1.008 (0.988–1.029)	0.433			1.012 (0.992–1.033)	0.230			1.023 (1.001–1.044)	0.037*	1.01 (0.98–1.05)	0.425
QT WAVE (msec)	1.005 (0.993–1.018)	0.405			1.001 (0.989–1.013)	0.894			0.995 (0.982–1.007)	0.408		
Corrected. QT interval	1.005 (0.992–1.017)	0.442			1.002 (0.990–1.014)	0.741						
$S_{1/2}+R_{5/6}$ (mV) (msec)	1.062 (1.001–1.127)	0.047*			1.076 (1.014–1.142)	0.015*	0.98 (0.89–1.09)	0.727	1.100 (1.034–1.170)	0.002*	1.00 (0.91–1.10)	0.988
R-R MIN (mm)	1.093 (0.954–1.251)	0.201			1.078 (0.944–1.231)	0.266			1.066 (0.931–1.219)	0.356		
R-R MAX (mm)	1.092 (0.971–1.229)	0.141			1.097 (0.977–1.232)	0.118			1.122 (0.995–1.265)	0.061		
R-R mean (mm)	1.097 (0.965–1.248)	0.157			1.093 (0.964–1.241)	0.166			1.102 (0.968–1.255)	0.142		
R-R SD (msec)	1.193 (0.662–2.150)	0.557			1.448 (0.800–2.623)	0.222			2.222 (1.163–4.248)	0.016*	1.63 (0.69–3.87)	0.264
ECG	1.930 (0.773–4.816)	0.159			2.316 (0.944–5.679)	0.067			2.236 (0.926–5.400)	0.074		

Note: CAT – catalase; CI – confidence interval; GR – glutathione reductase; GSH – reduced glutathione; GST – glutathione transferase; GPx – glutathione peroxidase; MDA – malonic dialdehyde; OR – odds ratio; SOD – superoxide dismutase; TAS – total antioxidant status. All variables with $p < 0.05$ was included in the multivariate; * – Statistically significant at $p \leq 0.05$.

Performance of the lifetime CVDR, 10 Years CVDR and corrected QT interval risk prediction models in predicting CVD risk. Cutoff points greater than 46, 2.7, and 402 with the best trade-off between sensitivity and specificity significantly defined lifetime CVD risk, the 10 years CVD risk and the corrected QT interval among the study population (AUC (95 % CI) = 0.631 (0.521–0.740), 0.651 (0.542–0.761), and 0.692 (0.584–0.800) respectively, $p < 0.05$). The positive predictive value (PPV) and negative predictive value (NPV) of the chosen cutoff point were 60.3, 66.7, 78.9 and 64.3, 67.3, 67.7, respectively (Figure 2).

Risk stratification of the studied divers and seafarers according to the proposed risk prediction models. According to the preset cutoff points, 70.0 % of diver were at high risk of having lifetime CVD compared to 46.0 % of the marine seafarers ($p = 0.015$). Similarly, 68.0 % and 60.0 % of diver were at high risk of having 10 years CVD risk and prolonged corrected QT interval compared to 43.0 % and 16.0 % of the controls respectively ($p < 0.001$) (Table 3).

Basically, CVR prediction models are important in CVDs prevention and management. It is critical to find such biomarkers that indicate the presence of preclinical

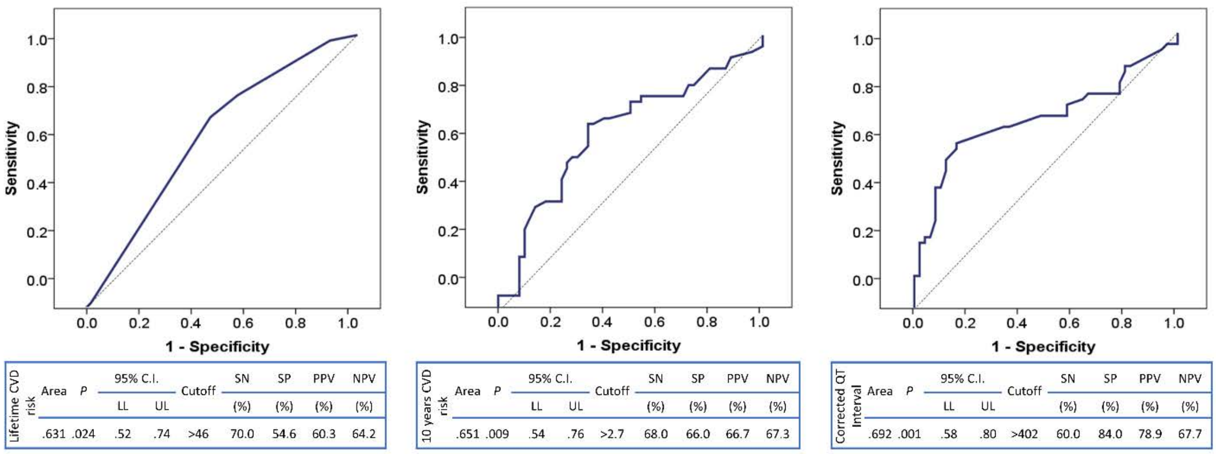


Figure 2. Performance of different risk prediction models in predicting CVD risk

Table 3

Risk stratification of the studied divers and seafarers according to the proposed risk prediction models

Parameter	Divers (n = 50) abs.	Divers (n = 50) %	Marine seafarers (n = 50) abs.	Marine seafarers (n = 50) %	Comparison test (χ^2)	Validity of differences (p)
Lifetime CVD risk						
No risk (≤ 46)	15	30.0	27	54.0	5.911	0.015*
Positive risk (> 46)	35	70.0	23	46.0		
10 years CVD risk						
No risk (≤ 2.7)	16	32.0	33	66.0	11.565	< 0.001*
Positive risk (>2.7)	34	68.0	17	34.0		
Corrected QT interval						
No risk (≤ 402) (milliseconds)	20	40.0	42	84.0	20.543	< 0.001*

Note: χ^2 – Chi-square test. All variables with $p < 0.05$ were included in the multivariate; p – p value for comparing between the studied groups; * – statistically significant at $p \leq 0.05$.

disease in individual subjects like blood biomarkers of atherosclerosis. The ASCVDR score estimator is used in clinical practice to determine the vascular element of the CVR [17–19]. However, clustering of biomarkers as “multi-markers” increases sensitivity and, consequently, stratification of CVR assessments. In this regard, novel biomarkers include OSBMs, ECG, and trace metals.

The present comparative cross-sectional study was conducted to assess the CVR in professional divers using the ASCVD estimator and some novel biomarkers including electrophysiological changes in the ECG, some OSBMs and some trace metals [12, 20, 21].

Consistent with previous reports, high BMI was prevailing among divers [22, 23] and correlated with an increase in the 10 years and lifetime risks of CVD[3] [18, 24]. The mean WHtR was significantly lower in divers than in controls and correlated with prolonged corrected QT interval, which reflects disturbance in the electrophysiological status. This is agreed with the previous studies that reported WHtR as a predictor of CVD risk [17, 18, 25–27].

The main aim in the present study was to assess the CVR in professional divers by using the ASCVD estimator. The mean lifetime, 10 years and optimal CVD risks were significantly higher in divers than in marine seafarers. Moreover, the optimal CVD risk in divers was greater than that of the general population (74.0 % vs 34.0 %, respectively) in the 10 years CVR. The study [10] showed that the prevalence of some cardiovascular symptoms and diseases might be higher in male former divers than in the general population and that diving might have adverse long-term cardiovascular effects. For the marine seafarers, it was 66.89 % more than the optimal CVD for the 10 years risk. So, compared with divers it is still less by 7.12 %. Oldenburg and co-workers showed that German seafarers are twice to three times at more risk for 10 years CVD risk [28, 29], although in the present study, seafarers were at lower CVR. This may be attributed to the age difference between this our study controls as opposed to the German seafarers.

Electrophysiological changes revealed by ECG were obvious among our diver cohort. Indeed, electrophysiological changes are more common and important clues as they are more liable to aggravate arrhythmias in divers. Adding electrophysiological changes to the CVR assessment will help also in risk stratification. Electrophysiological changes precipitating arrhythmias are more relevant etiological factor for cardiac related deaths rather than ischemic coronary vascular changes [30–33]. It is worth noting that electrophysiological changes seen in ECG are the strongest predictive parameter in the study of the CVR. It showed significant difference than other tested parameters in the ROC curve analysis of the optimal, 10 years and lifetime CVD risk. There were no other studies, which described corrected QT wave except a single recent study[4]. The authors reported significant change in the pulse rate, corrected QT, and T wave before and after diving but did not mention any cutoff point.

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[3] Lamon-Fava S., Wilson P.W., Schaefer E.J. Impact of body mass index on coronary heart disease risk factors in men and women: the Framingham Offspring Study. *Arterioscler. Thromb. Vasc. Biol.*, 1996, vol. 16, no. 12, pp. 1509–1515. DOI: 10.1161/01.atv.16.12.1509

[4] Salah H., El-Gazzar R.M., Abd El-Wahab E.W., Charl F. Oxidative and cardiovascular stress among professional divers in Egypt. *medRxiv: the preprint server for health sciences*. Available at: https://www.medrxiv.org/content/10.1101/2022.10.20.22281338v1.article-metrics (December 07, 2024).

The role of race metals and OS in the pathogenesis of CVDs is well established [21, 34, 35]. Oxidative stress is linked to increased levels of Cu^+ and decreased levels of Fe^+ and Zn^+ [35–37]. Also, blood Ca^+ level may increase arterial wall stiffness and subsequently the 10 years CVD risk as assessed by the Framingham score [38]. This is in line with the present work, where the evidence for disturbed electrolytes and trace metal levels as well as increased OS was found in our examined divers as manifested by abnormal levels of OSBMs. In the present study, on univariate analysis, lower levels of Na^+ and higher level of Cu^+ and Ca^+ were significantly associated with CVR although they did not appear in the logistic regression model. This could be attributed to the small sample size and large number of variables used in the analysis. Few researches mentioned the effect of diving on the trace metals, especially the saturation deep diving, which affects the hemoglobin iron level[5].

ROC curve analysis was done in this study to detect the sensitivity of the studied biomarkers in CVRA compared to the ASCVDR estimator as an established and approved tool. The greater the AUC is the more sensitive and specific the test parameter will be. The analysis was run for the optimal CVD risk, 10 years CVD risk and the whole lifetime risk. The best performance was noticed for ECG changes. Indeed, ECG changes are of utmost importance they are the most specific parameter related to the CVD risk. This comes in agreement with a study done by Tocci et al. (2017), which demonstrated for the first time that other biomarkers could be added independently to global risk estimators for CVD risk assessment [39]. Furthermore, our findings support the postulation that adding biomarkers could allow better individual CVR detection. The ECG changes were also found to be a more specific biomarker as the OS changes could occur in other physiological and pathological conditions. ECG changes as a biomarker are characterized by large availability, simple interpretation, and cost-effectiveness and should therefore be preferred in the CVD risk assessment [12].

In the present study, smoking, duration of employment, OSBMs, some trace metals, ECG change denoting left ventricular hypertrophy ($S_{1,2}+R_{5,6}$) were significantly associated with CVR in both divers and seafarers. Nevertheless, smoking was the single predictor of CVR in multivariate logistic regression analysis, probably because other variables in the model were affecting the CVR through a cross-interacting manner. Collectively, OSBMs and trace metals need further research to predict their effects with larger sample sizes.

The proposed lifetime CVR, 10 years CVR and the corrected QT wave interval prediction models showed better sensitivity and specificity in predicting CVR when compared to the ASCVDR estimator. Lifetime and 10 years CVR scores of 46 and 2.7 respectively were significant in estimating CVR. Above these points, divers are considered at higher CVD risk. Likewise, a corrected QT wave interval score of 402 msec was significant in estimating CVR. Above this point, divers are considered at higher CVD risk. This was in agreement with a study investigated the arrhythmia factors in scuba divers and

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[5] Nakabayashi K., Mizukami H., Hashimoto A., Oiwa H. Change in red blood cell production rate during a 330 msw saturation dive simulation. *Undersea Biomed. Res.*, 1991, vol. 18, suppl., pp. 32.

concluded that QT prolongation can be recorded in divers after diving. Prolongation of the QT wave increases the CVR of arrhythmia [31]. In addition, the risk stratification of divers and seafarers that was based on the total scores of the proposed lifetime CVR, 10 years CVR and the corrected QT wave interval prediction models and their preset cutoff points showed statistically significant differences between the two groups. This suggests that the performance of the proposed indices is comparable to the ASCVDR estimator in predicting the CVDR. Thus, the ASCVDR estimator could assess the vascular CVR factors, while the electrophysiological factors could be determined by the corrected QT interval.

Conclusion and recommendations. Professional divers are at higher risk of cardiovascular diseases as measured by ASCVD estimator in term of increased 10 years risk score as well as life time compared to the same levels reported among the control group. Cardiovascular risk assessment of professional divers is thus recommended in the periodic medical examinations and during fitness examinations. During the periodic examination of the divers and seafarers for fitness the following should be emphasized: 1) careful monitoring of systolic blood pressure; 2) use of the ASCVD estimator for assessing CV risk. Analysis of the results should be done considering cutoff points of ≤ 46 and ≤ 2.6 for the life time and 10 years risk detection respectively; 3) calculation of the corrected QT wave interval in the resting ECG with a cutoff point of ≤ 402 milliseconds should be considered for further assessment and investigation by specialized cardiologist for diving fitness. Although highly predictive, oxidative stress biomarkers such as SOD and trace metals levels (Cu^{+}/Zn^{+}) should not be done as routine unless their role in CVR assessment is reproduced and validated in further research on larger sample sizes.

Preventive measures for CVR factors and promoting better quality of life should be advised for professional divers and seafarers by emphasizing and not limited to: 1) tight smoking prevention and control programs, 2) nutritional health education encouraging consumption of antioxidants and Zn supplements, 3) health education for prevention and control of cardiovascular diseases.

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Research article

NEUROANTIBODIES AS RISK MARKERS FOR THE DEVELOPMENT OF AUTOIMMUNE PROCESSES IN CASE OF VIBRATION DISEASE

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The aim of the study was to identify the features of changes in the content of neuroantibodies reflecting the risk of developing autoimmune processes in patients with hand-arm vibration syndrome (HAVS), complicated and uncomplicated arterial hypertension (AH).

A retrospective study was conducted in a sample of men aged 40 to 60 years with a diagnosed hand-arm vibration syndrome caused by local vibration and in a group comparable per sex and age, including people who worked in conditions that excluded contact with occupational physical factors. Groups of patients with HAVS, complicated and uncomplicated AH have been identified. The levels of autoantibodies to specialized structures of nervous tissue and neurotransmitters were determined in all the examined participants using the ELI-N-Test ("Immunculus", Moscow).

The study revealed an increase in the levels of neuronal AT (MBP, S-100, GFAP, NF-200, V-Ca-channel, Glu-R, DA-R, M-OR, B-end) in patients with HAVS, both burdened and uncomplicated hypertension, relative to the comparison group. At the same time, the levels of AT to the opiate M-OR receptors in people with HAVS who were not burdened with hypertension were statistically significantly higher than in patients with comorbid pathology ($p = 0.04$). Discriminant analysis showed that individuals with HAVS burdened with hypertension were characterized by a decrease in the levels of AT to gamma-aminobutyric acid receptors ($F = 8.5$, $p = 0.001$) and to the myelin basic protein ($F = 13.7$, $p = 0.001$) in comparison with patients with HAVS without hypertension. The neuron-neuron interaction disorder in patients with AH was manifested by a mismatch of correlations between the levels of autoantibodies to S-100 protein and myelin basic protein ($R = 0.29$, $p > 0.05$), voltage-dependent Ca-channel ($R = 0.41$, $p > 0.05$), dopamine receptors ($R = 0.42$, $p > 0.05$), serotonin ($R = 0.33$, $p > 0.05$) and opiates ($R = 0.32$, $p > 0.05$).

Thus, increased levels of neuronal AT (MBP, S-100, GFAP, NF-200, V- Ca-channel, Glu-R, DA-R, M-OR, B-end) in patients with HAVS, both burdened and uncomplicated hypertension, are markers reflecting the risk of developing autoimmune processes upon exposure to vibration. The reported lower levels of AT to the GABA receptor and the myelin basic protein in patients with HAVS burdened with hypertension, when compared with those with HAVS without hypertension, are apparently due to the peculiarities of the clinical course of the disease and the formation of immune tolerance to these proteins. The obtained results can be used in carrying out diagnostic, preventive and therapeutic measures for people with HAVS, including in the presence of comorbid pathology.

Keywords: *occupational stress, hand-arm vibration syndrome, arterial hypertension, immune system, nervous system, autoantibodies, gamma-aminobutyric acid (GABA), myelin basic protein, opiate receptors.*

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As stated in the State Report published by Rospotrebnadzor in 2023, hand-arm vibration syndrome (HAVS) accounted for 45.3 % of all cases in patients with pathologies caused by physical exposures[1]. Recently, the research community has taken greater interest in comorbidities, which complicate the clinical course of occupational diseases, arterial hypertension (AH) in particular, since the disease is established in 47–52 % patients with HAVS [1]. The number of adult people with AH has grown from 650 to 1.28 billion people over the last 30 years [2].

Bearing in mind that the immune system is among the first to react to environmental exposures, occupational vibration included, it is still relevant to search for informative markers associated with elevated risks of developing autoimmune processes in patients with HAVS. The hand-arm vibration syndrome has been established to typically involve changes in levels of autoantibodies to nerve tissue proteins such as myelin basic protein (MBP), S-100 protein, neurofilament protein-200 (NF-200), glial fibrillary acidic protein (GFAP), and neurotransmitter receptors [3]. As regards AH, some available literature data report elevated levels of antibodies to MBP and S-100 protein in patients with chronic cerebral ischemia caused by hypertension [4]. At the same time, we have not managed to find a sufficient number of studies that focus on functional disorders accompanied with changed levels of neuronal antibodies and report risks of developing autoimmune processes in people with HAVS burdened with AH.

It should be noted that antibodies to neuroantigens of the brain structures penetrate the blood through the blood-brain barrier (BBB). Their growing levels are evidence of damage to nerve tissues and greater BBB permeability [5]. Antibody (AB) production is a physiological mechanism aimed at homeostasis maintenance. In total, changes in AB levels can indirectly describe the state of the immune system [6], which, according to literature data, is actively involved in AH pathogenesis. However, its role in AH development still remains ambiguous. Thus, IL-17A produced by T-helpers and IFN-γ stimulate the renin-angiotensin-aldosterone system thereby causing elevated blood pressure. Cell death in the peritubular capillaries occurs due to dendritic cells activating CD8+ T-lymphocytes, which may lead to the development of renal hypertension [7].

Comorbidities aggravate the main disease considerably, promote changes in its clinical manifestations and cause fatal complications [8]. Despite a wide range of clinical diagnostic procedures, certain difficulties still occur in identifying such comorbidity as AH including its resistant forms [9]. However, it seems promising to use up-to-date statistical methods including discriminant analysis, which makes it possible to reveal informative indicators and develop mathematical formulas for AH prediction and diagnosis.

Given all the above stated, **the aim** of this study was to identify the features of changes in the content of neuroantibodies reflecting the risk of developing autoimmune processes in patients with hand-arm vibration syndrome (HAVS), complicated and uncomplicated with arterial hypertension (AH).

Materials and methods. A retrospective clinical study was conducted in a sample of 40 men aged 40 to 60 years with diagnosed HAVS caused by local vibration; they all were treated in the clinic of the East-Siberian Institute of Medical and Ecological Research. The first group was made of patients with HAVS not burdened with AH; the second one, patients with HAVS burdened with stage 1 or stage 2 arterial hypertension. The exclusion criteria were acute communicable diseases at the examination moment,

[1] Razdel 1.2.2. Analiz sostoyaniya zdorov'ya rabotayushchego naseleniya i professional'noi zabolevaemosti [Item 1.2.2. Analysis of the employable population's health and occupational morbidity]. In: *O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2023 g.: Gosudarstvennyi doklad [On Sanitary-epidemiological welfare of the population in the Russian Federation in 2023: State Report]*. Moscow, Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2023, pp. 158–160 (in Russian).

exacerbated chronic diseases, coronary heart disease, cancer, autoimmune diseases as well as occupational diseases caused by chemical exposures. No patients with diabetes mellitus were included since the disease creates much higher risks of cardiovascular complications and damage to the nervous system thereby exerting substantial influence on the results. The reference group was made of 30 men comparable per age, who worked in conditions that excluded contact with occupational physical or chemical factors. All patients provided their written informed consent to participate in the study. The study was approved by a local ethics committee.

The patients provided their blood samples, which were taken into vacutainers with a clot activator. The vacutainers were then centrifuged for 15 minutes at 2000 rpm. Serum aliquots were put into Eppendorf tubes 1.5 ml volume, frozen and kept at -70 °C. Serum levels of the neuroantibodies (to neurofilament protein-200 (NF-200), glial fibrillary acidic protein (GFAP), S-100 protein, myelin basic protein (MBP), voltage-gated Ca-channel (V-gat. Ca-channel), glutamate receptors (Glu-R), dopamine receptors (DA-R), GABA - receptors (GABA-R), serotonin receptors (Ser-R), cholinoreceptors (Chol-R), M-opiate receptors (M-OR), B-endorphin (B-end)) were identified by using ELI-N-test systems (Immunkulus, Moscow) at the wave 450 long on a ELx800 microplate reader (BioTek, USA).

Mathematical and statistical data analysis was performed with IBM SPSS Statistics 26 and STATISTICA 10 software packages. The sample was checked for normality of the distribution by using the Shapiro – Wilk test. The patients' age and work records were given as simple mean and its error; all the remaining results, as median, upper and lower quartiles. The non-parametric Mann – Whitney test was used for quantitative comparisons in the analyzed groups depending on AH presence. Intergroup differences were deemed significant at $p < 0.05$. In Spearman's correlation analysis, correlation coefficients were considered significant at $p < 0.05$. The last stage involved conducting stepwise discriminant analysis to identify and substantiate the most informative indicators. Independent variables were represented by level of serum antibodies from the IgG class to nerve tissue antigens (NF-200, GFAP, S-100, MBP, V-gated Ca-channel, Glu-R, DA-R, GABA-R, Ser-R, Chol-R, M-OR, B-end); dependent ones, being in a group with diagnosed HAVS either burdened or not burdened with AH.

Results and discussion. Occupational vibration is known to be a stressor [10]. Significant AH risk factors include age older than 55 and occupational stress. Given that, the first stage in our study involved distributing the examined patients per their work records under vibration exposure and an age when HAVS was diagnosed in them. The analysis revealed them to be comparable in the analyzed groups (Table 1).

Table 1

Age and work records of the examined patients ($M \pm m$)

Indicator, units	Group HAVS without AH $n = 20$	Group HAVS with AH $n = 20$
Age, years	49.8 ± 1.5	49.2 ± 1.3
Work records, years	17.5 ± 1.3	18.4 ± 1.5

Note: differences are significant at $p < 0.05$.

Recently, antibodies to specific nerve tissue structures have been considered new generation markers in some neurological disorders[2]. Bearing this in mind, it seemed interesting to examine levels of neuroantibodies in blood serum of the patients with HAVS (Table 2).

[2] Poletaev A.B. Novye podkhody v rannem vyyavlenii patologicheskikh izmenenii v organizme cheloveka (immunokhimicheskii skrining kak osnova strategii perekhoda ot lechebnoi k preventivnoi meditsine) [New approaches in early detection of pathological changes in the human body (immune-chemical screening as the basis for transition from treatment to prevention)]: methodical guide for clinicians. Moscow, Immunculus Publ., 2011, pp. 64 (in Russian).

Table 2

Levels of neuroantibodies in the examined patients with HAVS, *Med (Q25; Q75)*

Indicator, units	Group HAVS without AH $n = 20$	Group HAVS with AH $n = 20$	Reference group
MBP, arbitrary units	0.272 (0.156; 0.457)^	0.183 (0.156; 0.404) ^	0.140 (0.118; 0.181)
GABA-R, arbitrary units	0.345 (0.150; 0.513)^	0.185 (0.148; 0.527)	0.177 (0.128; 0.252)
S-100, arbitrary units	0.538 (0.306; 0.643)^	0.424 (0.302; 0.610)^	0.228 (0.168;0.292)
GFAP, arbitrary units	0.471 (0.252; 0.586)^	0.325 (0.230; 0.581)^	0.282 (0.171; 0.364)
NF-200, arbitrary units	0.386 (0.253; 0.604)^	0.299 (0.239; 0.617)^	0.194 (0.158;0.258)
V-gat. Ca-channel, arbitrary units	0.315 (0.158; 0.591)^	0.213 (0.158; 0.573)^	0.152 (0.118; 0.197)
Chol-R, arbitrary units	0.289 (0.141; 0.589)^	0.178 (0.142; 0.589)	0.175 (0.128; 0.217)
Glu-R, arbitrary units	0.310 (0.194; 0.560)^	0.222 (0.184; 0.537)^	0.185 (0.150; 0.228)
DA-R, arbitrary units	0.295 (0.175; 0.482)^	0.205 (0.171; 0.456)^	0.179 (0.147; 0.254)
Ser-R, arbitrary units	0.417 (0.179; 0.576)^	0.236 (0.179; 0.577)	0.238 (0.188; 0.311)
M-OR, arbitrary units	0.308 (0.202; 0.451)^	0.241 (0.193; 0.408)*^	0.151 (0.122; 0.179)
B-end, arbitrary units	0.328 (0.182; 0.480)^	0.196 (0.168; 0.470)^	0.146 (0.118; 0.189)

Note: differences are significant at $p < 0.05$; * means significant differences between the Groups HAVS with AH and without AH; ^ means significant differences between the Groups HAVS without AH and the reference group, HAVS with AH and the reference group.

Comparison with the reference group established a significant increase in AB levels (to MBP, S-100, GFAP, NF-200, V-gat. Ca-channel, Glu-R, DA-R, M-OR, B-end) in both HAVS groups regardless of AH presence. We compared AB levels depending on the present comorbidity and established that the patients with HAVS not burdened with AH has significantly higher levels of autoantibodies to M-opiate receptors ($p = 0.04$), against those with HAVS burdened with AH. Levels of AB to GABA-R, Chol-R, and Ser-R were equal to those identified in the reference group in both HAVS groups with and without AH.

The correlation analysis revealed that people with HAVS combined with AH had weaker and insignificant correlations between levels of AB to S-100 protein and MBP ($R = 0.29$, $p > 0.05$), V-gated Ca-channel ($R = 0.41$, $p > 0.05$), dopamine receptors ($R = 0.42$, $p > 0.05$), serotonin receptors ($R = 0.33$, $p > 0.05$) and opiate receptors ($R = 0.32$, $p > 0.05$) (Table 3) whereas levels of all antibodies correlated with each other in the HAVS group without AH and the reference group (Tables 4 and 5).

Next, the discriminant analysis was performed to substantiate new diagnostic markers. It revealed several most significant informative signs of HAVS burdened with AH including lower levels of AB to receptors of gamma-aminobutyric acid ($F_{incl} = 8.5$, $p = 0.001$) and myelin basic protein ($F_{incl} = 13.7$, $p = 0.001$) against HAVS without AH (Table 6). Diagnostic coefficients F_1 (included in the HAVS group without AH) and F_2 (included in the HAVS group burdened with AH) were calculated per the following formulas:

$$F_1 = -3.938 + 25.067 \cdot AB - MBP - 9.6 \cdot Ab - GABA$$

$$F_2 = -2.058 + 5.317 \cdot AB - MBP + 3.838 \cdot Ab - GABA$$

Table 3

Correlations between neuroantibodies in patients with hand-arm vibration syndrome burdened with arterial hypertension

	S100	GFAP	MBP	NF-200	V-gat	Chol-R	Glu-R	GABA-R	DA-R	Ser-R	M-OR	B-end
S100	1.00	0.75	**0.29**	0.55	**0.41**	0.63	0.54	0.50	**0.42**	**0.33**	**0.32**	0.45
GFAP	0.75	1.00	0.65	0.76	0.67	0.85	0.74	0.81	0.72	0.66	0.59	0.68
MBP	0.29	0.65	1.00	0.76	0.93	0.84	0.84	0.90	0.94	0.94	0.84	0.78
NF-200	0.55	0.76	0.76	1.00	0.80	0.93	0.88	0.89	0.76	0.80	0.78	0.85
V-gat	0.41	0.67	0.93	0.80	1.00	0.89	0.88	0.90	0.92	0.97	0.86	0.90
Chol-R	0.63	0.85	0.84	0.93	0.89	1.00	0.92	0.96	0.87	0.89	0.82	0.89
Glu-R	0.54	0.74	0.84	0.88	0.88	0.92	1.00	0.91	0.82	0.86	0.76	0.82
GABA	0.50	0.81	0.90	0.89	0.90	0.96	0.91	1.00	0.91	0.93	0.88	0.90
DA-R	0.42	0.72	0.94	0.76	0.92	0.87	0.82	0.91	1.00	0.92	0.82	0.78
Ser-R	0.33	0.66	0.94	0.80	0.97	0.89	0.86	0.93	0.92	1.00	0.89	0.90
M-OR	0.32	0.59	0.84	0.78	0.86	0.82	0.76	0.88	0.82	0.89	1.00	0.88
B-end	0.45	0.68	0.78	0.85	0.90	0.89	0.82	0.90	0.78	0.90	0.88	1.00

Note: significance taken at $p < 0.05$ except S-100 and MBP, V-gat. Ca channel, DA-R, Ser-R, M-OP.

Table 4

Correlations between neuroantibodies in patients with hand-arm vibration syndrome without arterial hypertension (*R*)

	S100	GFAP	MBP	NF-200	V-gat	Chol-R	Glu-R	GABA-R	DA-R	Ser-R	M-OR	B-end
S100	1.00	0.94	0.88	0.90	0.92	0.92	0.89	0.88	0.88	0.93	0.89	0.91
GFAP	0.94	1.00	0.94	0.88	0.92	0.94	0.87	0.87	0.93	0.95	0.89	0.92
MBP	0.88	0.94	1.00	0.91	0.97	0.97	0.89	0.89	0.99	0.94	0.96	0.94
NF-200	0.90	0.88	0.91	1.00	0.97	0.96	0.83	0.90	0.92	0.95	0.94	0.91
V-gat	0.92	0.92	0.97	0.97	1.00	0.99	0.87	0.89	0.96	0.95	0.95	0.92
Chol-R	0.92	0.94	0.97	0.96	0.99	1.00	0.85	0.91	0.97	0.97	0.95	0.95
Glu-R	0.89	0.87	0.89	0.83	0.87	0.85	1.00	0.86	0.91	0.86	0.91	0.84
GABA	0.88	0.87	0.89	0.90	0.89	0.91	0.86	1.00	0.92	0.96	0.95	0.94
DA-R	0.88	0.93	0.99	0.92	0.96	0.97	0.91	0.92	1.00	0.94	0.97	0.94
Ser-R	0.93	0.95	0.94	0.95	0.95	0.97	0.86	0.96	0.94	1.00	0.96	0.97
M-OR	0.89	0.89	0.96	0.94	0.95	0.95	0.91	0.95	0.97	0.96	1.00	0.95
B-end	0.91	0.92	0.94	0.91	0.92	0.95	0.84	0.94	0.94	0.97	0.95	1.00

Note: significance taken at $p < 0.05$.

Table 5

Correlations between neuroantibodies in the reference group (*R*)

	S100	GFAP	MBP	NF-200	V-gat	Chol-R	Glu-R	GABA-R	DA-R	Ser-R	M-OR	B-end
S100	1.00	0.72	0.47	0.70	0.51	0.46	0.52	0.68	0.60	0.76	0.60	0.66
GFAP	0.72	1.00	0.67	0.74	0.74	0.63	0.69	0.63	0.57	0.65	0.62	0.78
MBP	0.47	0.67	1.00	0.62	0.85	0.44	0.57	0.47	0.45	0.60	0.38	0.68
NF-200	0.70	0.74	0.62	1.00	0.71	0.45	0.62	0.65	0.59	0.69	0.63	0.75
V-gat	0.51	0.74	0.85	0.71	1.00	0.52	0.63	0.55	0.50	0.59	0.44	0.69
Chol-R	0.46	0.63	0.44	0.45	0.52	1.00	0.77	0.66	0.75	0.53	0.29	0.57
Glu-R	0.52	0.69	0.57	0.62	0.63	0.77	1.00	0.80	0.84	0.66	0.51	0.64
GABA	0.68	0.63	0.47	0.65	0.55	0.66	0.80	1.00	0.92	0.82	0.49	0.67
DA-R	0.60	0.57	0.45	0.59	0.50	0.75	0.84	0.92	1.00	0.73	0.54	0.64
Ser-R	0.76	0.65	0.60	0.69	0.59	0.53	0.66	0.82	0.73	1.00	0.45	0.67
M-OR	0.60	0.62	0.38	0.63	0.44	0.29	0.51	0.49	0.54	0.45	1.00	0.68
B-end	0.66	0.78	0.68	0.75	0.69	0.57	0.64	0.67	0.64	0.67	0.68	1.00

Note: significance taken at $p < 0.05$.

Table 6

Informative indicators obtained by the discriminant analysis in the groups of the examined patients with HAVS both burdened and not burdened with arterial hypertension

Indicators	*F*-inclusions	Wilkes' lambda	Degree of freedom 1	Degree of freedom 2	*p*
Autoantibodies to GABA receptors, arb. units	8.454	0.865	2	1	0.001
Autoantibodies to MBP, arb. units	13.706	0.986	1	1	0.001

Note: *p* is the level at which differences are significant.

Validity of the proposed formulas was tested using a training sample: correct identification equaled 85 % in HAVS patients with AH (20 people) and 75 % in HAVS patients without AH (20 people).

It is worth noting that these results were obtained for relatively small groups. In further research, when new patients are included into training samples, it seems quite feasible to obtain an authentic mathematical model for assessing risks of autoimmune processes in people with HAVS both burdened and not burdened with AH.

At present, immunological markers, which can predict risks of various occupational diseases, HAVS included, are being investigated quite actively [3]. Humoral immunity indicators (immunoglobulins A, M, G) [11], pro-inflammatory (IL-1β, IL-2, IL-8, IL-10, IL-17, TNF-α) and anti-inflammatory (IL-4) cytokines [12] are being investigated as additional informative indicators reflecting involvement of the immune system in HAVS patients burdened with AH. However, not enough light has been shed on the role, which belongs to antibodies to specific nerve tissue structures and neuromediators relative to risks of developing autoimmune processes in patients with HAVS burdened with AH.

Natural antibodies to diverse antigenic determinants including neuron, neuroglia and receptor components are always present in the body [13]. Highly sensitive test-systems for ELISA tests allow measuring neuroantibodies in blood samples as opposed to methods, which require using only cerebrospinal fluid. An identified AB level can reflect the nerve tissue state and functioning of its components. In this study, we revealed elevated levels of neuronal antibodies (to MBP, S-100, GFAP, NF-200, V-gat. Ca-channel, Glu-R, DA-R, M-OR, B-end) in patients with HAVS both burdened and unburdened with AH against the reference group. Levels of antibodies to M-opiate receptors (M-OR) were significantly higher in HAVS patients without AH in comparison with those who had HAVS burdened with comorbidity ($p = 0.04$). Opioids are known to perform stress-limiting activity and to be a link in both urgent and long-term adaptation [14]. They reduce levels of adrenocorticotropic hormone, aldosterone, vasopressin, glucagon and cortisol and increase levels of insulin and testosterone. Elevated levels of antibodies to opioids can indicate pronounced failure to adapt to stressor vibration exposure.

In up-to-date research, vibration is shown to be a significant occupational stressor [10]. The body response to stress is known to have three stages: (1) anxiety; (2) resistance; (3) depletion[3]. All organs and systems in the human body participate in building adaptability and resistance to stress. The immune system is among the first to react to various stressor exposures. Both elevated and reduced AB levels have diagnostic significance. A titer of specific antibodies can grow in case of immune activation and decline in case of immunosuppres-

[3] Selye H. The general adaptation syndrome and the diseases of adaptation. *J. Clin. Endocrinol. Metab.*, 1946, vol. 6, pp. 117–230. DOI: 10.1210/jcem-6-2-117

sion[4]. Any shift in levels of neuroantibodies reflects staging in the development of pathological processes [6].

Strong positive correlations between all neuronal antibodies established in the reference group by correlation analysis show their adequate production by antibody-producing immune system cells in case vibration exposure is absent. The foregoing character of the established correlations was also identified in patients with HAVS not burdened with AH, which indicates unidirectional rise in AB levels in this group.

A mismatch of correlations between levels of S-100 protein and levels of some other markers was identified in the examined patients with HAVS burdened with AH. S-100 protein is responsible for intracellular and extracellular regulation of energy metabolism, cell differentiation and growth [15]. It is known to be a calcium-binding protein. A weakened correlation between levels of AB to S-100 protein and voltage-gated Ca-channel can be a sign of disrupted interaction between the compound and calcium ions and changes in synapse functioning. A weakened correlation between levels of AB to S-100 protein and dopamine, serotonin and opiate receptors may indicate developing emotional and volitional disorders [16] accompanied with changes in S-100 protein levels. A weakened correlation between levels of antibodies to S-100 protein and MBP may indicate damage to nerve tissue and a growth in the blood-brain barrier permeability [5, 17].

AH is a factor that aggravates HAVS clinical course; given that, we made an attempt to identify the most diagnostically significant indicators among all analyzed ones. The accomplished discriminant analysis established a decline in levels of antibodies to gamma-aminobutyric acid (GABA) receptor in patients with HAVS burdened with AH against those who had only HAVS. GABA is considered a key inhibition mediator in the brain. In addition, GABA drugs are known to normalize blood pressure in patients with AH [18]. The pathway of blood pressure reduction can involve inhibiting the baroreceptor by binding GABA with neuron receptors in the solitary tract of the medulla oblongata [19]. Lower levels of antibodies to myelin basic protein (MBP) in HAVS patients with AH against those with HAVS not burdened with AH may be another informative indicator. MBP is known to participate in forming the multilayer myelin sheath by creating complexes with lipids. When these structures crumble, MBP levels grow in blood and cerebrospinal fluid. Changes in levels of antibodies to MBP give evidence of the immune system response to myelin sheath destruction. As reported in previous studies, slower nerve impulse transmission along the proximal and distal axon sections identified in patients with HAVS, a decline in M-response amplitude and a longer latent period in animal experiments give evidence of active demyelination developing upon vibration exposure [20]. Several studies reported that patients with AH tended to have lower myelin contents in myelin sheaths of the brain structures [21, 22].

Conclusion. Therefore, elevated levels of neuroantibodies (to MBP, S-100, GFAP, NF-200, V-gated Ca-channel, Glu-R, DA-R, M-OR, B-end) in patients with HAVS both burdened and uncomplicated with AH are markers reflecting the risk of developing autoimmune processes upon vibration exposure. Identified lower levels of antibodies to GABA and MBP receptor in patients with HAVS burdened with AH against those patients with HAVS who did not have AH are obviously caused by a specific clinical course of the disease and developing immune tolerance to the foregoing proteins. Our findings can be used in carrying out diagnostic, preventive and therapeutic measures for people with HAVS including those who have comorbid pathology.

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[4] Poletaev A.B. Novye podkhody v rannem vyyavlenii patologicheskikh izmenenii v organizme cheloveka (immunokhimicheskii skrining kak osnova strategii perekhoda ot lechebnoi k preventivnoi meditsine) [New approaches in early detection of pathological changes in the human body (immune-chemical screening as the basis for transition from treatment to prevention)]: methodical guide for clinicians. Moscow, Immunculus Publ., 2011, pp. 64 (in Russian).

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Research article

WAYS TO REDUCE HEALTH RISKS IN REMOTE AREAS OF THE RUSSIAN FEDERATION BY IMPROVING HEALTH AND SANITARY CARE

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Healthcare in Russia is facing a serious challenge as the healthcare system needs improvement and any territorial differences in access to healthcare services should be eliminated. Use of a territorial approach to providing healthcare and sanitary services to the population requires solutions that should entail their availability, high quality and low costs.

The aim of this study is to identify promising areas where provision of healthcare and sanitary services can be improved in remote areas of the Russian Federation.

A prototype mobile consultation and diagnostic center Saint Panteleimon has been tested in the operation mode. The center is a train made of railway cars manufactured by the Tver Carriage Works JSC and equipped for providing therapeutic, surgical, ophthalmological and other healthcare services as well as for conducting instrumental research and laboratory tests.

The train followed routes within the Far Eastern and Siberian Federal Districts using the Eastern-Siberian and Zabaikalskaya railways. The total length of the routes was 7065 kilometers; they go through 59 railways stations. It took 86 days (75 of them workdays) to travel these routes completely.

Overall, 9493 diseases were diagnosed in 7263 people who visited the train. Each fourth disease was diagnosed in examined patients for the first time in their lives. Diseases of the circulatory system, endocrine diseases, diseases of the musculoskeletal system, diseases of the eye and adnexa prevailed among those diagnosed in people who applied for healthcare services. One hundred and sixty-two people out of the examined patients were sent to an in-patient hospital. The most common causes for hospital admission included diseases of the musculoskeletal system, neoplasms, diseases of the circulatory system and endocrine diseases. Functioning of railway mobile consultation and diagnostic centers will reduce risks of health losses among population living in remote areas due to available qualified healthcare and sanitary aid, result in longer life expectancy and help preserve active longevity.

Keywords: *healthcare and sanitary aid, remote areas, railway, consultation and diagnostic center Saint Panteleimon, risk of health loss, locomotive traction carriages, active longevity, low-mobile population groups.*

Primary healthcare plays the most significant role in mitigating health risks in remote areas. It makes the foundation of the healthcare pyramid, is in the greatest demand by people and has a substantial effect on population health. Annually, approximately 950 million cases are registered when people apply for primary healthcare[1]. Recently, some measures have been implemented in Russia with their aim to develop out-patient healthcare in close

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proximity to residential areas and workplaces. The ultimate goal is to build such a model, which is based on patients' needs as the top priority, rational use of time when healthcare services are provided, their availability and high quality.

As reported in [1], people living in remote areas tend to suffer from chronic diseases more frequently and their average life expectancy is reduced. It is difficult to get qualitative healthcare services in such areas due to small population numbers; elderly people with limited physical and financial mobility prevail in such communities. Moreover, there is always lack of qualified healthcare workers in these areas [2].

The healthcare system in the Russian Federation needs improvement and any territorial differences in access to healthcare services should be eliminated. Use of a territorial approach to providing healthcare and sanitary services to the population in remote areas requires solutions that should entail their availability, high quality and low costs [2–5].

In accordance with the RF Government Order dated October 09, 2019 No. 1304, the Departmental Targeted Program 'Modernization of the Primary Healthcare in the Russian Federation' was approved for the period of 2021–2025. This Program and the 'Development of the Primary Healthcare System' Federal Project are complementary lists of activities aimed at achieving the same goal, which is growing expectancy of health, active and full life for the country population. To solve the task, the Healthcare National Project is being implemented in the Russian Federation at the moment. Its major goals include a growth in the population number in the country and a growth in life expectancy at birth due to providing available healthcare, orientating at prevention as the basic principle in healthcare and, consequently, reducing mortality rates among the country population [3–6].

Certain difficulties typical for the eastern areas of the country arose when a network of healthcare organizations responsible for providing primary healthcare, including specialized one, was being created using a geoinformation system. They were mostly associated with rendering consultation and diagnostic services to people, who lived in remote, difficult to access and sparsely populated areas. Thus, at present there are 462 towns in the Russian Federation with their population below 20,000 people. Overall, approximately 6 million people live in them. These towns are located far from large urban agglomerations and it is rather difficult to render consultation and diagnostic services to their population or to create programs of scheduled specialized healthcare for them.

The aim of this study is to identify promising areas where provision of healthcare and sanitary services can be improved in remote areas of the Russian Federation.

Materials and methods. We have analyzed specific features of using medical equipment installed in five specifically designed medical trains called 'Zdorovye', 'Svyatitel Luka', 'Terapevt Matvey Mudrov', 'Akademik Fedor Uglov', and 'Khirurg Nikolai Pirogov'.

A prototype mobile consultation and diagnostic center Saint Panteleimon has been tested in the operation mode. The center is a train made of railway cars manufactured by the Tver Carriage Works JSC, specifically designed for rendering primary healthcare and equipped for providing therapeutic, surgical, ophthalmological and other healthcare services as well as for conducting instrumental research and laboratory tests.

The train followed routes within the Far Eastern and Siberian Federal Districts in six RF regions (Buryatia, Zabaikalskii Krai, Khabarovskii Krai, Amur region, Irkutsk region and the Jewish Autonomous Area) using the Eastern-Siberian and Zabaikalskaya railways.

Results and discussion. The railway mobile consultation and diagnostic center Saint Panteleimon consists of railway cars, which are specifically equipped for providing outpatient healthcare and conducting laboratory and diagnostic tests. Equipment and layouts of the train interior allow rendering healthcare services by healthcare experts in different fields (therapist, pediatrician, geriatrician, cardiologist, ophthalmologist, ENT doctor, endocrinologist, dentist, neurologist, surgeon, urologist, and obstetrician-gynecologist). High-precision equipment makes it possible to conduct x-ray and endoscopic examinations, ultrasound diagnostics, functional diagnostic and clinical laboratory tests. Healthcare services rendered by this mobile consultation and diagnostic center are fully available for low-mobile population groups.

The analysis was performed upon completion of six routes. The Saint Panteleimon Center covered 7065 kilometers over 86 calendar days (75 workdays). Healthcare services were rendered in 59 settlements with their population varying between 100 and 4500 people. 7263 people applied for medical aid, 675 of them were children (Table 1).

Over the analyzed period, 18,284 visits to a healthcare specialist were registered (including 823 visits by children) (Table 2). The Center was open for one day in each settlement; two days of work were rather rare. On average, one patient visited three different specialists a day and took part in five laboratory and diagnostic examinations together with getting their results explained to them.

Following the examinations, 162 patients were sent to an in-patient hospital for admission.

The number of visits to different healthcare experts is provided in Table 3.

Analysis of data provided in Table 3 established what medical specialties were in the highest demand; they included therapist, ophthalmologist, cardiologist, neurologist, endocrinologist, gynecologists, and geriatrician.

Table 1

The list of settlements (railway stations) where consolation and diagnostic services were rendered to population

Region	Settlements	The route length (km)	The number of people who visited the Center / of them, children
Far Eastern Federal District	Verkhnezeisk, Tutaul, Marevaya, Dipkun, Tungala, Dugda, Fevralsk, Isa, Etyrken, Alonka, Tyrma, Sogda, Elga, Nobii Urgal, Soloni, Suluk, Gerbi, Dzhamku, Amgun, Postyshevo, Evoron, Kharpicha, Bolen, Gorin, Khurmuli	3042	2595 / 374
Zabaikalskii Krai	Ekaterinoslavka, Mukhinskaya, Sivaki, Ushumun, Chalgany, Tygda, Gonzha, Gudachi, Taldan, Skovorodino, Bamovskaya, Urusha, Erofei Pavlovich, Amazar, Semiozernyi, Sbega, Mogocha, Ksen'evskaya.	2331	2646 / 193
Eastern-Siberian Federal District	Gorkhon, Novoil'nskii, Zaigraevo, Gusinoe Ozero, Zagustai, Naushki, Selenduma, Dzhida, Tataurovo, Selenga, Mysovaya, Tankhoi, Vydrino, Baikal, Kultuk, Slyudyanka-1, Andrianovskaya	1692	2022 / 108
TOTAL		7065	7263 / 675

Table 2

The number of visits to a doctor (out-patient care)

Region	Number / of them, children		
	Visits to a healthcare expert	Laboratory and diagnostic examinations	Sent to an in-patient hospital for admission
Far Eastern Federal District	8961 / 459	20,851 / 230	126 / 3
Zabaikalskii Krai	5548 / 255	10,495 / 152	31 / 0
Eastern-Siberian Federal District	3775 / 109	5918 / 48	5 / 0
Total	18,284 / 823	37,264 / 430	162 / 3

Table 3

The number of visit to different healthcare experts

Expert	Number of visits				
	Far Eastern Federal District	Zabaikalskii Krai	Eastern-Siberian Federal District	Total	Proportion (%)
Ophthalmologist	819	266	394	1479	11.80
Cardiologist	678	329	386	1393	11.11
Therapist	502	173	538	1213	11.86
Surgeon	386	126	368	880	7.021
Neurologist	539	248	353	1140	9.09
ENT doctor	367	185	288	840	6.70
Gynecologist	468	307	421	775	9.54
Endocrinologist	503	247	465	1215	9.69
Urologist	331	134	284	749	5.98
Pediatrician	280	71	107	458	3.65
Dentist	312	148	171	631	5.03
Geriatrician	896	169	0	1065	8.50
TOTAL	6355	3775	2403	12,533	100

X-ray, ultrasound and functional diagnostics (ECG) also turned out to be in high demand; endoscopic tests were not so popular. The most popular laboratory tests included biochemical blood test, tests to identify levels of hormones and tumor marker tests, tests to identify hepatitis viruses, examinations of the hemostasis system, gynecological smears, and microscopic examinations.

Table 4 provides data on the number of diseases diagnosed in patients who applied for primary healthcare by healthcare experts as well as based on conducted diagnostic and laboratory tests.

Nine thousand four hundred and ninety-three diseases were diagnosed in 7263 people who applied for primary healthcare (1.3 diseases per one patient). Each fourth disease was diagnosed in examined patients for the first time in their lives. Cardiovascular diseases, endocrine diseases, diseases of the musculoskeletal system, diseases of the eye and adnexa and diseases of the digestive system prevailed in the structure of diseases diagnosed in people who applied for primary healthcare. One hundred and sixty-two patients out of the examined people were sent to an in-patient hospital for admission. The most common reasons for hospital admission included diseases of the musculoskeletal system (arthritis, arthrosis, and osteochondrosis); diseases of the eye (cataract and glaucoma); neoplasms (uterus, ovaries, breast, urinary bladder, kidneys, skin, etc.); diseases of the circulatory system (unstable angina pectoris and atherosclerosis); endocrine diseases (type II diabetes mellitus). Availability, timeliness and quality of rendered healthcare services are known to have substantial influence on life expectancy at birth (LEB) [6–10]. The number of hospital beds is an indicator, which has been widely used so far to estimate how well people's demand in qualitative healthcare is satisfied and to measure economic efficiency of healthcare organizations. But at present this indicator is losing its leading position in assessment of healthcare quality in remote and hard-to-reach areas [11–15].

Similar travelling medical and preventive work was accomplished in remote areas by oncologists from the Tambov Regional Oncological Hospital; they consulted patients, did some methodological work and conducted joint examinations. As a result, there was a substantial growth in the number of people who underwent diagnostic tests and this led to a decline in the number of neglected cases and one-year cancer mortality rates. Ultimately,

Table 4

The number of diseases detected in people who applied for primary healthcare (including those diagnosed for the first time)

Nosologies	Detected diseases		
	Overall	Including those diagnosed for the first time	Proportion of first diagnosed diseases (%)
Registered diseases, total:	9493	2457	25.88
Of them: tuberculosis	1	1	100.00
Neoplasms, total:	206	30	14.56
Of them: malignant neoplasms	16	0	0.00
Diseases of the blood and blood-forming organs	33	4	12.12
Endocrine, nutritional and metabolic diseases	1381	181	13.11
Of them: diseases of the thyroid gland	680	117	17.21
Diabetes mellitus	285	23	8.07
Diseases of the nervous system	381	218	57.22
Diseases of the eye and adnexa	1018	424	41.65
Of them: cataract	452	247	54.64
glaucoma	117	30	25.64
Diseases of the ear and mastoid	411	237	57.66
Of them: conductive and sensorineural hearing loss	162	94	58.02
Diseases of the circulatory system, total:	2199	224	10.19
Of them: hypertensive diseases	1258	42	3.34
Ischaemic heart diseases	436	23	5.28
Cerebrovascular diseases	292	109	37.33
Diseases of the respiratory system	442	212	47.96
Diseases of the digestive system, total:	1073	379	35.32
Of them: stomach and duodenum ulcer	105	17	16.19
Diseases of the liver	40	2	5.00
Disorders of gallbladder, biliary tract	158	24	15.19
Diseases of the skin and subcutaneous tissue	57	9	15.78
Diseases of the musculoskeletal system and connective tissue	1051	340	32.35
Of them: arthropathies	347	120	34.58
osteopathies and chondropathies	276	128	46.37
Diseases of the genitourinary system	1092	157	14.37
Of them: urolithiasis	122	8	6.55
Congenital malformations	8	1	12.50
Pregnancy, childbirth and the puerperium	14	6	42.86
Injury and poisoning	41	6	14.63

this promoted a decline in the overall cancer mortality [16]. In addition, the studies [17–20] reported that a decrease in the number of in-patient hospital beds with simultaneous rise in volumes and quality of out-patient primary healthcare provided for population had a positive effect on LEB due to timely diagnostics of diseases and early start of therapy and, consequently, a decline in risks of a disease becoming chronic.

Conclusion. Design, construction and operation of the mobile railway consultation and diagnostic center Saint Panteleimon give evidence of correct managerial decisions aimed at implementing postulates fixed in the Healthcare National Project and the Program for State Guarantee of free-of-charge primary healthcare provided for the country citizens in 2024 and the planned period of 2025–2026. As the Center operated for three months, primary healthcare and sanitary services were provided for people in 59 remote and sparsely populated settlements. More than 7 thousand people were able to get access to qualified primary healthcare over the shortest period of time. More than 37 thousand of relevant diagnostic and laboratory tests were conducted; relevant treatment was timely selected and started. One hundred and sixty-two patients were sent to an in-patient hospital for admission. Operations of such railway centers can be considered a promising trend in reforming the primary healthcare system. Implementation of such projects will reduce risks of health losses among population living in remote areas, result in longer life expectancy and help preserve active longevity.

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Research article

ON ASSESSING HEALTH RISKS RELATED TO IMPLEMENTATION OF 5G NETWORKS

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This review covers publications with their focus on analyzing methodological approaches to assessing health risks that might occur due to implementation and development of 5G communication networks. Publications were sought in such databases as Pubmed, Scopus, Web of Science, MedLine, Global Health, and Russian Science Citation Index.

Results obtained by examining exposure to electromagnetic radiofrequency radiation in animal studies have revealed carcinogenic effects in some cases. However, population studies involving large samples of humans who are active mobile communication users have not established any significant effects that may cause health impairments. At the same time, some peculiar features of the 5G technology should be considered including extremely high network density, new scenarios of locating base stations, multiplicity of 5G-devices, networks relying on multiple different ranges (including use of decimeter-, centimeter- and millimeter-long waves). All this, together with use of signals having a great range width and new modulation types with their biological effects still remaining unknown, makes it possible to assume that an electromagnetic background in residential areas will undergo significant transformation involving growing intensity of modulated wideband electromagnetic radiation with a complex spectral structure. Conducted social surveys confirm people's concerns about health effects produced by 5G technologies. Accordingly, it is necessary to develop new methodological approaches to accomplishing investigations aimed at assessing health risks associated with implementation of such networks. This research work should consider technological peculiarities of 5G networks; results of such studies should give grounds for developing new safe standards and implementing relevant activities aimed at providing electromagnetic safety of the country population.

Keywords: *electromagnetic safety, 5G networks, literature review, electromagnetic radiofrequency radiation, animal studies, population studies, sociological surveys, perception of risks associated with electromagnetic radiation.*

At present, a new, the fifth generation of mobile communications 5G/IMT-2020 (5G)[1] is being implemented. It is considered the basis of the digital economy [1]. Given that, issues related to assessing population health risks associated with the use of these technologies are currently of particular relevance. The development of mobile networks using new technological solutions is expected to lead to a significant increase in mobile traffic, which is associated with the growing consumption of video services, a significant increase in the number of mobile devices connected to the network, increased use of appli-

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[1] International Mobile Telecommunications-2020 (IMT-2020 Standard) is a set of requirements issued by the Radiocommunication Sector of International Telecommunication Union (ITU-R) in 2015 for 5G networks, devices and services.

cations, online games and their updates. One of the most important functions performed by introducing and developing 5G networks is the use of the Internet of Things (IoT), i.e., a system for transmitting data between physical objects (‘things’) that will be equipped with special technologies enabling them to interact with each other and with the external environment, in many cases, without human intervention [2, 3]. It is also planned to continuously increase the number of such devices operating in the Internet.

5G networks have a different architecture from previous generations of mobile communications. They require a higher density of base stations and access points that generate electromagnetic radiation and provide a variety of wireless services. The evolution from 4G to 5G and then to 6G is accompanied by an increasing number of user devices per unit area. In 5G networks (IMT-2020), this number can reach up to 1 million devices per square kilometer, and in future 6G networks, it can increase to ten million devices [4]. Due to such a high density of user devices, the total electromagnetic background in 5G/6G networks may exceed permissible limits and become hazardous to health [5, 6].

The goal of this literature review is to analyze the results of different types of studies aimed at assessing the effects of electromagnetic fields (EMF) using 5G engineering knowledge, to consider methodological approaches to assessing health risks from 5G exposure, and to discuss directions for improving the methodology for conducting research on the effects produced by these new format networks.

Materials and methods. This study employs a literature analysis method, which has been used to prepare a review of scientific publications dedicated to the effects of EMF, including fifth-generation (5G) networks. The literature analysis aims to provide a systematic assessment of the literature identifying key trends, critical points, and gaps in the available scientific data. Literature was searched and analyzed using the following scientific databases: PubMed, Scopus, Web of Science, MedLine, Global Health, and the Russian Science Citation Index (RSCI).

The final inclusion of literature sources in the review was based on the following criteria.

Subject matter: studies related to the effects of EMF, particularly 5G networks, with a focus on human health.

Research type: selection covered both scientific articles presenting empirical research result and review papers, including systematic reviews and meta-analyses, published in peer-reviewed journals.

Language of publication: works published in English and Russian.

Publication period: The time frame was limited to studies published since 2000 to the present with a preference for papers published in the last five years in order to include the most recent data and trends.

During the selection process, 125 scientific sources were analyzed, of which 73 publications were included in the review based on the inclusion criteria. Each paper was analyzed in terms of methodology, results, and conclusions. In addition, a comparative analysis of the findings and a justification of the conclusions, based on the data contained in the publications, was made in the context of different types of studies on EMF and 5G.

Results and discussion. ***5G networks and population health.*** Assessing the health risks associated with 5G involves several disciplines, including biology, medicine, physics, economics, and law. However, research within each specific discipline tends to focus on a particular area with little attention to the other aspects. For instance, medical studies are generally dedicated to evaluating a potential relationship between EMF exposure and occurrence of disease, with little emphasis on experimental conditions. However, experimental conditions are often conservative and are far from representative of real-world exposure scenarios of next-generation wireless devices. Therefore, assessing the health risks associated with 5G exposure does not appear to be an easy task.

The question of possible health effects from exposure to radiofrequency (RF) energy is a matter of debate within the scientific community, but there is no conclusive evidence to date that significant risks exist. This highlights the need for further research and discussion in this area. For example, incidence of brain-related diseases, including higher nervous system disorders, mental health issues, and brain tumors is of increasing concern to society. The main possible effects on human health that can result from RF exposure are listed in Table 1.

Thus, exposure to RF-EMF could hypothetically lead to several types of health effects but the use of 5G equipment under realistic conditions is not expected to cause effects such as skin lesions, eye damage, and effects on glucose metabolism, as these phenomena are only observed at electromagnetic field levels that significantly exceed those produced by 5G equipment. The link between 5G and male fertility and electromagnetic hypersensitivity has not been scientifically proven [26, 27].

Next, we examine medical studies on the health effects of RF-EMF conducted on animals as well as population-based and sociological studies, the results of which may be relevant in studying implementation of 5G networks.

Animal-based studies. Over the past decades, numerous animal studies (for example, mice and / or rats) have been conducted to replicate RF-EMF exposure and to analyze the potential health effects associated with such exposure [28–31 and others]. However, it is worth noting that many of these studies have several shortcomings, including relatively small sample sizes, which limit the statistical power of the findings [32, 33], and insufficient experimental duration [33, 34] which call into question the long-term relevance of the

Table 1

Possible main consequences for human health can result from RF exposure

The possible consequences for human health	Description
Cancer	In 2010, based on an analysis of epidemiological studies, the International Agency for Research on Cancer (IARC) classified non-ionizing RF radiation from mobile phones as "Possibly carcinogenic to humans," placing it in category 2B [7, 8]. Research involving rats [9–12 and others] has also indicated a statistically significant increase in the risk of brain tumors, heart glial tumors, and parotid gland tumors linked to RF exposure.
Impact on the skin	Exposure to high power density RF radiation can raise the temperature of the affected body tissues [13]. Nevertheless, the human body's thermoregulation mechanisms can often accommodate modest localized heating. The significant RF absorption may cause a warming sensation on the skin, potentially resulting in mild skin burns [14].
Eye damage	Exposure to high levels of RF radiation with sufficiently high energy flux densities can lead to some ocular effects [15], including retinal damage, cataracts, and cornea problems.
Glucose metabolism	RF radiation can affect glucose metabolism in human cells [16], which can occur in the organs exposed to high levels of EMF, such as the brain.
Male fertility	Exposure to high levels of RF radiation may lead to a series of negative consequences for male reproductive health [17–19 and others], primarily a decrease in sperm fertility. However, the link between such effects and RF exposure from communication equipment has not been conclusively proven.
Electromagnetic hypersensitivity	Some studies (see, for example, [20–22]) have reported that people may associate symptoms such as headaches, stress, fatigue, sleep disturbances, heart pain, and increased blood pressure with RF exposure. Other studies (e.g., [23–25, and others]) have not shown a connection between these symptoms and levels of RF radiation, indicating that, to date, such a relationship has not been reliably confirmed.

results. To address these concerns, several international bodies, such as the World Health Organization and the National Toxicology Program (NTP), have established guidelines to ensure the quality of animal-based research investigating the development of serious diseases, particularly cancer [35–39]. These guidelines specify essential parameters, including a minimum of 50 animals per group for statistical robustness, recommended study duration of two to three years, and a requirement for at least three different levels of EMF intensity [40].

In light of these standards, noteworthy research efforts that meet these criteria include those conducted by the NTP [9, 10] and by the Ramazzini Institute [11].

The NTP studies [9, 10] are some of the longest experimental research to date aimed at evaluating the effects of RF-EMF on animals. These studies focused on 2G technology, but their results are often cited by opponents of 5G network deployment. In the NTP experiments, rats were divided into several groups and exposed to different levels of EMF for several hours a day until they died of natural causes. The experiment lasted for two years and included an initial assessment after the first 28 days and a final assessment at the end of the study. The RF devices used to generate the EMF used frequencies in the sub-GHz band for [9] and in the mid-band (1–6 GHz) for [10]. The radiated power of the RF devices was adjusted to achieve the specified exposure level in the chamber. Regular monitoring of the EMF levels was performed in each chamber to ensure compliance with the parameters set for the experimental conditions.

According to the findings of the study at sub-GHz frequency [9], carcinogenic activity was observed in Sprague-Dawley male rats, mainly manifested by the development of malignant schwannoma of the heart and other tumors (for example, malignant gliomas of the brain). At the same time, these effects were not observed in female rats. In the mid-band frequencies experiment [10], no clear signs of tumors were found in male or female rats. It is also important to note that the work [41] analyzes the results of the studies [9, 10] and concludes that RF exposure may contribute to an increase in DNA damage.

The Ramazzini Institute conducted a study to assess the impact of RF radiation on Sprague-Dawley rats [11]. The rats were exposed to RF-EMF exposure for several hours per day from prenatal life until death. According to the authors, their findings confirm the results of the NTP studies [9, 10] and previous epidemiological studies on mobile phones [42, 43, etc.], calling for a review of the IARC classification of RF radiation [8].

Next, this article examines the conducted animal studies in the context of 5G communications. 5G will operate in three main frequency bands:

1. sub-GHz band (< 1 GHz);
2. mid-band (1–6 GHz);
3. millimeter waves (30 GHz and above).

Research conducted by the NTP [9, 10] has focused on frequencies within both the sub-GHz band and mid-band frequencies. It is important to highlight that the 900 MHz frequency referenced in one of these studies [9] is very similar to the sub-GHz band used in the 5G technology; for example, Italy designates this frequency at 700 MHz. In addition, another study [10] used a frequency of 1900 MHz, which is related to 5G services in several nations, including the United States, although countries like Italy have opted for different designations. For instance, the Ramazzini Institute's research [11] used a frequency of 1800 MHz, which can be likened to mid-band frequencies related to 5G.

However, none of the studies [9–11] investigates the impact of frequencies within the millimeter-wave spectrum. The frequencies in this range exhibit distinct characteristics as they tend to penetrate body tissues less effectively than microwaves. However, it is essential to recognize that the studies produced by the NTP have primarily centered on 2G technologies, making the use of millimeter-wave frequencies impractical in this context. Therefore, the findings from studies [9–11] can only be partially used to assess the impact of 5G technologies. Many of the research parameters [9–11] appear to be quite different from those used in 5G equipment.

Variations encompass several aspects, such as exceptionally brief distances in comparison to actual ones encountered in 5G networks; substantially elevated EMF levels that far surpass those produced by 5G devices, leading to increased radiated power; prolonged duration of exposure; fundamental methods of transmission and modulation; and whole-body specific absorption rate (SAR)[2] values that do not have a direct correlation with local SAR when utilizing genuine smartphones [2].

Consequently, the findings regarding the health impacts of RF-EMF provided by the foregoing studies cannot be directly applied to the context of actual 5G network implementations.

In this regard, ICNIRP[3] highlighted in a specific statement that the studies [9–11] do not offer a cohesive, dependable, and broadly applicable set of evidence to warrant changes in exposure guidelines. To overcome these limitations, additional research is required.

Population-based studies. Research in this category aims to examine the relationship between the presence of serious diseases (such as brain tumors) in humans and the levels of radiation exposure from base stations and mobile phones. We do not focus on population-based studies of base stations exposure because the studies conducted for previous generations of mobile communication have shown that the exposure from base stations is much lower than that from mobile devices [44, 45, etc.]. Furthermore, the impact of base stations decreases significantly as users move away from the station [46–48, etc.]. Previous population-based studies [49, etc.] by the American Cancer Society [50] have not found a causal relationship between base station exposure and increased risk of tumor development. Nonetheless, given the deployment of 5G technology, characterized by an increasing number of base stations and their location in close proximity to each other [51, 52], it is important to note that questions regarding the impact of such stations on public health require further rigorous analysis. Progress in this area strongly underscores the necessity for research and discussion on the potential consequences of overall exposure.

Mobile phones are a well-known source of RF-EMF exposure in the vicinity of users (see, for example, [44, 45]). Therefore, we focus on population-based studies aimed at establishing causal relationships between tumor incidence and exposure to mobile phones. The main studies conducted in the past are also relevant in the context of 5G.

INTERPHONE study [53, 54] was coordinated by IARC. The study, based on the case-control approach, was carried out in thirteen countries in 2000–2012. The aim of the project was to study the impact of mobile phone use in people with severe diseases (e.g. glioma, meningioma, and acoustic neurinoma). The number of people involved in the study was of great importance involving more than 5,000 patients diagnosed with glioma or meningioma and 1,000 patients diagnosed with acoustic neurinoma. In addition, a control group was also considered which included people who did not have any of these tumor types.

The study used such methods as personal interviews and validation studies to obtain the most accurate data on mobile phone use, including the duration and frequency of the calls,

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[2] SAR is the specific absorption rate of electromagnetic energy. This indicator determines how much radiation a person receives in one second while using a smartphone. The SAR level is standardized in most countries and is used to assess potential health risks.

[3] ICNIRP (International Commission on Non-Ionizing Radiation Protection) is an independent organization officially recognized by the World Health Organization (WHO). Its main goal is to investigate the health risks associated with exposure to non-ionizing radiation and to provide recommendations for limiting exposure to minimize potential health risks.

age, and other relevant information (e.g. network operator, phone model, location of calls, user mobility, use of headset or hands-free function).

The results [53, 54] generally showed no significant association between mobile phone use and the risk of glioma, meningioma or acoustic neuroma. Some increase in glioma risk was found at high levels of RF-EMF exposure. Unfortunately, the various data errors make a more nuanced interpretation of these findings difficult.

Danish cohort study [55] was aimed at identifying a possible increase in the risk of tumor development in people who have a subscription to a mobile phone operator. The comparison group was the rest of the population without such a subscription. The study included two phases, starting with the first wave in 1982–1995 [40] and ending with the last one, covering the period 1990–2007 [55]. Despite a very large sample size (the number of subscribers in [55] exceeds 380,000), the study showed no link between the use of mobile phones, even if used for longer than thirteen years, and the risk of developing central nervous system tumors.

A large-scale project studying women's health [56] involved the respondents completing a questionnaire sent by mail. The study surveyed 1.3 million middle-aged women in the UK at various times during 1999–2009. The survey included questions aimed at assessing the impact of mobile phones, which were asked twice during the study period. The results showed no significant links between the frequency of mobile phone use and increased incidence of central nervous system tumors, or glioma, meningioma.

Next, we consider population-based studies [53–56] from the *perspective of evaluating the impact of 5G communication technology*. Table 2 summarizes the main parameters used in previous studies and how these parameters should be modified or supplemented when considering 5G equipment.

It should be noted that the assessment was conducted using traditional methods such as surveys, face-to-face/distance interviews, and (in some cases) the analysis of log files available from mobile network operators [53–56]. However, the spectrum of 5G services encompasses a variety of different functions such as data exchange and voice communications, so the measurement of mobile device activity cannot be based solely on data obtained from surveys and / or interviews. To obtain such information, it is advisable to install special

Table 2

Comparison of key parameters used in population studies [53–56] with those relevant in the 5G context

Parameters	Population-based studies	5G communication
Assessment	Questionnaires, personal interviews, long-distance interviews, mobile operator logbook	Cloud application, mobile operator logbook
Frequency of assessment	One-off, periodic	Uninterrupted
Type of Activity	Calls	Calls, video streaming, social networking, instant messaging
Intensity of activity	Number of calls	The number of minutes spent on each app, the amount of content downloaded
Connectivity	Phone number, operator	Phone number, operator, interfaces used, frequencies used, transmission information
Phone position	Head distance, use of hands-free devices	Proximity of the phone to the user, phone handling
Phone location	Country, place of residence	Country, place of residence, mobility of users
Phone information	Device model	Device model

user applications on phones that automatically transmit the measured data in a controlled cloud environment. In case this approach cannot be implemented (for example, due to privacy concerns), researchers should use files provided by mobile operators.

Other studies [53–56] with their focus on assessing frequency assume that user activity information is extracted either at the end of the considered period or on a periodic basis. In contrast, 5G requires continuous activity monitoring because of the strong temporal variations for data exchanged in applications installed on a 5G smartphone.

Finally, the methodology of the above studies focuses mainly on monitoring call duration. In this context, it seems very important to note that although 5G networks still provide voice services, the range of functions demanded by modern users is much broader, while voice communication has increasingly lost its leading position in recent times. Accordingly, research should monitor the time spent not only on call duration, but also, for example, on functions such as video streaming, social networking and instant messaging. Obtaining such data will enable creating the most accurate user profile, including exposure information for each type of service. In the context of 5G studies, it seems extremely important to record time spent on each application and to track the amount of transferred data.

Population-based studies typically take into account key characteristics such as phone number and mobile network operator. In the context of 5G research, this information should be supplemented by considering the usage time of each standard (for example, 5G, 4G, Wi-Fi). Another important characteristic relates to used frequencies (such as sub GHz, mid-band, millimeter waves) and indicators of performed handovers (which may influence the exposure).

Studies [53–56] use simple metrics such as distance to the head and use of speakerphone. In the case of 5G, it is important to take into account the position of the phone relative to the head/chest or other parts of the body. In addition, as mobile devices are used in different ways (e.g., for conversations, video viewing, text messaging, self-recording, etc.), it is also important to consider how the phone is held (for example, with one hand or two hands, in a vertical or horizontal position). Ultimately, this type of research identifies the user's location (in relation to the country, area of residence). These data can then be used, for example, to categorize users by area type (urban/rural). In the context of 5G, the mobility of users plays a key role and it is very important to ensure that this factor is also taken into account. Finally, when conducting population-based studies, one should also consider the model of the mobile device. As the exposure of the phone varies depending on the model, these data should also be collected when considering 5G equipment.

Thus, despite the extensive population-based studies conducted to assess the impact of mobile devices in legacy generation networks, their findings do not fully generalize to 5G. Consequently, a new set of population-based studies specifically focused on 5G is needed. This step requires a radical change in research methodology taking into account the parameters that need to be considered when making measurements and analyzing the obtained data.

Sociological studies. Informing the public about health risks has traditionally been based on calculating mortality estimates and publishing the resulting data in the hope that this will reduce anxiety. However, in many cases, even when experts and the public saw the results of the same estimates, they still disagreed about the magnitude of the perceived risks. This disagreement arose because members of the public based their perceptions of risk on the impact of multiple factors in addition to those objectively studied.

The study [57] was conducted to identify factors influencing public perception of the risks associated with EMF from 5G base stations. It showed that EMF from 5G base stations was perceived as a moderate health risk. The level of perceived risk was comparable to the perception of EMF risks from mobile phones, higher than the perception of risks from household chemicals, but lower than the perception of risks from cigarette smoking. In addition, the perceived risk of EMF from 5G base stations was most closely associated with the perceived risk of EMF from mobile phones and least associated with the perceived risk of drinking contaminated water.

Risk perception assessments showed a significant relationship with the sex of the subjects, assessment of how effectively the state policy was implemented, as well as the subjective perceptions of potential threats and health consequences associated with EMF exposure. Frederik Freidenstein et al. [58] found that a higher level of perception of RF-EMF exposure was associated with increased risk perception. Research also suggests that women tend to perceive risks as more serious than men do. A lower level of trust in government policies is also associated with an increased perception of risk from EMF sources. In addition, Kyunghee Kim et al. [59] found that people who scored higher on the dimensions of "personal knowledge" and "seriousness of risk to future generations" also had higher risk perception scores for mobile phone EMF.

Sociological studies have also identified factors that are associated with a lower perception of EMI risk from 5G base stations. Risk perception scores were lower in the 20–29 age group, current smokers, and non-drinkers. It has also been found [60] that older people perceive health risks as more serious than younger people. In addition, an increased sense of control was associated with lower risk perception [61]. In the study [57], the researchers hypothesized that placing a mobile phone charger nearby during sleep would lead to a lower risk perception because such behavior indicates indifference to EMF exposure; however, they found no significant association.

Marie-Eve Cousin and Michael Siegrist [62] showed that reading a brochure on mobile communication improved the objective knowledge of urban residents in Switzerland, but this came at the cost of increased anxiety. However, Liesbeth Klaassen et al. [63] reported that providing the public with information on EMF exposure improved knowledge and reduced risk perception. The authors of the study [57] constructed a multiple linear regression which showed that increased knowledge was associated with increased risk perception. This suggests that, obviously, subjects with a higher risk perception were apparently more active in gathering relevant information by relying on authoritative and trusted sources.

Methodological approaches to assessing the population health risk from 5G networks exposure. The main regulatory document guiding the assessment of health risks to the population from exposure to electromagnetic radiation is MR 2.1.10.0061-12[4] [4]. These methodical guidelines provide a systematized approach to assessing the impact of EMF on human health and may be useful for the initial risk assessment of EMF exposure from 5G networks. Nevertheless, it is important to take into account some clarifications and limitations when applying these guidelines in this area.

MR 2.1.10.0061-12 covers the frequency band up to 300 GHz, which includes frequen-

[4] MR 2.1.10.0061-12. Otsenka riska dlya zdorov'ya naseleniya pri vozdeistvii peremennykh elektromagnitnykh polei (do 300 GGts) v usloviyakh naselennykh mest: Metodicheskie rekomendatsii, utv. Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii G.G. Onishchenko 13 aprelya 2012 g. [Assessment of the risk to public health when exposed to alternating electromagnetic fields (up to 300 GHz) in populated areas: Methodical guidelines, approved by the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, the RF Chief Sanitary Inspector on April 13, 2012]. *KODEKS*: *electronic fund for legal and reference documentation.* Available at: https://docs.cntd.ru/document/1200095226 (May 18, 2024) (in Russian).

cies used in 5G networks. Thus, the main methodological approaches outlined in these guidelines can be applied to assess the impact of 5G. However, it is important to recognize that 5G uses frequency bands that vary over a wide spectrum, including higher frequencies than those used in previous generations of mobile communications. The parameters and characteristics of 5G networks differ significantly from previous generations of mobile communications [52, 64]. Thus, these networks use technologies such as MIMO[5] (Multiple Input Multiple Output) and small cells, which can lead to very different characteristics of EMF propagation and concentration. The research [65] also highlights that massive parallel signal processing and precise beamforming, together with the use of higher frequency bands, may cause existing measurement methods to produce significantly overestimated results when applied to 5G networks.

Thus, to achieve more accurate and informed risk assessment, it is important to conduct additional research that considers the unique parameters of 5G and includes new data from surveillance and epidemiological studies [64-66]. As a result, the scientific and methodological framework may change as new data become available, requiring adaptation of the approaches described in MR 2.1.10.0061-12.

Currently, there is paucity in publications with clear methodological approaches to assessing the health risks to the population from exposure to 5G networks. Guidelines from the International Commission on Non-Ionizing Radiation Protection (ICNIRP) have been used to develop fuzzy logic-based algorithms to assess the risks associated with non-ionizing radiation in the 5G environment [67]. Safe standards have been adapted to take account of new technological developments, and recent updates to the ICNIRP and IEEE C95.1 standards [6] have addressed concerns about millimeter band frequencies [68]. The assessment of health risks from exposure to 5G networks should include several key steps. Based on MR 2.1.10.0061-12 and the available literature on the issue of 5G exposure of the population, we can propose the following approximate algorithm.

Exposure Source Identification. Identification of EMF sources associated with 5G networks, including base stations, small cells, user devices, etc.

Exposure Assessment. Assessment of EMF levels that may occur in different 5G operating scenarios (e.g., urban, rural, and indoor environments) both at a given point in time and for the duration of their persistence. With the development of adaptive antenna technologies in 5G networks, application of statistical approaches to the assessment of maximum exposure levels from base stations, as reflected in international documents, is becoming increasingly relevant in the field of EMF hygiene assessment at the international level [64]. For Russia, this method, which focuses analyzing real exposure conditions, is new and requires an update of the regulatory framework, as well as comprehensive studies in cooperation with mobile operators, including testing methods for extrapolation of the results obtained by selective measurements.

Analysis of Health Effects Studies. A review and analysis of the available data on the potential physiological and biochemical effects of 5G radiation, including epidemiological, population-based, and animal-based studies [69, 70].

Dose-Response Assessment. A study of the relationship between the level of exposure (dose) and the observed health effects. This step involves identifying thresholds above which adverse effects may occur.

Uncertainty Assessment. The growing concern about RF-EMF cannot be ignored as

[5] MIMO (multiple-input and multiple-output) is a method for multiplying the capacity of a radio link using multiple transmission and receiving antennas to exploit multipath propagation, which deploys multiple antennas at both the transmitter and receiver to increase the quality, throughput, and capacity of the radio link.

the population is affected by greater levels of exposure due to the high density of transmitters required for 5G systems [71]. The main sources of uncertainty are inadequate and imprecise knowledge of potential hazards, difficulties in establishing thresholds for human exposure, and heterogeneity in data on EMF duration and shielding, which affects the reliability of the resulting estimates.

Final Risk Assessment. Synthesizing data and exposure information to estimate the overall risk to the population. This step may include development of models that show how effects may vary with the exposure level, exposure time, and other factors.

Recommendations for Risk Management. Formulating recommendations and strategies to minimize health risks such as setting exposure limits, monitoring population health, and education initiatives on the safe use of technologies. These recommendations are presented to management decision makers.

Monitoring and Revision. Establishing a monitoring system to track changes in technology levels and its potential impact on health with regular assessments of risk based on accumulating new data.

Health risk assessment of 5G networks is therefore multifaceted and requires integrating knowledge from different disciplines, primarily radiophysics, biology, medicine, epidemiology and sociology. The presented algorithm is useful for formulating evidence-based recommendations and policies for the use of 5G technologies providing a unified approach to assessing potential health risks to the population.

Conclusion. Conducting studies to assess the impact of 5G (and later 6G) networks on population health requires developing a new methodology based on the considered characteristics of new-generation networks. Accordingly, we cannot directly use the methodological approaches developed for 2G, 3G and 4G networks [72]. This circumstance poses new challenges for hygienic science in terms of developing a theory of hygienic regulation of RF-EMF in a complex electromagnetic environment with justification of new unified hygienic standards. Subsequent studies should pay special attention to dosimetry and temperature control of the environment during the experiment. It is also extremely important to monitor the long-term health effects associated with wireless telecommunications [73]. The results of future research will provide the basis for developing effective measures to ensure electromagnetic safety of the population and protection against the potential negative effects of 5G networks. The assessment and management of health risks from 5G networks is a multifaceted and constantly evolving process that requires an interdisciplinary approach, involvement of the scientific, medical, and technical communities, and a transparent discussion with the public. A key aspect is the integration of new scientific data into risk management strategies to ensure safety and well-being of the population.

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Research article

HIGH AMBIENT TEMPERATURES AND MENTAL HEALTH: RISKS, METHODS AND RESULTS

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This work is an analytical review. Initial research data have been taken from original studies published in peer-reviewed scientific journals in 2014–2024. The following search terms were used when searching for English language sources in PubMed database: (mental health OR mental disorders OR mental illness OR suicide) AND (high ambient temperatures OR heat stress OR hot weather OR heat waves). Russian language sources were sought in eLibrary using the following keywords: mental health; mental disorders; mental diseases; suicide; high ambient temperatures; heat waves; global warming.

The review has established the following. Effects produced by high ambient temperatures on mental health have only recently become a separate research topic within a broader context of 'Climate Change and Population Health' studies or, as the WHO terminology puts it, 'Population Health under Changing Climate'. In contrast to five previous reports, the Sixth Assessment Report of the Intergovernmental Panel on Climate Change contains a bigger section on impacts exerted by climate on mental health. Scientific evidence suggests with high confidence that exposure to high ambient temperatures and heat waves causes mental disorders. These disorders include anxiety, depression, acute post-traumatic stress, suicidal behavior, and use of psychoactive substances; they are diagnosed as both mild disorders and severe cases that require hospital admission. Effects of heat stress on human psyche are caused by complex interactions between physiological and psychological factors. The human body tries to maintain the thermal balance and this induces a whole cascade of physiological reactions, ranging from increased heart rate to dehydration. Physiological strain undermines mental health and causes sleep disorders, irritability, mental fatigue and cognitive disorders.

Keywords: *climate change, heat waves, high ambient temperatures, heat stress, mental health, risk factors.*

Heat waves are the periods that create significant discomfort for humans and are statistically associated with drastic mood swings, aggression and anxiety, especially among people with low socioeconomic status [1, 2]. This has even made researchers suggest a new concept, heat-related violence [3]. Moreover, the American Psychological Association has reported that a relative increase in mortality during heat waves has been thrice as high among patients with mental disorders compared to healthy people [4]. Also, suicide rates have been reported to rise during heat waves [5] and in early summer when weather typically gets hot [6]. The frequency of emergency ambulance dispatches due to suicidal behavior grew by more than four times in Shenzhen, China, during heat waves lasting for 3 or more days (*RR* = 4.53, 95 % CI: 1.23–16.68) [7]. In contrast to five previous reports, the Sixth Assessment Report of the Intergovernmental Panel on Climate Change[1] contains a bigger section on climate change impacts on mental health. Mental disorders have been established in people exposed to dangerous meteorological events such as floods, typhoons, storms or droughts in many countries across the globe. The same happens during fires or other emergencies.

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[1] Climate Change 2022: Impacts, Adaption and Vulnerability. Working Group II Contribution to the Sixth Assessment Report of the Intergovernmental Panel on Climate Change. In: H.-O. Pörtner, D.C. Roberts, M. Tignor, E.S. Poloczanska, K. Mintenbeck, A. Alegría, M. Craig, S. Langsdorf [et al.] eds. Cambridge, UK; New York, NY, USA, Cambridge University Press Publ., 2022, 3056 p. DOI: 10.1017/9781009325844

This review focuses on methods for investigating effects of climate change on mental health in greater detail in comparison with our previous reviews of health effects of climate change. This subject is still new for Russian researchers.

Materials and methods. This work is an analytical review. Initial research data have been taken from the original studies published in peer-reviewed scientific journals in 2014–2024. Several criteria were used in selection of relevant sources. Original studies had to contain the following:

1) quantitative data on temperature stress during a hot season during the study period or definition of heat waves since different authors tend to use different definitions;

2) descriptions of analyzed samples (the number of subjects and reference to a city or a country); we also considered meta-analyses, which generalized the results reported in several local studies in order to identify health effect modifiers;

3) a formulated statistical hypothesis and description of statistical methods used to test it. We took both direct epidemiological studies that involved establishing numerical relationships between a dose and a level of effects produced on mental health and the results obtained by survey data analysis, for example, about the number of complaints about certain symptoms. The studies of the first type were given priority in selection for review.

The following search terms were used when searching for English language sources in PubMed database: (mental health OR mental disorders OR mental illness OR suicide) AND (high ambient temperatures OR heat stress OR hot weather OR heat waves). Russian language sources were sought in eLibrary using the following keywords: mental health; mental disorders; mental diseases; suicide; high ambient temperatures; heat waves; global warming. References in publications, which were found using the above mentioned keywords, were analyzed by hand to search for additional relevant articles.

Main results. An original epidemiological study conducted in Odessa and the Odessa region is among the first Russian publications on the subject. It covered 11,200 suicides during the period between 2000 and 2016 [8]. The results of this study revealed seasonality in suicidal behavior as the number of suicides grew in May when daylight hours became progressively longer (the linear correlation coefficient was $r = 0.97$ at the significance level $p < 0.001$). A relationship was also established between suicide rates and high ambient temperatures since the typical seasonal spring-summer temperature rise was the most pronounced in May. Another study analyzed a relationship between frequency of suicides and geliogeophysical and technogenic factors in three cities located in the Murmansk region, that is, in high latitudes. The three cities were Monchegorsk, located near a nickel smelter, Apatity and Kirovsk, the cities famous for mineral fertilizer factories. Suicide frequency was higher in Monchegorsk, a city exposed to emissions from Severonikel Plant. Possible health effects of solar activity cycles tend to be more intensive in high latitudes [9]. A scoping review [10] of effects of high ambient temperatures on suicide rates worldwide reported that the results of multiple studies suggested the relation between suicide rates and high ambient temperatures.

Neurophysiological pathways of heat stress. When explaining possible pathways that could explain increase in hospital admissions for mental disorders during hot periods, researchers often turn to brain biochemistry. Heat stress induces an increase in plasma serotonin, which inhibits the production of dopamine (DA), a neurotransmitter that appears to influence brain functioning in complex task performance [11]. High ambient temperatures also affect the production of serotonin in platelets, which is associated with such diseases as schizophrenia and depression [12]. Overheating of neuron tissue can induce changes in temperature-sensitive processes in the brain, for example, synapse conductivity, cerebral circulation, production and metabolism of the most important neuromediators (catecholamine, noradrenaline, and gamma-aminobutyric acid), which affect the symptoms of schizophrenia and other mental disorders [13]. Overheating of the brain impairs the blood-brain barrier permeability, which can result in brain edema and functional disorders in the brain. Patients with schizophrenia reportedly have difficulties with thermal regulation [14]. High temperature inhibits the production of L-Tryptophan, a serotonin precursor; low concentrations of L-tryptophan in plasma are associated with major depression disorders [15].

Declining cognitive functions under high ambient temperatures can also be a pathway, since such patients may fail to perceive how hazardous heat is and to take relevant safety precautions. Similarly, patients with dementia should also be at higher risk since they may fail to take relevant protective actions during extreme heat. The increased level of physical discomfort that they experience under such weather can exacerbate dementia symptoms and lead to excitation [16]. Psychoactive drugs can reduce the body ability to perform thermal regulation. Strong heat stress can induce mental confusion and declining cognitive abilities in patients with schizophrenia [17].

High ambient temperatures as a risk factor affecting mental health. Epidemiological studies of the effects of high ambient temperatures on mental health can be divided into two uneven groups according to the procedure of selection of an exposure variable: (1) describing continuous relationship between a selected health outcome and variations in ambient temperature and (2) examining effects produced by heat waves as a discrete weather phenomenon when a binary heat wave indicator is used as an exposure. Most of studies belong to the first type. Thus, a systematic review [18] of literature indexed in databases such as PubMed, Embase, Scopus, Web of Science and PsycINFO, identified 44 studies describing continuous temperature relationships and only 12 studies that focused on heat waves. Accordingly, the results reported in the first-type studies are usually given as an increase in morbidity / mortality per specified change in temperature within the given percentile range, or per each 1 °C increase in temperature. However, if a temperature averaged over several days before the effect (T_{0-n}) is taken as an exposure variable, then the model measures the effects of stress accumulated over $n + 1$ day (the day when the effect started is considered the zero one). As we shall see, the results of studies that concentrate on the relationship between the effect and ambient temperature are most frequently reported exactly for such averaged temperatures. If the results are reported for extreme ambient temperatures T_{0-n} at the 95-th percentile or higher, then we actually speak about effects produced by heat waves. The second-type studies usually report increases in morbidity / mortality during heat waves in comparison with the remaining days or with specifically selected control days.

Let us first consider several examples of studies that focus on continuous relationships between mental health measures and ambient temperatures with emphasis on age-related differences. In the next section, we will consider the effects produced by discrete heat waves. During extreme heat, there was a growth in mental disorder hospitalizations and especially an apparent rise in levels of transient mental disorders in Hong Kong [19] and Shanghai [20]. Long-term exposure to heat in two Canadian provinces, Alberta and Ontario [21] led to increased number of emergency department visits for mental and behavioral disorders including such diagnoses as dementia, neurotic disorders, schizophrenia and personality behavior disorders.

In Hong Kong, Poisson Generalized Additive Model (GAM) was used to study the relationship between daily hospital admissions for mental disorders and a daily set of meteorological parameters including average daily ambient temperature. Overall, 44,600 hospital admissions were analyzed, which were registered in 2002–2011. To describe a smooth relationship between the number of hospital admissions and ambient temperatures, the Distributed Lagged Non-linear Model (DLNM) was used to account for the potential lagged effects. In the core model, the daily counts of mental-disorder admissions were regressed against the long-term trend (day of study), seasonal trend, holiday effect, day-of-week effect, and also levels of ambient air pollution, which at present is considered a conventional 'good practice' in such studies. Cumulative relative risks (*RR*) were estimated for the interquartile range of temperatures, that is, a relative growth in hospital admissions, which corresponded to an increase in ambient temperature between the 25^{th} percentile (19.4 °C) and the 75^{th} percentile (28 °C). The estimated *RR* = 1.09 (95 % CI: 1.03–1.15) for all age groups, but it reached 1.20 (95 % CI:

1.09–1.31) for elderly patients aged over 75 years. This indicates that the older age group is highly susceptible. At the same time, no risks were established for children younger than 15 years. The highest risks were established for transient organic psychotic conditions (transient disorders)[2], ICD-9 code 293, *RR* = 1.51 (95 % CI: 1.00–2.27), and recurrent affective psychoses, ICD-9 code 296, *RR* = 1.34 (95 % CI: 1.05–1.71). The authors of this study believe that higher relative risks found for the older age-group might be associated with a higher prevalence of cognitive problems among the older population. Previous studies have reported negative associations between temperature and cognitive function among Japanese [22] and Americans [23]. In Hong Kong, a U-shaped association was found between temperature and dementia admissions, that is, risks of dementia increased under high ambient temperatures [19].

In Shanghai, a quasi-Poisson generalized additive model (GAM) combined with a distributed lag non-linear model (DLNM) was used to analyze the lag-exposure-response relationship between daily mean temperature, relative humidity and hospital admissions for mental disorders. First, the distributed lags were up to 21 days; however, it was shown that lags up to 7 days would be quite sufficient since after day 7 a cumulative effect loses its statistical significance [20]. The model also considered an apparent relationship between hospital admissions and a calendar period (adjusted for a day-of-week, seasonal and long-term trends) and ambient air pollution with PM_{10}, SO_2 and NO_2. Overall, 94,000 hospital admissions during 2008–2015 were analyzed and a relative increase in hospital admissions was calculated, which corresponded to a temperature rise from its median value (18.3 °C) up to 99th percentile (33.1 °C). The maximum effect was reached at a lag of 0–1, that is, for the sum of temperatures on a hospital admission day and the previous day. The respective risk for all age groups was *RR* = 1.27 (95 % CI: 1.07–1.49). Obviously, this risk is much higher than in Hong Kong since it corresponds to the temperature rise up to the 99th percentile and not the 75th one. However, the authors report a respective result for the 75th percentile (24.5 °C), *RR* = 1.08 (95 % CI: 1.00–1.17), and it is almost the same as the result reported for Hong Kong. The authors of the study conducted in Shanghai report that this level of risk is mostly reached due to age groups ≥45 years since for this group *RR* = 1.32 (95 % CI: 1.08–1.62). The effect lost any significance for the age group 0–44 years and amounted to *RR* = 1.10 (95 % CI: 0.89–1.36); that is, ambient temperatures had practically no effect on hospital admissions.

The effects of high ambient temperatures on mental health have been observed not only in Asia but also in the Western hemisphere. Thus, a strong association was found in Toronto, Canada, between mean daily temperature at 28 °C and hospital admissions for all mental disorders and specifically for schizophrenia, mood, and neurotic disorders [24]. This temperature in Toronto corresponds to the 99th percentile of average daily temperature distribution. The ambient temperature that corresponded to the 50th percentile was taken as a reference one. The association was the strongest for the regressor $T_{0\text{-}4}$, that is, on the fifth day of continuous exposure to extreme heat. Relative risk for hospital admissions for all mental and behavioral disorders at $T_{0\text{-}4}$ = 28 °C was equal to 1.29 (95 % CI: 1.09–1.53).

In the USA, a relationship was found between a rise in average monthly ambient temperatures and a growing number of complaints about mental disorders (depression, stress, and emotional disorders), which a respondent had for the last 30 days prior to the day of a survey. Overall, 2 million people took part in the survey all over the country [25]. The maximum daily temperature averaged over the same period (T_{30}) was taken as an exposure variable. To simplify the design of this study a bit, we can say that all cities in the USA were divided into five groups with the 5 °C differences in this variable: the first (reference) group with 10 °C < T_{30} < 15 °C; the second group with 15 °C < T_{30} < 20 °C and so on, to the last group with T_{30} ≥ 30 °C. The number of complaints in the last but one group with 25 °C < T_{30} < 30 °C was higher by 0.7 %

[2] Similar to transient disorders of cerebral circulation.

than that in the reference group, and the number of complaints in the last group was 1.3 % higher than that in the reference group. Therefore, empirical evidence suggested the effect of rising average monthly temperatures on the prevalence of mental symptoms.

We have already mentioned this Canadian study [21], which used a case-crossover design in contrast to time series analysis. Let us look at it in greater detail. Specifically, each day with an emergency department (ED) visit was compared to several control periods for the same patient when he/she did not visit the ED. In this Canadian study, the control periods were selected as the same days on the different weeks during the same month. For instance, if an ED visit for mental and behavioral disorders occurred on the first Monday of January 2020, the control periods would be identified as those other Mondays during January 2020. Only the first ED visit during the respective month was considered. This study design was less prone to bias from effects of a day-of-week and a month-of-year and also accounted for individual-level confounders (e.g. smoking status) since 'the case controlled itself'. A case and its control would differ from each other by only weather and environmental conditions in a place where a patient lived, for example, levels of ambient air pollution. Conditioned logistic regression was applied to investigate influence exerted by these variables in 'case – control' pairs. A distributed lag non-linear model (DLNM) was used because it described lagged exposures to environmental factors that accumulated over several days. The greatest temperature effect would be reached when considering the lags between 0 and 5 days ($T_{0\text{-}5}$), that is, heat stress accumulated over five days prior to a hospital visit. Overall, the sample included almost 10 million (!) ED visits for mental and behavioral disorders over the period 2004–2020 in Alberta and Ontario provinces. An average daily temperature and humidity were retrieved from the Daymet North American Meteorological Database using a 1 km × 1 km grid approximating the coordinates of the zip code of a patient's place of residence. In this study, the authors calculated odds ratios (*OR*) of emergency department visits at the 97.5th percentile of average daily temperature distribution in reference to the 'optimal' temperature under which the number of ED visits was the lowest in a given administrative region. This optimal temperature was within the range between the 5^{th} and 95^{th} percentiles and was established by visual examination of the graph of the relationship between ambient temperature and the number of ED visits. ORs were calculated separately for each region and then the average weighted value was determined using meta-analysis. These values are presented in Table 1 for specific diagnoses and age groups. The greatest heat effects were found in the age group of 30–49 years; the lowest, in the age group ≤ 18 years. The highest risk among all analyzed diagnoses was established for substance use disorders.

Effects of heat waves. Medical visits for mental disorders were studied using 'case-crossover' method in Jinan, China (population is 6.8 million) during the four strongest heat waves in the summer of 2010 [26]. That summer was extremely hot; four heat waves were registered and lasted for 4, 3, 4 and 3 days, respectively. Each visit to a doctor during a heat wave was considered a 'case'; control days

Table 1

Odds ratio (*OR*) for visits to the emergency department during extreme heat and under optimal ambient temperature in Canada [21]

Analyzed group	*OR*	95 % CI
Any mental disorder, any age	1.15*	1.12–1.17
Age of 30–49 years	1.18*	1.15–1.22
Age ≤ 18 years	0.97	0.91–1.02
Substance use disorders	1.29*	1.24–1.33
Schizophrenia	1.15*	1.10–1.20
Neurotic disorders	1.15*	1.12–1.19
Dementia	1.16*	1.07–1.25

Note: * risk is significant at 95 % level, $p < 0.05$.

were selected on the same days-of-week one, two and three weeks prior to a heat wave as well as one, two and three weeks after it (provided that those control days themselves did not fall within a heat wave period). This study design is called ‘symmetric bidirectional’. This method is quite useful for examining short-term exposures when a time gap between an ED visit and a control day is longer than a typical period of exposure to an analyzed environmental factor; in this case, duration of a heat wave.

A heat wave was defined as uninterrupted sequence of three or more days when the maximum daily temperature was above 35 °C. Odds ratio of seeing a doctor for all mental and behavioral disorders (ICD-10 codes F00–F99) during a heat wave and on control days was calculated considering a possible time lag between 0 and 5 days from heat exposure to visiting a doctor. The largest odds ratios (ORs) during the heat waves for daily hospital visits for mental illness were 2.231 (95 % confidence interval (CI): 1.436–3.466) at a 3-day lag, 2.836 (95 % CI: 1.776–4.525) at a 2-day lag, 3.178 (95 % CI: 1.995–5.064) at a 3-day lag, and 2.988 (95 % CI: 2.158–4.140) at a 2-day lag for the first, second, third, and fourth heat waves, respectively.

Further results were obtained for a sample of all four heat waves taken together, and control days – the remaining days between June 01 and August 31. Odds ratios of hospitalization during heat waves (taking into account the abovementioned lags) and during the control period differed significantly depending on the following effect modifiers: age, place of residence, occupation, and marital status. Since these individual characteristics were not always available for the outpatients, modification of effects produced by heat was investigated only for the hospitalized patients.

Odds ratio for hospitalization during heat waves against the control period was three times higher for old people ≥ 65 years than that in the age group ≤ 64 years (*OR* = 3.034, 95 % CI: 1.802–5.139). The risk of heat waves on mental illness in urban areas was more serious than that in the rural or suburban areas (*OR* = 1.523, 95 % CI: 1.120–2.074). Outdoor workers (*OR* = 1.714, 95 % CI: 1.198–2.398) and singles (*OR* = 1.709, 95 % CI: 1.233–2.349) were more likely to suffer from mental illness during the heat wave periods.

As for specific diagnoses, the greatest effects of heat waves on hospitalization were found for schizophrenia, classification disorders, and delusional disorders (ICD-10 codes F20–F29), mood disorders (F30–F39) and especially for neurological, stress-related and physical disorders (F40–F49). The chances of hospitalizations due to the last group of diagnoses were almost five times higher during the heat waves than those in the control period.

The effects produced by heat waves lasting three days and longer on mortality and morbidity (judged as the number of hospital admissions) for various causes were examined in the Greater Metropolitan Sydney Region (5 million people). Among them, all mental disorders and some specific diseases were investigated including schizophrenia, dementia, and substance use disorders [27]. The analyzed data covered warm seasons (spring and summer) over the period between 1997 and 2010. The authors used the ‘case – crossover’ method. ‘Cases’ were represented by both separate days of moderate heat ($T \geq 95^{th}$ percentile of average daily temperature distribution over a warm half of year) or strong heat ($T \geq 99^{th}$ percentile), and ‘three-day severe heat events’. Three-day severe heat events were selected using a temperature averaged over a hospitalization day and two previous days (T_{0-2}) with the same threshold values of the percentiles. These selection criteria on average give 9 waves of moderate heat and 2 waves of strong heat per year. Just as in previously mentioned studies, control days were the same days-of-week within the same months as hot days. The authors reported a rather weak relationship between the number of hospitalizations and hot weather (Table 2).

Obviously, the effects on the old age group are not always stronger. Table 2 provides the results for single hot days with the zero lag between temperature and hospitalization. However, intensity of the effect may grow if we consider lags of several days; in this study, lags of up to three days were considered. The same concerns heat waves. We can take a lag of 1–3,

Table 2

Odds ratio *OR* (95 % CI) of hospitalization for mental disorders on hot and control days in Sydney [27]

Age group	Single hot days, lag 0		Three-day heat events, lag 0–2	
	Moderate heat	Severe heat	Moderate heat	Severe heat
Thresholds	$T_0 \geq 95$ %	$T_0 \geq 99$ %	$T_{0-2} \geq 95$ %	$T_{0-2} \geq 99$ %
Any age	1.01 (0.98–1.04)	1.08 (0.97–1.20)	1.03* (1.00–1.05)	1.05 (0.99–1.10)
Age ≥ 65	1.03 (0.96–1.09)	0.94 (0.81–1.09)	1.09* (1.02–1.16)	1.05 (0.91–1.20)

Note: $*p < 0.05$.

2–4 days etc. instead of 0–2 days; however, such lags were not investigated in this study. For example, when investigating specific diagnoses, the authors found that the maximum effect for hospitalizations for mood disorders was reached at a 1-day lag after the days of moderate heat, $OR = 1.06$ (95 % CI: 1.00–1.12). The greatest absolute effects were established for substance use disorders, $OR = 1.08$ (95 % CI: 0.97–1.20) and for hospitalizations for dementia, $OR = 1.14$ (0.99–1.31).

This Australian study has an obvious drawback since it did not consider the duration of heat waves. In this respect, we should mention a study conducted in Vietnam with its focus on effects produced on hospital admissions for mental disorders by heat waves of different duration [28]. Overall, the authors analyzed 21,443 hospital admissions to the Hanoi Mental Hospital in 2008–2012. In this study, the authors defined extreme heatwaves using consecutive days of a temperature higher than normal skin temperature (above 34 °C). Therefore, they used the threshold of 35 °C for the maximum daily temperature T_{max}, which corresponded to the 90th percentile of its year-round distribution.

Binary indicators $T_{0-2} \geq 35$ °C or $T_{0-6} \geq 35$ °C were used to identify days with accumulated heat stress. The authors interpret such 'cases' as the effects produced by heat waves not shorter than 3 days or not shorter than 7 days. Note that this approach is different from a conventional one, when all days during an interrupted heat wave are considered "cases". Thus, the condition $T_{0-2} \geq 35$ °C means that only the last day is the indicator for a three-day heat wave; or, the three last days are indicators for a five-day heat wave; etc. Thus, the effects of accumulated heat stress are investigated. In this study, over five years, 175 single days were observed with the maximum temperature above 35 °C. Of those events, 61 included at least three consecutive days with such conditions, and ten events of these included at least seven consecutive days with such temperatures. Increases in hospital admissions were estimated exactly for these samples in comparison with the remaining days within the analyzed period.

A negative binomial model adjusted for a day-of-week, seasonality and long-term trend was used for regression of hospital admissions against the binary ambient temperature indicator. Such a model is used for overdispersed dependent variable, when its distribution is considerably different from Poisson's. Table 3 provides data on estimated relative risks of hospital admissions for all mental disorders, specific diagnoses and susceptible population groups.

Obviously, among specific diagnoses, the highest risks were found for organic disorders and specifically for the codes F04–F06 (organic amnesic syndrome, delirium and other mental disorders due to brain damage) as well as for mental retardation. The authors mention such effect modifiers as place of residence (higher risks were established for rural population) and older age. For example, risks of heat waves were found to be twice as high for people aged ≥ 61 years against those established for all age groups.

Meta-analysis of risks established in local studies. Many local studies have been conducted recently. Subsequent meta-analysis of obtained local-specific results is used to study possible causes for their heterogeneity; that is, to investigate possible effect modifiers. Let us consider a systematic review [18], which used meta-analysis of random effects of both high ambient temperatures and heat waves.

Table 3

Relative risks of single days and heat waves, *RR* (95 % CI) for hospital admissions for mental disorders in Hanoi [28]

Analyzed group	Single days	3-day waves	7-day waves
Any mental disorder (F00–F99)	1.04 (0.95–1.13)	1.15* (1.005–1.31)	1.36* (1–1.90)
Rural population (any diagnosis)	N/A	1.26* (1.04–1.52)	1.69* (1.08–2.64)
Age ≥ 61 years (any diagnosis)	N/A	1.31 (0.8–2.15)	3.2* (1.63–6.29)
Organic, including symptomatic, mental disorders (F00–F09)	1.21 (0.95–1.54)	1.37 (0.97–1.95)	**3.62* (1.76–7.42)**
Organic amnesic syndrome, delirium and other mental disorders due to brain damage (F04–F06)	1.31 (0.94–1.82)	**1.52* (1–2.40)**	**4.76* (1.74–13.18)**
Mental retardation (F70–F79)	1.14 (0.83–1.55)	**1.68* (1.08–2.62)**	2.3 (0.8–6.88)

Note: *$p < 0.05$.

A relative increase in the effect size per 1 °C was selected as a quantitative measure in meta-analysis of studies of high ambient temperatures. Therefore, when analyzing the studies reporting a relative risk between the two percentiles of temperature distribution, it was necessary to know the absolute temperature range in °C, for which this relative risk was established, and to calculate the natural logarithm *ln*(*RR*), assuming there was a log-linear relationship between a risk and temperature within the given range [29]. Regarding high temperatures, the meta-analysis of 15 studies investigating *mortality* for all mental disorders established a pooled growth in the effect by 2.2 % for each 1 °C increase in temperature, *RR* of 1.022 (95 % CI: 1.015–1.029); the effect was approximately 1.5 times stronger among people older than 65 years compared to those younger than 65 years. Accordingly, relative risks of mortality for each 1 °C increase were *RR* (≥ 65) = 1.025 (95 % CI: 1.015–1.035) and *RR* (< 65) = 1.017 (95 % CI: 1.005–1.028). As for specific causes, the greatest mortality risk was attributed to substance-related mental disorders (*RR* = 1.046; 95 % CI: 0.991–1.101), followed by organic mental disorders (*RR* = 1.033; 95 % CI: 1.020–1.046).

The meta-analysis of 21 studies with their focus on morbidity (hospital admissions or emergency department visits for any mental disorder) estimated a pooled effect as a 0.9 % increase for each 1 °C increase in temperature, *RR* = 1.009 (95 % CI: 1.007–1.015). The authors reported a very narrow confidence interval for this estimate ($p < 0.001$) unlike to the typical results reported in individual local studies, which were covered by the review. An advantage of meta-analysis is an increase in statistical significance of pooled effect estimates since the more precise is individual risk estimate, the higher relative weight it gains in calculation of the pooled effect estimate. A relative increase in morbidity per 1 °C was twice as high for the elderly people relative to the middle-aged ones: respectively, *RR* (≥ 65) = 1.010 (95 % CI: 1.005–1.015), and *RR* (< 65) = 1.005 (95 % CI: 1.003–1.006). Therefore, elderly people are considered the most susceptible population group in this study. When examining specific mental diagnoses, the authors found the greatest effects on morbidity per each 1 °C increase in temperature for mood disorders, *RR* = 1.011 (95 % CI: 1.003–1.018); organic mental disorders, *RR* = 1.008 (95 % CI: 1.001–1.015); schizophrenia, *RR* = 1.007 (95 % CI: 1.002–1.011); neurotic and anxiety disorders, *RR* = 1.007 (95 % CI: 1.001–1.013).

Large number of local studies that estimated the effects of high ambient temperatures on mental health allowed the authors of the review [18] to analyze such effect modifiers as climate and income per capita. Five climatic zones were included in the study (following the Koppen – Geiger climate classification); among them, the highest risks of high ambient temperatures were established in tropical and subtropical climate; the lowest, in continental climate. Just as expected, countries with higher incomes per capita on average had lower risks than middle-income countries.

The authors of the review [18] also made an effort to adjust the obtained pooled risk estimates allowing for publication bias, when only selected results or the highest risks are reported. Special methods are available for such adjustment including funnel plots or trim-and-fill technique. The adjusted effect estimates turned out to be slightly lower but still significant. Thus, an adjusted effect on mortality for each 1 °C increase in temperature was *RR* = 1.014 (95 % CI: 1.011–1.017); and the effect on morbidity was *RR* = 1.007 (95 % CI: 1.004–1.010).

Meta-analysis of results reported in the studies of heat waves is possible only for those studies where authors use similar definitions of heat waves when selecting a temperature measure (average daily or maximum temperatures), threshold temperature percentiles and wave duration. Therefore, only those studies were included in the meta-analysis, which used average daily temperatures as the exposure metric, a heat threshold temperature was selected at the 95th percentile, and all heat waves longer than 3 days were considered. The analysis of nine such studies with their focus on *morbidity* found a relatively low total risk during heat waves, *RR* = 1.064 (95 % CI: 1.006–1.123). Only five studies were included in the meta-analysis of effects produced by heat waves on mortality; however, the pooled risk turned out to be statistically insignificant and the authors did not report it.

High ambient temperatures and workers' mental state. The WHO pays special attention to workers' mental health at the workplace. As estimated by this organization, 15 % of working age population has mental disorders and this leads to a tremendous loss of 12 billion workdays every year; this corresponds to annual economic loss of 1 trillion USD[3]. Several reports on this topic have been published in Russian by the WHO and its Regional Office for Europe; they cover prevention of mental diseases, guidelines on mental health protection at workplace[4] and other relevant topics. Risks for mental health increase in heating microclimate, both at a workplace and at home. A study of effects produced by heat on mental health in Jinan, China [26] established a considerable rise in odds ratio of hospital admissions for mental disorders for outdoor workers relative to those who worked indoors during a heat wave. Some indirect evidence of it can be found in another study conducted in Peru [30]. On average, each additional outdoor work hour per day (under approximately 28 °C) increased the mean number of mental disorder symptoms by 13 % (95 % CI: 1–25 %). Resting in a shaded place during a break decreased frequency of these symptoms by 27 % (95 % CI: 0–47 %). Therefore, it is extremely important to have optimal work and rest regimes in hot weather in Russia just like in many southern countries.

A survey was conducted in a large cohort of Thai workers (more than 40 thousand people). It revealed a significant relationship between workers who often suffer from heat stress at workplace and those who complain about psychological distress [31]. The respondents gave their own estimates of psychological distress by answering three questions concerning anxiety symptoms: 'in the past 4 weeks, how often did you feel (1) nervous, (2) restless or fidgety, or (3) felt so tired everything was an effort?' Having summed up the answers, the researchers identified those who suffered from psychological distress and those who did not have any complaints. Logistic regression was used to calculate odds ratio of getting psychological distress for workers exposed to heat stress at their workplaces in comparison with unexposed ones. Naturally, more workers complained of poor mental state among those exposed to heat stress. A risk of getting psychological distress due to exposure to heat stress at workplace grew with workers' age. Very interesting results were obtained for such effect modifiers as work in office / physical work, work in urban area / work in rural area (Table 4). The variable 'office / physical

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[3] Mental health at work. *WHO*, 2024. Available at: https://www.who.int/news-room/fact-sheets/detail/mental-health-at-work (November 11, 2024).

[4] WHO Guidelines on mental health at work: Executive summary. Geneva, WHO, 2022, 14 p. Available at: https://iris.who.int/bitstream/handle/10665/363156/9789240057760-eng.pdf (November 11, 2024).

Table 4

Influence of age, job type and area on the statistical relationship between heat stress at workplace and psychological distress [31]

Age group, type and area of work	The number of respondents exposed to heat stress, *N*	Odds ratio of getting psychological distress, *OR* (95 % CI)
Age of 15–29 years	3906	1.80** (1.62–2.01)
Age of 30–44 years	3234	1.86** (1.62–2.14)
Age ≥ 45 years	336	2.35* (1.42–3.88)
Bangkok/office	251	2.62** (1.84–3.74)
Bangkok/physical	58	1.10 (0.36–3.38)
Urban/office	945	2.04** (1.62–2.56)
Urban/physical	150	1.41 (0.75–2.65)
Rural/office	1142	2.35** (1.90–2.90)
Rural/physical	212	2.49** (1.50–4.11)

Note: *$p < 0.05$; **$p < 0.01$.

work' differently affected this risk in urban and rural areas. Thus, a considerably higher risk of getting psychological distress under exposure to heat stress was identified for office workers in urban areas whereas this risk was higher for those involved in physical work in rural areas.

The effects of heat on construction workers were examined in Texas, USA [32], where 100 workers took part in a survey. The responses revealed that excessive heat affected workers mentally (difficulty concentrating, lack of focus, irritability, and frequent mood swings). Significant increases in frequency of these symptoms were established using the non-parametric Kruskal – Wallis test for outdoor workers compared to those who worked indoors.

A similar survey was conducted in Japan [33] among 115 construction and 204 traffic control workers who also had to work outdoors in hot weather. The survey revealed that construction workers subjectively suffered more from heat than traffic control workers. In particular, in hot weather, construction workers more frequently suffered from such mental symptoms as sleep disorders, overall fatigue, tiredness, irritability and impatience.

Sixteen traffic police workers were interviewed in Ahmadabad, India. They had to perform their work duties outdoors in summer and were exposed to high ambient temperatures ranging between 32 and 37 °C [34]. Sixty-nine percent of the respondents complained about loss of work capacity due to heat exposure; 56 % complained about loss of coordination; 38 % reported increased irritability and anxiety. Traffic police officers, just like couriers, communal service workers and other outdoor workers, are examples of professional groups with high occupational health risks in terms of effects produced by heat on mental health.

The WHO Policy Brief on mental disorders under climate change[5] postulates that climate change aggravates many social and environmental risk factors for mental health and psychosocial problems. This may lead to emotional stress, new developing mental impairments and deterioration of medical condition for people who already have such disorders. Therefore, considering climate-related health risks, special attention should be paid to mental health issues and provision of relevant psychosocial support.

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[5] Corvalan C., Gray B., Villalobos C., Sena A., Hanna F., Campbell-Lendrum D. Mental Health and Climate Change: Policy Brief. Geneva, WHO, 2022, 16 p. Available at: https://iris.who.int/bitstream/handle/10665/354104/9789240045125-eng.pdf?sequence=1 (November 12, 2024).

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Research article

OCCUPATIONAL RISKS OF HEMOCONTACT VIRAL INFECTIONS FOR HEALTHCARE WORKERS: A SYSTEMATIC LITERATURE REVIEW

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At present, multiple studies report that healthcare workers (HCWs) are a specific occupational category exposed to various infections due to contacts with bloodborne pathogens in blood and other body fluids. Healthcare provision involves risks of transmission of human immunodeficiency virus (HIV), hepatitis B and C viruses (HBV and HCV) and other bloodborne pathogens for healthcare workers due to injuries with sharp objects through damaged skin or mucous membranes.

Literature data indicate that HCWs can get infected with bloodborne pathogens due to influence of several risk factors (peculiarities of a pathogen, its prevalence in a given population and among patients, intensity and duration of a contact with a pathogen). Risks of infection are associated with a division profile, work records, and some other factors. According to published data, the number of actual needlestick injuries and injuries caused by other sharp objects among HCWs prevails over the number of registered injuries and accounts for 22–82 % depending on a country, rules, and methodology applied for identifying the injury rate. Research works aimed at investigating hemocontact risks have established that underestimation of such data influences effectiveness and timeliness of implemented prevention activities. Risks of getting infected with hemocontact infections can grow substantially in case healthcare workers fail to follow personal protective measures or algorithms of relevant post-contact prevention. Observations of post-contact behaviors adopted by healthcare workers have revealed that 3.3–30 % of them either do not use any post-contact practices or do not always follow the relevant procedure of conducting them.

Optimization of activities aimed at identifying and preventing risks of hemocontact infections among healthcare workers will prevent occupational pathology in this contingent.

Keywords: *healthcare workers, risks of infection, risk factors, hemocontact infections, hepatitis B, hepatitis C, occupational risks, post-contact prevention.*

At present, the global healthcare is facing a very serious challenge associated with risks of hemocontact infections, which can be transmitted in healthcare organizations responsible for healthcare provision. The World Health Organization (WHO) reports the rate of global HAIs to reach 0.14 % and its annual growth to equal 0.06 % [1], which creates risks of occupational infection for healthcare workers (HCWs) [2]. Multiple studies show that HCWs are a specific occupational group prone to getting infected with various communicable diseases due to contacts with pathogens in blood and body fluids [1, 3–6]. The results obtained by s systemic review and meta-analysis indicate that approximately 36.4 % of HCWs (95 % CI: 32.9–40.0) have occupational contacts with patients' blood every year [7]. As a result, they can get infected with more than 60

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known infectious agents (viruses, bacteria, rickettsia, parasites, and yeasts) [8]. Any patient with viremia [7, 9], parasitemia [10], bacteremia [11], or fungemia[1] is known as a potential source of such infections and can infect HCWs due to a needlestick injury (inflicted with a needle or any other sharp object) through mucosa or damaged skin. Healthcare provision involves risks of transmission of human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) [3, 6–7, 9–11], cytomegalovirus, parvovirus B19, simple herpes virus and other microorganisms [8, 11]. Such pathogens as herpes-viruses, including Epstein-Barr virus (EBV) and cytomegalovirus, are established to be able to penetrate the blood periodically or constantly in case of some latent infection forms and under certain conditions [12].

Risks of hemocontact infections are shown to depend on biological peculiarities of a specific microorganism [1, 3–11]. Out of more than 20 blood-borne pathogens, which cause such infections as malaria, syphilis, hemorrhagic fevers, etc., only three viruses (HBV, HCV, and HIV) cause most cases of occupational pathology among HCWs reported in research literature [3, 6, 7, 9–11]. This is due to their prevalence and severity of complications. In addition, literature sources provide data on prospective observation of HCWs, who are exposed to occupational risks, only for HBV, HCV, and HIV. It is rather difficult to assess risks of transmission for other pathogens due to few documented cases [8].

Hepatitis caused by hepatitis B and hepatitis C viruses is established to hold the 6th rank place as a global cause of mortality and morbidity. As estimated, in 2016 approximately 292 million people had chronic HBV-infection and more than 71.1 million had chronic HCV-infection [13–15]. Multiple published studies give evidence that exposure to HBV is the most prevalent and common occupational health risk for healthcare workers [7, 8, 16–19]. HBV is a hepatotropic virus transmitted through blood or other body fluids and able to cause acute or chronic hepatitis B. It is extremely contagious and risks of skin-to-skin contact HBV-infection can vary between 6 and 30 % [17]. Seroconversion speed after an accidental needlestick injury is estimated to equal approximately 10 % among non-immunized healthcare workers and it can reach 30 % in case a patient is a HBV carrier [8]. At present, vaccines remain the main hepatitis B prevention measure for healthcare workers; they were first introduced as far back as in 1981.

HCV is a hepatotropic virus, which is mostly transmitted under parenteral exposure through blood [17]. Russian researchers estimate HCV prevalence to reach 2.5–4.1 % among the country population [20]. At the same time, the existing HCV prevalence among healthcare workers, which does not always exceed the whole population level, is shown to be able to determine likelihood of infection[2]. The risk of transmission upon a contact with HCV-positive blood is known to equal approximately 1.8 %, which is considerably lower than that of HBV [8, 21, 22]. Risk of HCV infection through contacts with other body fluids and tissues is considered to be low. Infection rarely happens upon contacts with mucosa and undamaged skin [23]. At present, it is impossible to prevent HCV infection after a contact; however, early treatment of hepatitis C in the acute phase

[1] Glaser J., Garden A. Inoculation of cryptococcosis without transmission of the acquired immunodeficiency syndrome. *N. Engl. J. Med.*, 1985, vol. 313, no. 4, pp. 266. DOI: 10.1056/NEJM198507253130414

[2] WHO. Aide-mémoire for National Blood Programmes: Blood safety. Geneva, WHO, 2002. Available at: https://www.who.int/publications/i/item/WHO-BCT-02.03 (December 25, 2024).

could significantly reduce the rate of chronicity [24].

HIV is well-known to be less transmissible and less able to survive in the environment as opposed to HBV and HCV. Potentially, the pathogen can be borne in blood and body fluids including sperm and vaginal secretions with visible traces of blood. HIV can be transmitted from person to person upon direct contacts with blood, sperm, rectal secretions, vaginal secretions, or breast milk [25]. The first case of HIV transmission from a patient to a healthcare worker was reported as far back as in 1984 [8]. Mean risk of HIV transmission to healthcare workers is estimated in various studies as equal to approximately 0.3 % (95 % confidence interval CI = 0.2–0.5 %), and approximately to 0.09 % (95 % CI = 0.01–0.5 %) after a percutaneous contact with infected blood [8]. The risk of infection transmission through exposure on undamaged skin was not quantified, but, according to some estimates, it was lower than upon exposure on mucosa. The risk caused by percutaneous exposure was shown to have a positive correlation with contacts with a high volume of blood, high viral burden, a type of a procedure / injury, and damage to deep tissues [8, 26, 27]. The WHO data indicate that these factors can increase the risk of HIV transmission from a contaminated sharp object by 5 % [8, 28]. Timely post-contact prevention (PCP) accomplished within 72 hours after the contact and administration of post-contact preventive drugs are considered effective ways to prevent HIV-infection.

Approximately three million contacts with blood-borne pathogens are established to happen annually across the globe; of them, 170,000 are HIV infection, 2 million are HBV, and 0.9 million are HCV [1, 17]. Needlestick injuries resulted from direct occupational contacts with patients are reported as a significant risk factor causing transmission of hemocontact infections to HCWs [5, 6, 29–34]. Approximately 400 thousand needlestick injuries happen every year in hospitals across the United States [17, 35]. And needlestick injuries are established to not only increase the risk of hemocontact infections among HCWs but also raise administrative costs for hospitals [36, 37]. A study with its focus on needlestick injuries among HCWs was conducted in the USA in 2016; as a result, the mean costs were 747 USD per person including direct economic costs of 425 USD per injury and indirect costs of 322 USD per injury [36, 38].

The results of a retrospective 10-year study accomplished in hospitals in China show that HCWs can get infected with hemocontact infections due to exposure to a wide range of various factors. Most accidents were caused by sharp injury, with 439 (84.6 %) cases, followed by blood or body fluid splash, with 80 (15.4 %) cases ($P < 0.001$) [2].

According to surveys accomplished by foreign researchers, the rate of needlestick injuries caused by HCWs' occupational activities was 25 % in the study by B. Ouyang et al. and 38.3 and 9.7 % respectively as reported in the studies by D. Wang et al. and S. Voide et al. [37–40]. Differences in these rates are thought to be associated with such factors as inclusion of different HCWs' occupational groups in research, levels of HCWs' occupational competence, as well as with some other reasons. Risks caused by unsafe injection practices were also confirmed in a study by A. Prüss-Üstün et al., where the authors showed that the proportion of infections caused by HBV, HCV, and HIV could reach 39 %, 37 % and 4.4 % respectively for healthcare workers prone to occupational percutaneous injuries [41, 42]. The risk of infection after a needlestick injury reached 23–62 % per hepatitis B and 0–7 % per hepatitis C for healthcare workers who were not provided with post-contact prevention [43].

Findings reported in foreign studies indicate that the risk of hemocontact infections is determined not only by peculiarities of a specific pathogen but also a place and intensity of a direct contact with blood [44–47]. It can vary depending on duration of a contact, a virus titer and its prevalence in a population [17]. The risk of occupational exposure to hemocontact infections for HCWs grows with their growing prevalence in patients treated by HCWs [8]. The risk of transmission is established to be influenced by such factors as injury depth (deep needlestick, a big diameter of a needle, a big spot of damaged skin), volume of blood, and a host immunity level[3] [7, 17]. Multiple studies show that likelihood of hemocontact infection for HCWs is influenced by work records [48, 49], work in operation rooms [18], unsafe use and withdrawal of needles, procedures for used sharps disposal [19, 50–52], and some other factors [19, 53].

Demographic and sex-related peculiarities of healthcare workers exposed to risks of occupational contacts with blood are reported in many foreign studies. A study accomplished by A. Garus-Pakowska et al., found that occupational contacts with blood were almost 3.5 times more frequent among female healthcare workers than among their male peers [18]. People aged ≤ 25 years or junior healthcare workers among the mid-level ones were identified as group risks of hemocontact infections [1, 6, 18, 50, 51, 54, 55]. A. Zafar et al. also reported that young doctors were the most susceptible to needlestick injuries [56].

Comparative characteristic of exposure to risk factors per HCWs' occupational groups revealed that healthcare workers with occupations involving frequent invasive procedures and acute care were the most susceptible to them. Some studies confirm that HCWs' activities in surgical departments, emergency care, and intensive care units were more largely associated with occupational exposure to blood-borne pathogens [17, 31]. Needlestick injuries rates were established to be authentically higher in surgical hospitals (including operation rooms) than in therapeutic ones ($P = 0.001$) [31]. General surgeons were found to face the highest level of occupational exposures in Italy as well as in some other countries [39, 57, 58]. Chinese researchers report more frequent occupational contacts with pathogens (more than 10.5 %) in neurosurgery departments [19]. Reduction in use of sharps and active PPE use are proven to be an effective way for avoiding most occupational contacts with blood-borne pathogens [59].

Some studies show that the risk of hemocontact infections is far higher for mid-level healthcare workers, who at present account for the highest proportion of all HCWs [2, 7, 16, 29, 48, 58, 60, 61]. For example, a retrospective 10-year study by H. Feng et al. reported the proportion of such HCWs to reach almost 50 % (47.2 %) and most of them were women (75.1 %) aged predominantly 23–27 years (39.9 %) [2].

Nurses who accomplish invasive procedures, have more frequent multiple contacts with blood and body fluids in comparison with physicians or attendants [2, 62]. As a result, they are exposed to considerably higher risks of hemocontact infections. They constantly have to perform various invasive procedures and interventions (blood sampling, intravenous injections, inserting various catheters, etc.) and often get injured when accomplishing their occupational tasks [18, 19, 51, 54, 55, 63]. An acute injury, which accounted for 84.6 %, was shown to be the main reason for occupational exposures among mid-level HCWs [2]. According to data reported in a review by Italian

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[3] WHO. Aide-mémoire for National Blood Programmes: Blood safety. Geneva, WHO, 2002. Available at: https://www.who.int/publications/i/item/WHO-BCT-02.03 (December 25, 2024).

researchers, the rate of needlestick injuries varied between 2.2 and 10.77 per 100 nurses a year. The major causes could be traced back to a large night shift, working in the operating block and in the medical departments, and the failure to use adequate devices [64].

R. Praisie et al. showed that the most common exposure was needle prick (86.2 %), followed by splash of fluids (7.4 %). The majority of HCWs were from the nursing department (44.4 %), and the most commonly reported place of exposure was the Emergency Department and Intensive Care Unit (ICU) (30.3 %), followed by inpatient wards [65]. In another study, nurses who worked over 8 hours per day were reported to have higher risks of exposure (OR = 1.199, 95 % CI: 1.130–1.272, $P < 0.001$, respectively) [66]. The occupational risk of exposure to pathogens associated with providing 1–2 types of safety-engineered injection devices was 1.275 times of that of providing 5–6 types (OR = 1.275, 95 % CI: 1.179–1.379, $P < 0.001$) [66].

Data from systemic reviews and meta-analyses published by foreign researchers showed that prevalence of needlestick injuries and associated risk factors was the highest in the morning shift (0.44; 95 % CI: 0.36–0.53, $I^2 = 97.2$ %), in emergency units (0.20; 95 % CI: 0.16–0.24, $I^2 = 93.7$ %) and intensive care units (0.20; 95 % CI: 0.16–0.24, $I^2 = 94.3$ %) [67–69]. Risks of occupational exposures were 1.947 times as high for healthcare workers provided with 1–2 PPE types against their peers provided with 9–10 PPE types (OR = 1.947, 95 % CI: 1.740–2.178, $P < 0.001$) [66]. Unsafe needles disposal and absence of safety devises were two major reasons for needlestick injuries among healthcare workers [66, 70–72].

Findings reported in some studies also show that the number of needlestick injuries among HCWs prevails over the number of registered injury cases. The proportion of unreported needlestick injuries varies between 22 and 82 % in this occupational group depending on a country. Rules and procedures applied to establish the injury rates [19, 38, 73–76]. Thus, J. Sun et al. point out that approximately 77.2 % of hospitals in China face the issue of underreported data about risk factors associated with occupational hemocontacts; only 22.8 % of such contacts are reported [75]. Physicians tend to report infection cases much less frequently than nurses and attendants as authentic differences have been established in frequency of such reports ($\chi^2 = 32.66$; df = 4; $p < 0.001$) [43, 47].

In their study, H. Bahat et al. established a high level of underreporting as regards injuries that happened in operation rooms; lack of time and low levels of hemocontact infections in patients were the most common reasons why HCWs did not report about their injuries [77]. Persistent underreporting of needlestick injuries is established to considerably decrease effectiveness of risk management activities and undermines priority and timeliness of preventive activities aimed at eliminating them [78, 79].

Recently, evidence has been reported in some studies that healthcare workers tend to suffer from post-traumatic stress disorder, anxiety and depression after needlestick injuries; this affects their quality of life and mental health[4] [80]. A longitudinal study on psychological stress reactions of healthcare workers after injury, which was conducted by Y. Liu et al. [19], showed that the highest anxiety and depression levels occurred one month after an exposure H. Wang et al. [81] found that healthcare workers' psycho-

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[4] Protecting health and safety of health workers. *WHO*, 2016. Available at: https://www.who.int/activities/protecting-health-and-safety-of-health-workers (May 12, 2023).

logical stress reactions had been growing for six months after a hazardous contact.

Analysis of literature sources with their focus on observing post-contact behaviors in various occupational groups of healthcare workers gives evidence that from 3.3 % [2] to 30 % of exposed HCWs did not take any post-contact actions [82] and / or not always followed recommended algorithms on taking those [48].

In conclusion, it should be noted that given the global concern as regards this healthcare challenge, the Occupational Safety and Health Administration (OSHA) issued the Bloodborne Pathogens and Needlestick Prevention standard as far back as in 1981. In 2000, the document was revised and added with requirements fixed in the Needlestick Safety and Prevention Act (H.R. 5178) regarding implementation of new technologies and use of effective and safe medical devices [17]. However, effectiveness of any recommendations largely depends on whether healthcare workers take relevant actions and make timely reports about injuries [48].

Actions to mitigate occupational risks associated with HCW’s contacts with bloodborne pathogens should concentrate on the following:

– performing stricter control of healthcare workers’ training on prevention of hemocontact infections;

– standardizing performed invasive practices and procedures;

– developing systems for reporting monitoring and control of hemocontact risks and stricter surveillance over post-contact prevention.

It is important to ensure that future prevention strategies include optimization of screening aimed at revealing markers of hemocontact infections in healthcare workers and vaccine prevention against hepatitis B as well as more active promotion of PPE use [19]. In addition, integrated approaches to labor protection and safety measures including engineering and administrative measures and PPE use should be implemented for controlling, eliminating or mitigating occupational risks for HCWs [6, 83, 84]. Therefore, optimization of activities aimed at identifying and preventing risks of hemocontact infections among healthcare workers will prevent occupational pathology in this contingent.

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Research article

WORKING CONDITIONS, HEALTH AND OCCUPATIONAL RISK FACTORS OF TEACHERS EMPLOYED AT HIGHER EDUCATION AND VOCATIONAL EDUCATION INSTITUTIONS (LITERATURE REVIEW)

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Working conditions have a direct effect on health of employable population. This fact is evidenced by both Russian and foreign studies. At present, the educational process is being intensified and digital technologies are being implemented in education quite actively. All this creates high workloads on all educational workers, teachers included. Success and efficiency of teaching are determined by teachers' health, which largely depends on working conditions.

The aim of this study was to generalize and analyze Russian and foreign publications that focus on occupational risks, working conditions and their effects on health, life quality and psychoemotional state of teachers employed at higher education and vocational education institutions.

Publications on the subject were searched in the largest electronic resources eLIBRARY, PubMed and on official websites of peer-reviewed scientific journals with subject items covering the issues selected for analysis. The search depth was 15 years (2009–2024).

As a result, we established that most publications on assessing teachers' working conditions and health covered professors and lecturers of medical higher education institutions. High work intensity was the main adverse occupational factor (hazard category of working conditions 3.1–3.3), which, according to some authors, tended to be higher for higher positions and lecturers with senior academic degrees. Other adverse occupational factors for teachers include physical (electromagnetic fields, workplace illuminance, and microclimate), chemical, and biological ones.

Analysis of the obtained results has revealed that a new approach is required for preserving high levels of work ability, preventing diseases and neural-emotional burnout. Such an approach should be based on providing working conditions that conform to established safe standards and timely psychological support, organizing and conducting qualitative preliminary and periodical medical examinations. It is necessary to accomplish timely assessment of working conditions and health of teachers employed at modern educational establishments.

Keywords: *working conditions, health, occupational risks, incidence, work intensity, occupational and work-related factors, teachers employed at educational establishments.*

At present, multiple studies published by both Russian and foreign experts investigate working conditions and their effects on workers from various occupational groups [1–7].

Studies with their focus on teachers' working conditions and their health are especially interesting in contemporary education. A.S. Abdullina with colleagues [8] point out that teaching is a human – human activity and is an emotionally and intellectually straining profession. As the educational process is intensifying and digital technologies are being

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implemented in education quite actively, all educational workers, teachers included, have to face higher workloads. Volumes and peculiarities of job responsibilities are a significant factor affecting teachers' work ability and performance [9]. Teacher's work is diverse and includes a great variety of activities depending on a position, having an academic degree or rank; this includes educational, methodical, scientific research, organizational activity and others. Foreign researchers note that teachers are exposed to risks of multiple negative health outcomes. High levels of emotional burnout typical for teachers are a likely reason for this. Their findings showed that teacher burnout was consistently associated with somatic complaints (e.g., headaches), illnesses (e.g., gastroenteritis), voice disorders, and biomarkers of hypothalamic-pituitary-adrenal-axis dysregulation (cortisol) and inflammation (cytokines)[1] [10–12].

Nowadays, great attention is paid to not only teachers' personal traits but also their professional competences and their ability to keep up with up-to-date trends in education. And to fulfill their job responsibilities effectively and successfully, teachers should be healthy and health is known to greatly depend on working conditions.

The aim of this study was to generalize and analyze Russian and foreign publications that focus on occupational risks, working conditions and their effects on health, life quality and psychoemotional state of teachers employed at higher education and vocational education institutions.

Materials and methods. Publications on the subject were searched in the largest electronic resources eLIBRARY, PubMed and on official web-sites of peer-reviewed scientific journals with subject items covering the issues selected for analysis. The search depth was 15 years (2009–2024).

Results and discussion. The literature review has revealed that great attention is paid to investigating effects produced by working conditions on health of employable population. Multiple studies have established that the character and specificity of working conditions influence the structure of morbidity [1–3, 13–15].

As regards assessment of working conditions and health of teachers employed at higher and vocational educational establishments, prevailing studies on the subject concentrate on examining working conditions of teachers employed at medical higher educational institutions (medical HEIs). Thus, E.S. Tregubova and A.S. Nekhoroshev [16] analyzed the results obtained by workplace assessment and data obtained by testing aimed at revealing occupational stress and burnout among HEI teachers in their study. After that, they performed a comprehensive sanitary-hygienic and sociological assessment of work-related factors in a medical HEI and established that teachers' working conditions belonged to the hazard category II and psychosocial risks were the main adverse occupational factor. I.A. Mishkich and others [17] conducted a survey among teachers employed at a medical HEI to assess working conditions at their workplaces. To do that, they employed an original questionnaire and analyzed the workplace cards that assessed working conditions at 22 departments for 4 years (2007 to 2011). The survey revealed that teachers were the most concerned about sensory loads, namely high voice burdens and long periods of concentrated observation; the next place per significance in raising anxiety belonged to emotional burdens (high responsibility for decisions they made); intellectual loads caused by the necessity to switch attention and make decisions rapidly held the third place. About half of the respondents mentioned emotional overstrain. Some other mentioned negative factors included drawbacks of the work regime (educational loads being too high), elevated air speed, poor natural illuminance, contacts with bacterial pathogens and specific smells at workplace. The analysis of the workplace

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cards allowed the authors to conclude that teachers' work had the hazard category I-II per work intensity relying on such indicators as intellectual, sensory and emotional loads. Working conditions at four departments were assigned into the hazard category 3.3 per the biological factor; the hazard category 3.2 was determined for working conditions at one department and the hazard category 3.1 at two departments due to levels of adverse chemicals being higher than MPL in workplace air; in addition, the hazard category 3.1 was established for working conditions at 8 departments per 'ionizing electromagnetic fields' and at 10 departments per 'workplace illuminance'. Microclimate and noise levels conformed to safe ranges at all analyzed departments. Using a specifically designed questionnaire, D.A. Tolmachev [18] interviewed 209 teachers working full-time at clinical departments of the Izhevsk Medical Academy (31.6 % males and 68.4 % females). This allowed the author to create a social-hygienic profile of lifestyle and working conditions of teachers employed at this medical HEI. He found teachers' health to be poor; their lifestyle did not promote health protection; their attitude towards health was rather destructive. The questionnaire was drawn up following the recommendations by A.V. Reshetnikov and I.S. Sluchanko. The questions were grouped per specific blocks according to identified health-affecting factors such as social-hygienic, behavioral, socioeconomic and socio-demographic ones. Approximately half of the teachers (41.3 %) reported they had to work for more than 8 hours a day; 79.7 ± 6.9 % felt tired after work; each second teacher had to take some paperwork home. When answering questions about harmful hygienic occupational factors, some respondents mentioned poor workplace illuminance, temperature at workplace not conforming to safe standards, poorly operating supply-and-exhaust ventilation (18.2 ± 3.3 %; 35.3 ± 3.1 %; 39.6 ± 2.8 % respectively). It was also noted that most teachers did not have health-protection behavior patterns: only 8.1 ± 2.5 % of the respondents did morning exercises; only 6.6 ± 1.9 % did sports regularly; 22.9 ± 3.4 % of the respondents had one or two meals a day; 59.9 ± 3.8 % always had 3 meals a day; 17.2 ± 3.3 % of the respondents had four or more meals a day. HEI teachers mentioned absence of free time and poor financial state as the basic reason for failing to pursue a healthy lifestyle (22.9 ± 3.4 % and 33.0 ± 3.1 % respectively). As for behavioral risk factors, the author found that non-smokers prevailed among the respondents (69.0 ± 4.7 %); 62.3 ± 2.0 % of the teachers admitted alcohol use and mentioned several reasons for that including a desire to ease off nervous and mental strain (48.5 %), to get pleasure (38.3 %), influence of family / friends (20.5 %), unwillingness to stop drinking (7.4 %). Fifteen point five ± 3.5 % of the respondents complained about frequent acute diseases; 52.7 ± 2.4 % mentioned having chronic diseases. N. Barkhuizen et al. (2014) reported the relationship between psychoemotional climate, dispositional optimism, requirements and resources at workplace, work engagement, organizational commitment and poor health and burnout among teachers employed at higher educational institutions in South Africa [19].

In 2021, I.A. Mishkich with colleagues performed an occupational-specific assessment of work intensity for surgeons and teachers employed at higher and secondary medical educational institutions [20]; conducted a hygienic assessment of workplace factors; had a survey; analyzed data obtained by periodical medical examinations provided for teachers; conducted some physiological tests (blood pressure measurement, ECG and Holter monitor tests as methods to assess the cardiovascular system state). In addition, they calculated the total risk of fatal cardiovascular events per the SCORE scale and risks of health impairments in teachers caused by unhealthy behaviors. Comprehensive physiological and hygienic studies established neuro-emotional work intensity to be the leading adverse occupational factor for teachers; it was assigned into the hazard category 2.0 for teacher assistants and to the hazard category 3.1 for professors and associate professors. Higher work stress was established for teachers exposed to work intensity corresponding to hazard categories 3.1–3.2 of working conditions (associate professors, professors and surgeons) against assistants exposed to the hazard category 2.0 per work intensity. The authors reported negative changes in the cardiovascular system in surgeons (elevated heart rate, changes in some ECG indicators). They also found chronic diseases in 85.7 % of the examined teachers; cardiovascular diseases prevailed in the structure of morbidity. Teachers aged 40–65 years were exposed to a high and very high absolute risk of fatal cardiovascular events; teachers older than 60 years (25.8 %) all had very high risks of such events; teachers younger than 40 years, predominantly assistants, did not have a high relative cardiovascular risk provided that work intensity was within its optimal levels at their workplaces. Priority behavioral risk factors identified among teachers of medical HEI and colleges included low physical activity, not getting enough sleep, irregular meals and smoking — bearing in mind considerable awareness of health-protecting behaviors in this occupational group (91.1 %). Data obtained by a survey reported in the study by O.G. Khurtsilava and others [21] gave evidence that most teachers at medical HEI and colleges did not consider themselves healthy (73.3 %). Health complaints tended to be common; in the authors' opinion, they were likely caused by teachers' critical attitudes towards their health and professional knowledge and mostly described the emotional burnout syndrome. L.A. Sokolova and A.M. Turysheva [22] assessed working conditions for teachers employed at the I.M. Mechnikov's Medical University; examined their effects on health; substantiated a system of preventive activities aimed at health protection. Hygienic assessment of working conditions was conducted using the results obtained by using Special Assessment of Working Conditions (SAWC) for basic occupational groups at 53 HEI departments; a specific study focused on examining work intensity at teachers' workplaces. Teachers' health (n = 30) was assessed using medical records. Changes in teachers' health state were predicted according to the Guide R 2.2.2006-05[2] and Guide R 2.2.1766-03[3]. The study established the examined teachers to be exposed to chemical, biological, and physical factors (the hazard category 3.1–3.2) as well as work-related factors associated with high work intensity (the hazard category 3.1–3.3), which was higher for teachers with higher positions and academic degrees. The greatest work intensity at teachers' workplaces is typical for management activities, research, delivering lectures to big audiences and practical sessions in groups. According to the Guide R 2.2.2006-05, these activities belong to the hazard category 3.2–3.3. Working conditions of such hazard categories can apparently crate risks of work-related diseases of the central nervous and cardiovascular systems, eyes and musculoskeletal system. A.G. Setko and S.P. Trishina [23] examined working conditions for teachers employed at clinical departments of a medical HEI and involved in both teaching and medical practice. To do that, the authors examined work-related factors at specific workplaces with subsequent assessment in conformity with the Guide R 2.2.2006-05; they also assessed risks of injury and provision with PPE. As a result, they found that working conditions were permissible for most teachers (82.5 %). Adverse working conditions were established for 17.5 % of the examined teachers (72 workplaces); of them, the hazard category 3.1 was established for 28 workplaces, the hazard category 3.2 for 32 workplaces, and

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[2] 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 1, 2005. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200040973 (November 27, 2024) (in Russian).

[3] R 2.2.1766-03. Guidelines on occupational risk assessment for workers' health. Organizational and methodological aspects, principles and criteria; approved by G.G. Onishchenko, the RF Chief Sanitary Inspector, the First Deputy to the Minister of Health, on June 24, 2003, came into force on November 1, 2003. *KonturNormativ*. Available at: https://normativ.kontur.ru/document?moduleId=1&documentId=364401 (November 27, 2024) (in Russian).

the hazard category 3.3 for 12 workplaces. Formaldehyde levels were found to be 1.4 to 3.8 times higher than MPL in workplace air at those departments where wet embalming chemicals were used; the ripple ratio was higher than MPL at 100 % of the assessed workplaces but working conditions were still estimated as permissible due to shortness of this exposure; adverse biological exposures were present at 17 % of workplaces at the phthisiology and pulmonology department (working conditions assigned in the hazard category 3.3); the authors also detected violations as regards purchasing and distributing protective clothing, protective footwear and other PPE. E.B. Anishchenko with colleagues [24] estimated work intensity and occupational risks for 40 medical HEI teachers aged between 29 and 74 years, who held the positions of teacher assistant, teacher, associate professor and professor. To perform hygienic assessment of work intensity per the Guide R 2.2.2006-05, the authors conducted a time-study of three work shifts, assessed occupational risk categories in conformity with the Guide R 2.2.1766-03 and employed a method called Matrix of Outcomes and Probabilities according to the State Standard GOST R 58771-2019[4] to estimate rates of health risk escalation for workers. The findings gave evidence of teachers' working conditions corresponding to the hazard category 3.2 per work intensity; the occupational health risk was medium (considerable); the risk category per severity of identified hazardous health events was medium (T3); likelihood of manifested outcomes of a hazardous health event was high (B4); the risk rate was medium (C12). M.D. Zaltsman and B.B. Kurmashev [25] performed a hygienic assessment of work intensity for teachers employed at the Department for Life Activity Safety and Ecology of the M. Tynyshpaev's Kazakh Academy of Transport and Communications using the Guide R 2.2.755-99[5]. As a result, they found that working conditions corresponded to the hazard category I per this factor due to intellectual and sensory loads. M.V. Boguslavsky with colleagues [26] proposed teachers of the Udmurtia State University to estimate their working conditions by taking part in a survey. The highest scores were given to working conditions associated with personal engagement into the educational process such as moral and psychological climate in a team and adherence to work ethics; the lowest scores were given to a possibility to get some fringe benefits, going to conferences at other establishments and performance of the valid contract. Basic complaints made by teachers as regards work of administrative staff were associated with excessive bureaucracy of the management and educational processes.

Psychoemotional loads make a considerable contribution to work intensity. E.B. Anishchenko with colleagues [24] examined the functional emotional state (health, activity, and mood) and level of occupational (emotional) burnout among teachers of a medical higher educational institution using the SAN method developed by V.A. Doskin and others and the Maslach Burnout Inventory (MBI) adapted by N.E. Vodopyanova. As a result, they established a medium level of burnout against high psychoemotional exhaustion, favorable health and mood self-scores and unfavorable activity levels, which is caused, in the authors' opinion, by growing fatigue. Just as in the previous study, A.A. Agibalova and others [27] employed the Maslach Burnout Inventory modified by N.E. Vodopyanova and E.S. Starchenkova to diagnose occupa-

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[4] GOST R 58771-2019. Risk Management. Risk Assessment Technologies: The National Standard of the Russian Federation, approved and validated by the Order of the Federal Agency on Technical Regulation and Metrology issued on December 17, 2019 No. 1405-st. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200170253 (December 11, 2024) (in Russian).

[5] Guide R 2.2.755-99. Hygienic Criteria for Evaluation and Classification of Labour Conditions by Indexes of Harmfulness and Danger of Industrial Environment and Working Process Difficulty and Intensity; approved and validated by G.G. Onishchenko, the RF Chief Sanitary Inspector, on April 23, 1999. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/1200004531 (December 16, 2024) (in Russian).

tional burnout in teachers of a medical HEI. Prior to taking part in a survey, teachers employed at the Pacific State Medical University were divided into two groups: the first group was made of teachers who did not have any medical practice; the second, teachers who combined these two activates. Levels of 'emotional exhaustion' were found to be higher in female teachers; 'depersonalization' was higher in male teachers who also had some medical practice and in female teachers who worked only at the University; 'occupational efficiency' was low only in male teachers from the second group and medium in the remaining respondents. The highest burnout level was identified in teachers with their work records shorter than 5 years and longer than 25 years. The proportion of teachers with high and extremely high burnout levels was slightly greater among those who combined teaching and medical practice than among their peers who worked only as teachers (68.42 and 62.5 % respectively).

Another research team from the Kazakh National Medical University [28] used the Maslach Burnout Inventory by K. Maslach and S. Jackson adapted by N.E. Vodopyanova and E.S. Starchenkova, Samootsenka (self-esteem) inventory by G.V. Rezapkina and Z.V. Rezapkina and verbal questioning (to check whether the respondents had any somatic diseases) to estimate effects produced by burnout and self-esteem on development of somatic diseases in medical HEI teachers and secondary school teachers. The highest burnout levels were identified in primary school teachers (86.6 %) and 46.6 % of them had either high or too high burnout levels; the lowest burnout levels were identified in medical HEI teachers since only 33.3 % of them had emotional burnout, which was only low or medium. Similar results were obtained by using the self-esteem inventory: 7 out of 15 primary school teachers had high scores of negative self-esteem and 3 people from this group had the lowest score of positive self-esteem; on the contrary, positive self-esteem prevailed among HEI teachers (60 %) and another 40 % had unstable medium self-esteem whereas negative self-esteem was not identified at all. Morbidity rates turned out to be the highest among primary school teachers; the lowest, among HEI teachers. Essential hypertension, coronary heart disease and cholelithiasis were the most common somatic pathologies identified in both HEI and school teachers. In conclusion, the authors reported a direct relationship between high levels of negative self-esteem, high emotional burnout levels and high morbidity rates on the example of primary school teachers; for their early detection, the authors thought it was necessary to implement a screening program. E. Wischlitzki with colleagues (2020) conducted a systemic review with its focus on managing psychosocial risks in teaching [29]. The main conclusion drawn by them is that scientific literature has very few works about how to best manage psychosocial risks in teaching. The authors believe that relevant causes of occupational strain in the teaching profession must be identified and assessed reliably. Low-threshold interventions should be implemented, and the outcome must be evaluated afterward.

N.I. Latyshevskaya with colleagues [30] investigated sex-specific peculiarities of physical health in medical HEI teachers close to the retirement age and beyond it (55–70 years). To do that, they accomplished relevant anthropometric measurements, checked the patients' blood pressure, estimated their physical health and adaptation potential, calculated the ageing coefficient and biological age using formulas developed by A.G. Gorelkin and B.B. Pinkhasov. The authors established authentic differences per most indicators of the morphofunctional state associated with cardiovascular risk: they were higher among men against women. Still, more obesity cases were authentically established among female teachers and this explains identified differences per the ageing coefficient, which turned out to be higher among women. N.K. Smagulov and others [31] examined the work-related effects on body resistance in teachers of a medical HEI in three age groups: younger than 30 years, 30–49 years, and 50 years and older. To achieve the research goals, the authors analyzed morbidity with temporary disability over 2016–2018, estimated the analyzed morbidity per nosologic forms and levels of work ability, and performed a survey using an inventory for assessing preventive and medical activity and for identifying respondents' health self-esteem as well as a questionnaire to estimate actual health. As a result, the authors revealed morbidity with temporary disability to be latent among medical HEI teachers. According to the survey results, most respondents had some health issues. Diseases of the circulatory system, musculoskeletal system and digestive system were prevalent among teachers aged 30–49 years and 50 years and older. Low physical activity, imbalanced nutrition, being negligent of one's health and self-treatment were the main reasons for poor health and high morbidity levels. In 2021, N.K. Smagulov with colleagues investigated what influence physical activity had on health of teachers and physical trainers employed at the Surgut State University using physiological, sociological, and statistical methods [32]. The study results allowed concluding that teachers had much lower physical activity and the functional strain of the cardiovascular system tended to be higher in them. The trophotropic system was established to prevail in the examined physical trainers; the ergotropic system was revealed to be activated in teachers. M.A. Lisnyak and others [33] examined health of teachers employed at the Siberian Law Institute of the Ministry of Internal Affairs of the Russian Federation using analytical, sociological (questioning), and statistical methods and data taken from medical histories. The basic conclusion was that somatic health of the examined teachers required close attention of healthcare workers. The authors emphasized the necessity to consider the fact that morbidity among teachers tended to be latent since a relatively big proportion of people refused to visit a doctor in case of disease due to various reasons. This should be taken into account when conducting periodical medical examinations of teachers employed by HEI of the Ministry of Internal Affairs. The authors also mentioned the necessity to differentiate the system for mandatory periodical preventive medical examinations and regular medical check-ups.

Active implementation of distance learning, which relies on using IT, has changed teachers' work and lifestyle. O.Yu. Milushkina and others [34] performed a hygienic assessment of use of information and communication technologies and lifestyles of 1452 teachers employed at secondary schools, vocational institutions and higher education institutions in distance (online) learning. Use of specifically designed inventories allowed establishing that HEI teachers were more responsible when organizing their work with gadgets. The authors also found that twice as many HEI teachers deemed physical activity to be important for health and were aware of risks associated with its low levels; most HEI teachers paid special attention to their diets and tried to have balanced nutrition. During a period when distance learning was prevalent, teachers had to face several times longer duration of working with digital devices, greater loads on the visual and motor analyzer, greater psychoemotional strain and considerable changes in customary lifestyles. T.V. Ryabova and R.G. Petrova [35] investigated risk factors of mental disorders and ways to eliminate them in HEI teachers during the COVID-19 pandemic. To achieve the study aim, the authors conducted a survey, which relied on a Goggle-from and included authors' sociological questions and those identifying the level of neuro-psychic strain. As a result, they established that risk factors able to cause mental disorders included elevated workloads and, consequently, overstrain as well as strict supervisor control. In distance learning, 86.1 % of the respondents had strain accompanied with various body aches, insomnia and irritability; 65 % of the teachers suffered from moderate neuro-psychic strain; 25.2 % had full-blown strain. Stress and strain had a positive effect on work activity of 20.6 % of the teachers. More than a half of the respondents (70 %) were satisfied with their work ability.

A.M. Magometova with colleagues [36] examined health of teachers employed at medical higher and post-graduate education institutions using medical statistical analysis methods. As a result, they established that prevalence of diseases of the central nervous system, cardiovascular system and musculoskeletal system grew as work records became longer and was also associated with work tasks performed by heads of departments and teachers. The study showed that the heads of the departments and teachers did not adhere to responsible behavior as regards regular medical check-ups and it resulted in deterioration of their health. The authors also mentioned poor preventive activities provided for teachers and consequent high levels of morbidity among them and emotional burnout identified in the head of the departments.

N.V. Polunina with colleagues [37] investigated the burnout syndrome in HEI teachers using the analytical methods, data taken from medical histories and information and statistical documents and the social-hygienic method (to conduct a survey); more than 2500 teachers from technical and humanitarian HEIs in Moscow took part in the study. The study found that one teacher on average had 4 to 5 burnout symptoms and morbidity tended to be higher among female teachers (two thirds of the participants). Health of teachers from humanitarian HEIs was worse against health of teachers employed at technical HEIs. Diseases of the respiratory, digestive, cardiovascular, musculoskeletal and genitourinary systems as well as injury and poisoning prevailed in the structure of morbidity. High work intensity, long time spent in a forced posture, unsatisfactory salary and work were the major reasons for developing mental burnout as established by the authors.

Experts believe comfortable and favorable working conditions to be a basic criterion of good life quality. Life quality of HEI teachers has been examined by both Russian and foreign researchers. Experts pay special attention to examining life quality of teachers employed at medical HEIs[6] [38–40]; some studies focus on examining life quality of teachers employed at military higher education institutions [41] or on physical and mental components of life quality of teachers from classical HEIs [42–44]; some studies develop an author's approach to improving quality of life for teachers [44]. Basic methods employed by researchers for life quality estimation include surveys using such inventories as SF–36, WHO QOL-100, GSRS (Gastrointestinal Symptom Rating Scale) and additional questions to perform more comprehensive assessment of influence exerted by external factors on quality of life (financial position, housing, diet, bad habits, constitution peculiarities etc.).

Basic research results reported by A.K. Uristemova and others [45] indicated that borderline mental disorders tended to be more prevalent among teachers employed at medical HEI against other occupations. The authors deemed their findings to be rather alerting since anxiety-depressive disorders more and more often became the cause for high suicide rate among healthcare workers. M.A. Shapovalova and others [46], researchers from the Astrakhan State Medical University, estimated the psychoemotional state of 48 teachers employed at various departments of the University, who combined teaching and various administrative positions. To do that, the authors employed the State-Trait Anxiety Inventory (STAI) (created by Spielberger and adapted by Khanin) and the Beck Depression Inventory (BDI) adapted by N.V. Tarabrina. The results established high personal anxiety in the respondents; situational anxiety also tended to grow among them. By personal interviewing, the authors established that the teachers were nervous and anxious due to excessive workloads and absence of proper rest; depressive disorders were not identified; the authors pointed out that it was necessary to develop mental support programs for the teachers employed at the University. A.S. Abdullaeva with

[6] Tolmachev D.A. Kompleksnaya otsenka zdorov'ya i kachestva zhizni prepodavatelei meditsinskogo vuza [Complex assessment of health and life quality of teachers employed at a medical HEI]: the abstract of the thesis … for Candidate of Medical Sciences degree. Moscow, 2012, 24 p. (in Russian).

colleagues [8] developed a psychological and pedagogical support program for teachers; it was aimed at preventing stress, creating internal resources and self-regulation in teachers and was implemented in the Astrakhan State Medical University. Twenty teachers from various departments took part in it. The program consisted of three stages: diagnostics, psychological correction, and repeated diagnostics to assess mental health indicators. These efforts helped achieve positive dynamics in individual psychological characteristics of teachers' personality. Mastered techniques for emotional state management had a positive effect on teachers' psychoemotional state and helped improve their mental health.

Conclusion. The literature analysis has shown emotional overstrain and improper work regime (excessive educational loads) to be the major health risk factors for teachers employed at vocational and higher education institutions. The higher is a position and academic degree, the more intense is teachers' work. The greatest work intensity is established in cases when teachers also have some management responsibilities, conduct some research or deliver lectures to big audiences. Chemical and biological contamination inside lecture rooms is a significant risk factor for teachers from medical educational institutions.

Some studies report low adherence to health-promoting behaviors among teachers who tend to have low physical activity, irregular meals and unhealthy diets, smoke and do not have enough sleep. Still, this occupational group is found to be well-informed about how to achieve health promotion.

Health risks are realized through more frequent insomnia and irritability, neuropsychic strain, elevated prevalence of diseases of the central nervous and cardiovascular systems as well as the musculoskeletal system.

Analysis of the obtained results has revealed that a new approach is required for preserving high levels of work ability, preventing diseases and neural-emotional burnout. Such an approach should be based on providing working conditions that conform to established safe standards and timely psychological support, organizing and conducting qualitative preliminary and periodical medical examinations. It is necessary to accomplish timely assessment of working conditions and health of teachers employed at modern educational establishments.

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