Founder: Federal Scientific Center
for Medical and Preventive
Health Risk Management
Technologies Federal Service
for Surveillance on Consumer
Rights Protection and
Human Wellbeing

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Editor and corrector – M.N. Afanaseva
Technical Editor – A.A. Nizhegorodova
Translator – N.V. Dubrovskaya

The publication 30.12.2020.
Format 90×60/8.
Order No. 50/2021.
Edition is 500 copies.
The price is free.

The Journal is registered by The Federal Service For Supervision Of Communications, Information Technology, And Mass Media (Roscomnadzor). Register certificate СМИ – ПИ No. ФС 77-52552 issued on January 21, 2013

Address of the publisher and printing house:
29 Komsomolsky ave., Perm, 614990,
Russia, tel.: +7 (342) 219-80-33

Printed by the Publishing House of Perm National Research Polytechnic University (29 Komsomolsky ave., Perm, 614990, Russia, tel.: +7 (342) 219-80-33)

Subscription number:
catalog "Russian Post"
annual subscription – 04153
semi-annual subscription – 83927

ISSN (Print) 2308-1155
ISSN (Online) 2308-1163
ISSN (Eng-online) 2542-2308

HEALTH RISK ANALYSIS

Theoretical and practical journal. Start of publication: 2013.

4 issues per year

4

October 2020 December

CONTENTS

UDC [616-036.21: 578.834.1] (476)
DOI: 10.21668/health.risk/2020.4.01.eng

Read online

Research article

PREVALENCE OF BEHAVIORAL RISK FACTORS THAT CAUSE CONTAGION WITH COVID-19 AMONG POPULATION IN BELARUS: RESULTS OBTAINED VIA CROSS-SECTIONAL STUDY

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Our research objects were behavioral risk factors that could cause contagion with coronavirus infection (hereinafter called COVID-19).

Our research goal was to assess prevalence of behavioral risk factors that could cause contagion with COVID-19 among population in Belarus.

The present work contains results obtained via online questioning that included 7,590 respondents and employed a specifically designed questionnaire covering most common behavioral risk factors of contagion with COVID-19. The factors were related to adherence to recommendations on physical and social distancing, use of personal protective equipment, and sticking to personal hygiene rules; the questionnaire also asked respondents to give a subjective estimate of their health and whether they had specific symptoms typical for COVID-19. Data analysis involved assessing prevalence of behavioral risk factors, and occurrence of a relation between specific factors and values of prevalence ratio.

We determined prevalence of the most common behavioral risk factors and assessed to what extent risk factors influenced prevalence of subjective complaints by patients that they had symptoms typical for COVID-19. It was shown that certain behavioral risk factors authentically influenced prevalence of subjective symptoms of the disease. Subjective symptoms were more widely spread among respondents who regularly went to work as well as those whose family members regularly went to work or an educational establishment; among respondents who used public transport, went to shopping centers and catering facilities every day; among respondents who didn't keep social distance, didn't pay proper attention to personal hygiene, didn't use antiseptics, and had a habit to touch their face with their hands; among smoking respondents; among respondents who attended mass events, family and corporate parties; and also respondents whose relatives, close friends, or colleagues had returned from abroad.

Our research results can be used for carrying out information campaigns aimed at COVID-19 prevention; they can also give grounds for performing more profound studies on assessing contributions made by various behavioral factors into risks of contagion with COVID-19.

Key words: *behavioral risk factors, questionnaire, coronavirus, COVID-19, pandemic, social distancing, personal hygiene, public health.*

On January 30, 2020 WHO Director-General declared the current COVID-19 outbreak to be an emergency in public healthcare that was of international importance [1]. The declaration was made following conclusions made on a meeting held by the Committee on Emergencies in conformity with the International Sanitary Regulations. A new coronavirus strain had significant pandemic potential and it predetermined its rapid spread all over the world. As per the WHO data on June 23 2020 there were 8,974,795 confirmed COVID-19 cases registered all over the world including 469,159 deaths [2].

Unprecedented actions aimed at preventing the infection spread were taken in every country as a response to this new biological threat of a scale previously unknown to the

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world. Lockdown was introduced due to, among other things, strong emotional and motivation-related barriers that distorted people's adherence to following anti-epidemic recommendations voluntarily and it could result in substantial economic losses, both for each person and a state as a whole. Moreover, while there is no efficient vaccine, a probability still exists that in case lockdown is eased, a new infection outbreak will occur [3]. It indicates that there is a necessity to supplement lockdown measures with efficient actions aimed at raising people's adherence to behavioral models that allow them to protect themselves and their relatives and friends from contagion [4].

COVID-19 pandemic led to a wide-scale campaign held by public health organizations and aimed at spreading knowledge about individual protection from contagion such as hand hygiene, physical distancing, proper respiratory behavior, use of personal protection equipment and antiseptics, etc. However, despite all their attempts to promote knowledge on COVID-19 prevention, studies and questionings performed among population in different countries indicate that people are not well aware about ways of contagion, manageable and unmanageable factors that cause contagion risks and individual protection from infection [5–8].

A significant role in efficiency of anti-epidemic activities implementation and ability to manage this emergency situation belongs to people's hygienic education and their readiness for conscious adherence to individual prevention. Given that, it is necessary to determine how well aware people are about COVID-19 as it will allow assessing whether they are ready to change their behavior and accept behavioral patterns recommended by public healthcare authorities; it will also allow determining priority tasks to be solved within hygienic education.

As per data obtained in several research works quick online questionings that require minimal efforts and can cover a lot of respondents during quite a short period of time can be a valuable instrument for assessing and monitoring knowledge and perception of an infection by people in the heat of an outbreak [5, 9].

Scientific studies aimed at studying pathogenesis, clinical signs, treatment procedures, and developing a vaccine for specific COVID-19 prevention have great significance in struggling against the pandemic; however, a study on behavioral risk factors aimed at more efficient management of epidemic processes is of equal importance for creating a system of anti-epidemic activities.

Our research goal was to assess prevalence of behavioral risk factors that could cause contagion with COVID-19 among people living in Belarus.

Data and methods. The study was conducted via an online questioning that seemed to us the most optimal way to obtain information on behavioral risk factors as it allowed us to collect initial data over a short period of time in a situation when certain limitations were imposed during the heat of the outbreak. The questioning involved using a specifically designed questionnaire that consisted of 23 questions covering basic behavioral risk factors that could cause COVID-19 contagion and were related to adherence to recommendations on physical and social distancing, use of personal protection equipment, and personal hygiene; there were also questions concerning respondents' subjective assessment of their health and occurrence of symptoms specific for COVID-19.

The online questioning was performed on the official website belonging to the Scientific and Practical Centre of Hygiene. Information about questioning was spread via social networks and mass media in order to attract as many respondents as possible.

Apart from data collection, the questioning was aimed at providing sanitary education for people and it was achieved via offering certain recommendations on how to correct behavioral risk factors; the recommendations were given to respondents after the online questioning was completed by them.

From April 17, 2020 to June 23, 2020 7,590 people took part in the questioning.

All the obtained data were statistically processed and analyzed with STATISTICA 13 software package. Data analysis involved calculating absolute and relative frequencies. For extensive parameters, we calculated 95 % confidence interval as per Wald procedure and the data were given as P (95 % CI). Significance of discrepancies between data that characterized qualitative properties was determined with contingency tables 2×2 basing on Pearson's correlation coefficient χ^2. To assess what effects were produced by a certain factor, we calculated prevalence ratio (PR) and its confidence interval (95 % CI).

Critical significance value (p) in statistical hypotheses testing was taken at 0.05.

Results and discussion. Social distancing (staying at home) and physical distancing when visiting a public place are most efficient measures that prevent COVID-19 contagion [10, 11]. Having analyzed answers given by respondents to questions on social and physical distancing, we revealed that 52.9 % (51.9–54.0) respondents continued working at their workplaces according to their normal routine, 26.2 % (25.2–27.2) worked remotely, and 20.9 % (20.0–21.8) didn't work or had to take a vacation. Most respondents (89.1 % (88.4–89.9)) lived in an apartment (living space) with their families or other people. And family members of those respondents who were able to not contact their colleagues working remotely or having a vacation also tended to remain at home more frequently than family members of people who still had to go to work, 59.8 % (58.2–61.4) against 40.4 % (38.9–41.9) (χ^2 = 285.58, p < 0.001). Only 27.9 % (26.9–28.9) respondents took public transport to travel around; the rest preferred a bicycle, their own car, or walking on foot; only 9.3 % (8.7–10.0) gave a negative answer to a question about keeping physical distance from other people in public places, the rest kept a 1 meter distance (48.6 % (47.5–49.7)) or 1.5–2 meters distance (42.1 % (41.0–43.2).

Most respondents (86.7 % (85.9–87.5)) didn't go to any catering facilities over the last two weeks; 5.7 % (5.2–6.2) went to a restaurant or a café once in two weeks; and 7.6 % (7.0–8.2) once a week or more. 24.0 % (23.0–25.0) went to a shop or a chemist's once a week or even less frequently; 53.8 % (52.7–54.9) went shopping every 3–4 days; and 22.2 % (21.3–23.1) did it every day. Only 2.2 % (1.9–2.5) respondents took part in mass events (concerts, sport events, etc.) over the last two weeks, and 25.1 % (24.1–26.1) took part in family parties, parties with friends or colleagues.

Having analyzed discrepancies in keeping social distancing by respondents who went to work and those who worked remotely/were on vacation, we revealed that respondents who didn't go to work were overall more committed to adhering to distancing rules. Thus, respondents who didn't contact their work team went to shops and chemist's more rarely as only 15.2 % (14.0–16.4) people in this category went shopping daily against 28.5 % (27.1–29.9) from those who went to work every day (χ^2 = 376.58, p < 0.001); they more rarely neglected physical distancing when being in a public place: 7.3 % (6.5–8.2) respondents working remotely/being on vacation against 11.1 % (10.1–12.1) among those who went to work every day (χ^2 = 97.09, p < 0.001); they also visited family, office, or friendly parties less frequently: 23.7 % (22.3–25.1) respondents in this category against 26.4 % (25.0–27.8) among those who went to work every day (χ^2 = 7.03, p = 0.008).

Physical distancing is a significant prevention measure but other behavioral factors can also make a substantial contribution into risks occurrence. According to some data, a habit to touch one's T-zone on the face can also be important [3, 4]. In our research the questioning revealed that 68.4 % (67.4–69.5) respondents had this habit.

Several research works indicate that smoking considerably increases a possibility that COVID-19 will have aggravated clinical course; first of all, it is due to negative effects produced by tobacco smoking on the respiratory organs and immune system [12, 13]. Besides, smoking is obviously related to regular contacts between hands and the facial T-zone and it can be an additional behavioral risk factor that can cause contagion. Our research revealed that 28.9 % (27.9–29.9) respondents smoked. Smokers tended to touch their face more frequently than non-smokers, 72.7 %

(70.8–74.6) against 66.7 % (65.4–68.0) accordingly ($\chi^2 = 26.08$, $p < 0.001$).

Sticking to personal hygiene rules to a great extent predetermines individual risks of COVID-19 contagion [13]. Respondents gave the following answers to questions concerning personal hygiene: 70.2 % (69.2–71.2) washed their hands when it was necessary but not rarer than 5–6 times a day; 20.3 % (19.4–21.2) did it approximately every 3 hours; and 9.6 % (8.9–10.3), approximately every 6 hours. 54.0 % (52.9–55.1) used antiseptics to treat their hands when it was necessary but not rarer than 4–5 times a day; 26.6 % (25.6–27.6) did it 2 or 3 times a day; and 19.4 % (18.5–20.3) respondents didn't use antiseptics at all. 39.3 % (25.8–42.9) respondents from those who washed their hands only once in 6 hours didn't use antiseptics to treat their hands; 58.8 % (57.5–60.1) respondents from those who washed their hands not rarer than 5–6 times a day also treated them with antiseptics not less than 4–5 times a day.

Proper respiratory behavior is also considered by the WHO to be effective prevention from COVID-19 contagion [14]. There was a question in the questionnaire, «How do you use handkerchiefs when it is necessary?» and 71.5 % (70.5–72.5) respondents gave an answer «I use a Kleenex and throw it away immediately»; 9.6 % (8.9–10.3) stated that they used the same Kleenex several times; and 18.8 % answered they used a cloth handkerchief.

Available scientific data allow us to assume that COVID-19 virus can spread over a distance exceeding 2 meters, and viruses can persist in a room as suspended particles for a long period of time thus extending a dangerous distance up to 10 meters and even more [15]. Given that, it is quite clear that airing plays a significant role in prevention. Our respondents were asked about airing; 25.3 % (24.3–26.3) aired their apartments or offices at least once a day, 45.4 % (44.3–46.3) did it 2 or 3 times a day, and 29.3 (28.3–30.3) aired their apartments or offices not less than 5–6 times a day.

Use of medical face masks is also a part of prevention activities that allows control over infection spread; they can make for creating a barrier for COVID-19 spread. Face masks can be worn by healthy people as personal protection equipment (to protect them during contacts with a sick person) or they can be a tool for control over an infection source (that is, when they are worn by sick people in order to prevent further infection spread). Still, an issue related to wearing medical face masks as personal protection equipment applied to protect the respiratory organs in everyday life is being discussed at the moment. Recommendations given by the WHO on use of masks to prevent COVID-19 spread state that now there are no convincing scientific data that directly indicate it is absolutely necessary for healthy people to widely use face masks everywhere [15]. On the other hand, there are available research works on spread of the infection by people who carry it without any symptoms or have just fallen sick and don't have any obvious symptoms but are still contagious; these research works imply that a role played by wearing face masks in preventing COVID-19 contagion can be underestimated [16–19]. Our online questioning revealed that a bit more than a half respondents (58.7 % (57.6–59.8)) wore a mask when being in a public place and 54.3 % (52.8–55.8) out of them changed it every 2–3 hours if they used a three-layer mask and every 8 hours if they used a mask equipped with a filter. And here respondents who went to work gave a negative reply to the question about masks more frequently than those who worked remotely or was on vacation, 62.4 % (60.9–63.9) against 55.4 % (55.8–57.0) accordingly ($\chi^2 = 38.01$, $p < 0.001$).

Regular contacts with people who run high risks of contagion also increase a possibility of falling sick with the disease and require additional prevention activities. Thus, having a family member who is a medical worker and constantly contacts infected patients can considerably increase risks of contagion; contacts with people who have returned from regions where the situation with the epidemic is unfavorable in the beginning of the epidemic development also make a substantial contribution into individual risks occurrence [20]. As per data obtained via the questioning, 9.3 %

(8.7–10.0) respondents lived with a person who worked in public healthcare, and 5.1 % (4.6–5.6) respondents had close contacts with a person who came back from abroad or other regions in Belarus over the last two weeks. We analyzed subjective complaints made by the respondents about symptoms typical for COVID-19 (no sense of taste or smell, stuffy nose, running nose, cough, body ache, and fever) over the last two weeks; the analysis revealed that 42.1 % (38.5–45.8) out of 39.3 % (38.2–40.4) respondents who had those symptoms lived in one apartment with medical workers; there was no statistical significant discrepancy from a share of respondents who had those typical symptoms but didn't have medical workers in their family (39.0 % (37.9–40.2)) (χ^2 = 2.55, p = 0.11). But respondents having close contacts with people who had returned from abroad or other regions in Belarus had subjective complaints authentically more frequently than those who didn't have such contacts (58.2 % (53.3–63.1)) against 38.3 % (37.1–36.3)) accordingly) (χ^2 = 61.58, p < 0.001) (PR 2.15 (95 % CI 1.77–2.62).

Having analyzed answers given by respondents who had medical workers in their families, we also revealed that they used a mask to protect their respiratory organs in public places more frequently than those who didn't have medical workers in their families, 65.5 % (62.0–69.0)) against 58.0 % (57.6–58.4)) accordingly (χ^2 = 14.91, p < 0.001).

Commitment to prevention activities among people who live together with respondents also plays a significant role in contagion risks occurrence. Subjective complaints about typical symptoms were 1.28 (1.21–1.35) times more frequent among respondents living with people who tended to neglect personal and respiratory hygiene, didn't keep distancing and didn't use personal protection equipment in public places than among those living with people who adhered to recommendations on prevention. Respondents who were committed to prevention activities but lived with people who neglected them also authentically more frequently stated that they had contagion symptoms. Thus, respondents who wore a face mask in public places but lived with people who didn't adhere to personal hygiene rules and other recommendations on prevention had typical symptoms during the last two weeks authentically more frequently than respondents who lived alone or with people who adhered to recommended prevention activities, 50.5 % (46.9–54.1) against 36.2 % (34.7–37.8) accordingly (χ^2 = 53.61, p < 0.001), PR 1.40 (1.28–1.52).

Data on influence exerted by different behavioral factors on a probability that subjective COVID-19 symptoms occur in a respondent are quite interesting; they are presented in Table 1.

Our research results indicate that a whole lot of behavioral risk factors authentically exert their influence on prevalence of subjective complaints about having typical COVID-19 symptoms. Subjective symptoms of the diseases were 1.2 (1.13–1.27) times more frequent among respondents who went to work regularly; 1.24 (1.18–1.32) times more frequent among respondents whose family members went to work or study regularly; 1.15 (1.08–1.22) times more frequent among respondents who took public transport to travel around the city; 1.26 (1.19–1.34) times more frequent among respondents who went shopping every day; 1.24 (1.15–1.33) times more frequent among respondents who went to catering facilities; 1.40 (1.30–1.51) times more frequent among respondents who didn't keep a proper physical distance when being in a public place; 1.13 (1.07–1.2) times more frequent among respondents who didn't pay enough attention to their hands hygiene; 1.11 (1.04–1.19) times more frequent among respondents who didn't use antiseptics to treat their hands; 1.49 (1.39–1.59) times more frequent among respondents who had a habit to touch their face with the hands; 1.25 (1.18–1.33) times more frequent among smoking respondents; 1.52 (1.39–1.66) times more frequent among respondents having close contact with people who came back from abroad or other regions in Belarus; 1.58 (1.39–1.78) times more frequent among respondents who visited mass events; and 1.22 (1.15–1.30) times more frequent among respondents who visited family or office parties.

Table 1

Influence exerted by behavioral risk factors on a probability of subjective COVID-19 symptoms occurrence

No.	Analyzed factors	A share of respondents who state they have specific COVID-19 symptoms, %	χ^2	PR
1.	Going to work as usual Working remotely/vacation	42.6 (41.1–44.1)* 35.6 (34.0–37.2)	39.46	1.20 (1.13–1.27)
2.	Respondent's family members who live with him/her go to work/study as usual Respondent's family members who live with him/her work remotely/are on vacation	43.5 (41.9–45.1)* 35.0 (33.5–36.5)	57.95	1.24 (1.18–1.32)
3.	Taking public transport to go around Using a car, a bicycle, or walking	43.4 (41.3–45.5)* 37.7 (36.4–39.0)	20.67	1.15 (1.08–1.22)
4.	Going shopping or to a chemist's every day Going shopping or to a chemist's every three days or rarer	46.9 (44.5–49.3)* 37.1 (35.9–38.3)	53.15	1.26 (1.19–1.34)
5.	Going to catering facilities Not going to catering facilities	47.1 (44.0–50.2)* 38.1 (36.9–39.3)	29.81	1.24 (1.15–1.33)
6.	Not keeping a proper physical distance Keeping a proper physical distance	53.2 (49.5–56.9)* 37.9 (36.8–39.1)	62.97	1.40 (1.30–1.51)
7.	Not wearing a mask in public places Wearing a mask in public places	40.4 (38.7–42.1) 38.5 (37.1–39.9)	2.73	–
8.	Washing hands every 3 hours or rarer Washing hands when necessary but not less than 5–6 times a day	42.8 (40.8–44.8)* 37.8 (36.5–39.1)	16.81	1.13 (1.07–1.20)
9.	Not using antiseptics to treat hands Using antiseptics to treat hands	42.7 (40.2–45.2)* 38.5 (37.3–39.7)	9.07	1.11 (1.04–1.19)
10.	A habit to touch one's face with the hands No habit to touch one's face with the hands	43.8 (42.5–45.2)* 29.5 (27.7–31.3)	140.91	1.49 (1.39–1.59)
11.	Smoking No smoking	45.9 (43.8–48.0)* 36.6 (35.3–37.9)	56.74	1.25 (1.18–1.33)
12.	There are medical workers among family members who live together with a respondent There are no medical workers among family members who live together with a respondent	42.1 (38.5–45.8) 39.0 (37.9–40.2)	2.55	–
13.	Close contacts with people who returned from abroad or other regions in Belarus over the last two weeks No close contacts with people who returned from abroad or other regions in Belarus over the last two weeks	58.2 (53.3–63.1)* 38.3 (37.2–39.4)	61.58	1.52 (1.39–1.66)
14.	A visit to a mass event (s) over the last two weeks No visits to a mass event (s) over the last two weeks	61.2 (53.9–68.5)* 38.8 (37.7–39.9)	34.88	1.58 (1.39–1.78)
15.	Visiting a family / an office party etc, over the last two weeks No visits to a family / an office party etc, over the last two weeks	45.5 (43.3–47.7)* 37.2 (35.9–38.5)	41.53	1.22 (1.15–1.30)

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

Conclusions. Results obtained in the present research can be used as a basis for information campaigns carried out by public healthcare organizations and mass media and aimed at clarifying how to prevent COVID-19 and other acute respiratory viral diseases. The results indicate that it is necessary to develop and implement specific sanitary education programs in order to provide people with useful knowledge and to create more responsible attitudes towards anti-epidemic activities. When developing such programs, it is obligatory to apply a complex approach that allows taking into account all behavioral risk factors since our research results revealed that most respondents were influenced by several factors simultaneously. Our research also allowed revealing that a family produced a significant effect on personal behavior and commitment to preventive activities and it also should be taken into account when developing approaches to individual prevention.

Our results can also be applied for monitoring over behavioral risk factors in order to make operative managerial decisions in a situation when an epidemic process is developing dynamically; they can be a basis for more profound examinations focusing on assessing a contribution made by different behavioral factors into risks of COVID-19 contagion.

Funding. Research has been accomplished to use of funds belonging to the Scientific and Practical Center for Hygiene.

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

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Received: 14.07.2020
Accepted: 09.11.2020
Published: 30.09.2020

UDC 616.9–036.8; 51-76; 519.237
DOI: 10.21668/health.risk/2020.4.02.eng

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Research article

DEPENDENCE BETWEEN MORTALITY IN REGIONS AND PREVALENCE OF ACTIVE SARS-CoV-2 CARRIERS AND RESOURCES AVAILABLE TO PUBLIC HEALTHCARE ORGANIZATIONS

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The paper dwells on certain mathematical models showing how epidemics develop, namely, logistic ones, SIR-model, and some others. There is also a review of articles that focus on such models showing dynamics of incidence with COVID-19 infection. These models are often successfully applied for data collected in a whole country but on a regional level there are difficulties due to peculiarities of calculating mortality figures in Russia. In this case regression models can be useful with their obvious advantage at the initial stage in an epidemic process. They also include exogenous variables that influence mortality, for example, a number of doctors and nurses per a hospital, how well hospitals are equipped with ALV devices, and a number of available beds in them.

Our research goal was to build up a linear regression model that could be used as a basis for estimating regional mortality caused by COVID-19 as well as for more efficient distribution of all the resources mentioned above.

The model is built as per a set of resource parameters including data on «active cases». Preliminary three variables that showed data on resources available to communicable diseases departments in hospitals were transformed into a new single one via linear transformation. Then the model was tested on a training sample containing an endogenous variable on mortality and four factor ones including prevalence of active virus carriers. Regions were included into training data with different lags; they were included into such daily samples when death cases were registered rarely. Then the estimated model was applied with other values. It turned out to be quite efficient in estimating COVID-induced mortality for regions from trainings samples as well as for several others (for certain intervals).

As a result, we built a regression model and estimated its precision; the model showed a relation between mortality in a region and prevalence of active SARS-CoV-2 carriers and availability of resources to hospitals in it. It can be useful when these resources are distributed. It can also be used to build SIRD, SEIR, and SEIRF models at a regional level when choosing parameters in them related to mortality. A methodology itself that can be similarly applied for other epidemic processes also deserves certain attention.

Key words: *regression model, mortality estimation, COVID-19, coronavirus infection, logistic equitation, SEIR, SIR, ALV.*

There are a lot of scientific works on issues related to SARS-CoV-2 pandemic; they can be found on *elibrary* web-site and some others. For example, K.V. Zhmerenetskii and E.N. Sazonova concentrate on epidemiologic and other peculiarities typical for COVID-19 in their review; other authors examine and discuss issues related to collecting data on morbidity and mortality as well as validity of statistics [1–7]. O.M. Drapkina and I.V. Samorodskaya declared in their work that it was necessary to build prognostic mathematical models; in particular, the present work focuses exactly on the matter [3]. S. Kozlovskii, apart from morbidity and mortality accounting, considers modeling question in his work as well [5].

Let us turn our attention to issues related to mathematic modeling of an epidemiological process (EP) as importance of building up a sufficiently precise model for COVID-19 has been widely recognized [3, 5, 8]. Such a model can give grounds for more efficient decision-making and it will allow reducing mortality, easing off negative consequences of the epidemic, and saving resources. Different approaches to building models showing EP dynamics are described in a review by M.A. Kondratyev in which he considers artificial neural networks, simulation and statistical modeling, etc. If we simplify a classification of approaches proposed in his work, we can spot out two types of models, deterministic and stochastic ones [9].

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First of all, we are going to give a brief description of models belonging to the first type and how to apply them to simulate COVID-19. When building up a model taking into account peculiarities in EP development, experts divide population living on a certain territory (a country or a region within it) into several sectors such as «susceptible to virus», «infected», etc. First, a block diagram showing EP development over time is built; it describes the possible transitions of persons from one sector to another with different intensities (model parameters). The latter are estimated in a different way; some – according to data taken form literature, others – as per statistic data collected for a given territory. Transfers between sectors in a block diagram are formalized basing on a system of differential equations. Thus, Baroyan-Rvachyov's model that was later implemented in *EpidMod* computer system used a system of non-linear integro-differential equations in partial derivatives with relevant boundary and initial conditions; it was taken as per analogic models existing in hydrodynamics. Models based on equations in partial derivatives of a function of two variables (time and a patient's age) exist at the moment [10]. However, most models that describe EP development over time are based on a system of ordinary differential first-order equations. SIR model was created quite a long time ago and its abbreviation comes from English words «susceptible», «infected», and «recovered» [5, 8, 9, 11]. Later its certain modifications were developed; they were as SEIR, SEIRF, SIRD models, etc.; the last two obviously take into account a decrease in a number of infected people due to mortality: D letter means death caused by an infection and F means death caused by complications. Starting from late 1990-ties, *elibrary* has been accumulating works with such models and now there are more than a hundred of them stored in it; most of them are performed by foreign researchers. SIR and SEIR models are widely used now to analyze dynamics of processes going on in social networks when experts examine how specific information is being spread through them [12]. SIRD model is used in a work by P.V. Khrapov, A.A. Loginova to analyze data on COVID-19 for the RF and some other countries [11]. A similar model, but in its finite-difference form, was applied in a research work by O.V. Drugova, E.A. Pavlov et al. when they examined COVID-19 dynamics in Nizhniy Novgorod region [13]. Here, the number of people divided into four sectors (or compartments) was chosen as the main variables of the model, namely «susceptible» (S); «infected» (I); «recovered» (R); and «deceased» (D); it was assumed that up to 30 % in sectors I and R cannot be detected. After all the parameters were fitted, the model was adjusted to actual data on initial part of COVID-19 growth in the region; and then it was used as a basis for predicting further dynamics in the epidemic.

Baroyan-Rvachyov's model belongs to SEIR type where E letter means another sector, namely «exposed» (people who are going through incubation stage). The sector is determined by a period of time starting from a moment when new coronavirus enters a human body in a dose sufficient for contagion and up to a moment when a person falls sick with COVID-19. M.V. Tamm applies an expanded SEIR model in his work taking certain peculiarities existing on some territory into account; they can be population age groups etc. [14]. After all the parameters are fitted, the model is used to analyze several scenarios of fighting against this new EP in Moscow. A.V. Matveev applied a SEIR-type model in his work that has been modified taking COVID-19 peculiarities into account; the model was implemented with *AnyLogic* simulation modeling tool [15]. As a result, a few scenario calculations were accomplished for two capital cities and recommendations were given on equipping hospitals with beds for contagious patients with coronavirus and artificial lung ventilation (AVL) devices; a forecast on a number of deceased was made.

Another model that applies a stochastic approach to estimating is described in a work by A. Godio and F. Pace et al. [16]. They also use a generalization made for EP by L. Peng and W. Yang et al. [17]. As a result, a SEIR-model was developed that uses a number of specific parameters. They were estimated as per research data obtained by A. Godio and F. Pace et al.; in particular, there was a mortality coefficient $k(t)$ that depended on t counting and efficiency of treating patients. Besides, S. Pengpeng and Shengli et al. [18] suggested another SEIR-model taking into account reduced contagiousness of infected people who didn't have any COVID-19 symptoms as well as using variability in incubation duration. et al. [19] described a SIR-model and two SEIR-model modifications in their work. Unknown parameters in the research were found via fitting the suggested model to data obtained in People's Republic of China from January 23 to February 10. As a result, a short-term forecast was made and it was estimated when a peak in contagion number was expected in China; the work also contains a code for the program in *MATHLAB*.

A.V. Nikitina, I.A. Lyapunova C. et al. [19] described a SIR-model and two SEIR-model modifications in their work. They suggested certain changes for these modifications that took into account peculiarities related to how immunity was acquired as well as a lag occurring in detecting infected people; they also examined sensitivity of the described models. These results can be applied in a model building for COVID-19. Also, almost 50 years ago Russian researchers started to use a SEIRF model and N.F. Gamalei's National Research Center for Epidemiology and Microbiology created relevant software for it at the end of the 20th century. This model is applied by Z. Liu, P. Magal et al., and F. Ndaïrou, I. Area et al. in their works to process data on COVID-19, and in the latter one it is built already with 8 sectors; there is an expression for *D(t),* a number of people who died on a day *t*, that includes three parameters [20, 21]. We should note that the model (1) which we suggest in the present work can be useful for selecting values of a parameter *k(t)* mentioned by A. Godio and F. Pace et al. or selecting parameters in the expression $D(t)$ [16, 21].

Apart from an approach that involves building and finding solutions to a system of differential equations, there are simpler ways to do modeling. They are used in many works focusing on predicting what characteristics an examined EP might have basing on finding a solution to an ordinary differential equation created by P. Verhulst and its generalizations [22–25]. That mathematician applied it a very long time ago to analyze population growth in dynamics as per time *t*. The equation is widely spread in biophysics; at present it is applied in modeling a growth in number $N(t)$ of persons infected with SARS-CoV-2 as per data collected in People's Republic of China and Sweden [22]. This work focuses on three models based on Verhulst equation, gives relevant solutions, and also dwells on predicting problem. After *N(t)* value has been differentiated, we can estimate both a moment when an EP reaches its peak and a number of necessary beds in hospitals according to the research performed by A.A. Kurkin, O.E. Kurkina et al. [22]. One of the described generalized models leads to a differential-difference equation. The model takes into account incubation period that occurs in EP development as well as the fact that approximately 4 % people who fall sick with COVID-19 might die due to it.

Models belonging to this type are less sensitive to quality of available statistical data than sector-type models that have been described above. They are built on daily counts of a time series, in particular, for a series on a number of people who fell sick with COVID-19 or died due to it, and include certain parameters. For example, N. Fabiano and S.N. Radenović fitted Verhulst model to the data on a number of Italian citizens who fell sick with COVID-19 [23]. In another research work the model was modified taking into account specific features of the infection and it allowed obtaining a precise analytical solution when certain assumptions were introduced [24]. Parameters of the solution were estimated as per data collected in China and, as a result, there was good congruence between the model and EP dynamics, both for people who were sick and overall number of deaths in People's Republic of China [24].

Verhulst model is also used in its discrete variant which has two parameters. This logistic equation started to be widely used to examine various processes after it was introduced by M. Feigenbaum, an American scientist. Feigenbaum's discrete model was applied to examine a number of infected people in a dozen countries and two megacities in a research work by E.M. Koltsova, E.S. Kurkina et al., and its parameters were estimated as per an overall number of people who fell sick with the infection in China [25]. There were 4 variants of growth in overall number of infected people in Moscow and the mildest one was called «Israeli». As per this variant, by the end of the EP there will have been totally 300 thousand people living in Moscow infected with SARS-CoV-2 and it is well in line with 248 thousand people detected on August 10 with daily growth equal to 700 cases.

Finally, V.V. Boyarintsev, R.S. Pal'min et al. [8] revealed certain regularities in EP development in their research basing on analysis of overall number of infected people *I(t)* living on a given territory. As a result, basing on a set of hypotheses-assumptions, they suggested a recurrent formula for calculating *I(t)* on a *t*-th day in EP. Basing on it, dependence as per *t* was obtained for a function showing how a share of infected people was distributed, and then forecasts were made for different countries and Moscow as well.

However, a lot of researchers who examine EP basing on SIR-models and their modifications note that obtained solutions are not stable and it prevents them from making reliable forecasts how EP is going to develop over a period longer than a week [5, 8]. A.V. Matveev also states that forecasts have only approximate results [15]. S. Kozlovskiy and O. Boldyrev note that many parameters applied in EP models are to be estimated as per regional statistics in case the models be applied to describe the process in a specific region [5]. And many specialists on statistic data believe regional statistical data to be of low quality [4, 5, 7]. As per experts' estimates, corruption in statistical data has been growing since late April 2020. M.V. Tamm also has no trust in figures on mortality in regions [5, 14]. Moscow is commonly recognized as an etalon region when it comes to transparency and authenticity of data on mortality caused by COVID-19. As for RF regions, more qualitative data are provided by the Rosstat and regional register offices. The latter provide monthly data on their official web-sites stating the overall number of deaths over a month but without reasons that caused them; it should be mentioned that such publications are issued with considerable delays [4, 6, 7]. Besides, certain parameters are unknown at initial stages in EP development, and it is due to this fact that maximum simplest models are applied at these stages as such models contain minimum number of parameters [22]. Such models include regression analysis models and time series models.

If we consider non-deterministic EP models that naturally take into account existing data noisiness, than we should examine a work by D.V. Melik-Guseinov, N.N. Karyakin et al. [26], where several regression models for analyzing mortality caused by COVID-19 in the RF as a whole were built up and estimated. Thus, Model 1 in its variant 2 is given as $ln(Y) = ln(X)\cdot\beta_1 + \beta_0$, where *Y* is a number of new death cases over the last day and *X* is a number of new incidence cases over the same day*;* β_0, β_1 are parameters in the model that are to be estimated. After substituting β_0, β_1 estimates taken from the research by D.V. Melik-Guseinov, N.N. Karyakin et al. as per least square procedure (LSP) the authors obtained a linear regression model with determination coefficient $R^2 = 70$ % [26]. Besides, they suggested Model 2 with $R^2 = 80$ %; it was built basing on Model 1 after introducing one more variable X_2 or «a number of severe COVID-19 cases in *j*-th region».

I.A. Lakman, A.A. Agapitov et al. suggest ARIMA model that is rather hard to build as well as an adaptive Holt – Winters' ARIMA model or Box – Jenkins' «autoregressive moving average» [9, 27]. When they are used together with SIRD model, it allows making highly precise forecasts for short-term morbidity, mortality, and survivability among COVID-patients on a specific territory. However, it is assumed for a SIRD-model that coefficients applied to estimate probabilities of contagion, recovery, or death are stable over a time period *t* and it is not in line with Russian practice. It results in a necessity to re-adjust a model frequently in order to obtain reliable forecasts [27].

Due to all the above mentioned difficulties modeling is less frequently applied for regions in the RF than for countries, Russia as a whole, or Moscow. Besides, some statistical models have some advantages in comparison with sectional or logistic ones. Therefore, sometimes both approaches are combined as it was made in research works outlined above where an Erlang distribution analogue was used together with a SEIR-model [9, 27–29]. Linear multiple regression models seem quite promising among statistical ones [9]. Their advantages include a well-developed theory; for example, one can build confidence intervals, calculate elasticity coefficients, etc. Such a model can be easily built provided that a user is well-qualified to work with *IBM SPSS*, *Statistica*, *EViews,* or *Deductor* software. It is also present in Excel, *MATLAB* computer statistic programs, *Wolfram Mathematica* etc., *Python* or *R* (*R-Studio*) environment. Finally, it is quite easy to take additional factors into account that can influence COVID-19 mortality. For example, we can add a variable that describes clinical process gravity for a patient, or how available medical aid is to him or her; there can be a variable showing whether a patient smokes tobacco or electronic cigarettes and if yes than how frequently; there can be other factors added into the model.

We should also note that at present well-known scientific centers and universities are trying to build relevant models for EP in general and COVID-19 EP in particular. Among them there are Center for Mathematical Modeling of Infectious Diseases (CMMID) at the London School of Hygiene and Tropical Medicine, Center for Hygiene and Epidemiology at the Imperial College (London), Geneva University, Basel University, a lot of universities in the USA and other countries [5, 14]. Thus, US Centers for Disease Control publish their weekly estimates on EP development obtained by 24–26 research teams, mostly Americans, for overall number of patients who died due to COVID-19 [30]. These estimates are given on a date *t* as point and interval predictions for the next 4 weeks. A wide set of models is used in the process; thus, 11 research groups apply various SEIR models (and its stochastic variants SEIS, SEIRD, or SEIRX); 5 groups, SIR-model and its SEIR modification. Agent models, artificial neural networks, time series models, regression models – both linear and non-linear one with the «ridge» estimator of covariance matrix (UM model) are not so frequent [9, 30]. Several groups examine a situation existing in a particular US state. Also there are several foreign researchers who are trying to model COVID-19 dynamics in Russia [5, 31].

Our research goal was to build a linear multiple regression model that could give grounds for estimating COVID-19 mortality in a specific region and give a point prediction for it at an initial stage in EP. It can also be used to provide better substantiation for how to allocate certain resources available to public healthcare organizations in RF regions.

Data and methods. The model was built as per data on prevalence of active SARS-CoV-2 carriers at an initial stage in EP development in a specific region as well as with taking into account how well hospitals in it were provided with resources or necessary equipment. First we created a table containing data on «objects and variables» where objects were multi-dimensional observations (or *p*-dimensional vectors) collected in $n = 40$ RF regions, and initial variables were $p = 7$ parameters. Two out of them change every day, namely COVID-19-related mortality rate among population and a ratio between active virus carriers and average population number in a region over 2019, in other words, their prevalence («factor» or «exogenous variable» X_1)[1] [32]. The rest five indicators were taken from Rosstat[2] data collected over 2018 and 2019, research works by Yu. Apukhtina and S. Zobova, and from an article by A.A. Sokolov [33, 34]. They described how well regional hospitals were equipped with: X_2 (artificial lung ventilation devices in reanimation, 2019) as per 10^5 people; X_3 (doctors with sanitary and anti-epidemics specialties, 2018) per 10^5 people; as well as infectious disease doctors (2019), nurses (2018), excluding obstetrician nurses; and beds for contagious patients with communicable diseases (2019).

To substantiate our selecting these variables, let us note that there were factors influencing lethality during EP listed in several research works [3]. They included a situation in public healthcare in a period prior to EP as well as quality and availability of medical aid. Variables X_2, X_3… reflect it partially. A lot of them are taken into account in decision-making in foreign countries [13]. Thus, specialists in a university in Germany developed *CoronaVIS* system for monitoring over resources available to hospitals in the country, namely, number of

[1] Russian statistical yearbook. 2019. *Rosstat*. M., 2019, 708 p. (in Russian).
[2] Public healthcare in the RF. Supplement to the collection (data as per RF regions). *Rosstat*, 2019. Available at: https://rosstat.gov.ru/folder/210/document/13218 (06.08.2020) (in Russian).

beds and devices for oxygen therapy [35]. After an online inquiry has been made, one can instantly see a map of a given territory with actual data on how many beds are occupied and how significant is load on artificial lung ventilation devices in a specific hospital (its coordinates also available); there are also diagrams showing loads on the nearest hospitals over a day. It allows avoiding «bottlenecks» in delivering a patient to a hospital as we'll as optimizing their distribution over different hospitals. The IHME institute at Washington University developed models for predicting frequency of patients' deaths as well as number of occupied hospitals beds and ALV devices [30, 36]. Experts from a college in New York together with scientists from three universities created a calculator working within Excel; it allows estimating loads occurring due to patients with COVID-19, and one can see availability of beds in hospitals and loads on ALV devices in them in an electronic table. As a result, there is a model showing loads on infectious and reanimation departments in hospitals in a specific region taking into account a number of occupied beds, both ordinary ones and those aimed at intensive care [37].

Preliminarily all the above mentioned variables that described availability of necessary resources to hospitals (infectious disease doctors, nurses, and beds for patients with communicable diseases) were turned into a new one as per method of principal components. And here a slight modification was used; it was previously suggested by S.A. Aivazian [38, 39]. An algorithm used to calculate this variable given here as $(X_4)^*$ included several steps. First, each variable (a parameter) maps into [0, 10] segment where 10 corresponded to the maximum value in the training data table, and 0 to the minimum one. Then estimator of S covariance matrix including three variables was calculated. Then all eigenvalues and eigenvectors of the matrix S were calculated; one of the vectors set the weights required to calculate $(X_4)^*$ variable.

The learning sample containing n=40 RF regions was obtained after excluding 3 Federal cities, Moscow Region, and three regions it had common boundaries with, as well as the next 11 Regions: Astrakhan, Bryansk, Volgograd, Voronezh, Kaliningrad, Kemerovo, Murmansk, Orel, Penza, Pskov, and Rostov; all Autonomous Areas; Republic of Kalmykia, Komi Republic, Republic of Mari El , Chuvash Republic, several North Caucasian regions and some others, as well as Altay, Krasnodar, and Stavropol Territories; and some regions where data on mortality were not published in spring. Statistic data provided in many of them are being criticized [7].

As a result, we built a non-adaptive linear regression model

$$Y = \beta_0 + \beta_1 \cdot X_1 + \beta_2 \cdot X_2 + \beta_3 \cdot X_3 + \beta_4 \cdot (X_4)^* + \varepsilon, \quad (1)$$

where Y is mortality caused by COVID-19;

X_1, …, $(X_4)^*$ are four «factors» outlines above;

ε shows influence exerted by neglected variables on Y;

β_0,…, β_4 are unknown parameters estimated by as per a sampling [9].

Value of ε in the formula (1) is determined as random; by definition its mathematical expectation $E(\varepsilon)$= 0 and variance $var(\varepsilon)=\sigma^2$, and it is unknown. Estimators for β_0,…, β_4 and σ^2 are found as per LSP in Excel as per a training data table. Let us express estimators of β-coefficients via b_0,…, b_4. The table contained value sets $\{Y, X_1, X_2, X_3, (X_4)^*\}$ for all n regions and those sets were included into the table with different counting as per t. It was assumed that a number of new deaths M published over a day t for a specific region was a random value that approximately had binomial distribution; and m, a number of active COVID-19 cases detected among N people living in a region was interpreted as m for independent Bernulli tests over a set made up of N objects and M out of them had a property that was significant to us – «there was with death » [32]. As m grows, M value distribution gets closer to Poisson regularity, however, probability of death due to COVID-19 P_t in a region over a day t is not known precisely. To estimate it, we considered a sequence over 7–10 with growths in a number of deaths per a day t. Then, basing on binomial distribution, we built up a 95 % confidence interval and its middle was taken as P_t estimate. Then we took average value P^* for these estimates as per a given sequence of days. A mixture of Poisson distributions is known to also have Poisson distribution but with different intensity. As a result, when creating the training sampling, we selected a lag in a time series in such a way so that a value of P^* estimate of probability of a COVID-death was within ($3\cdot10^{-5}$, $9\cdot10^{-5}$), that is, it was lower than one death case per 1 million people. For example, Ulyanovsk Region was included into the table with data on May 11, 2020, and its value P^* calculated over a period from May 06 to May 17, 2020, is equal to 0.000049. Follow there are two comments.

Note 1. As 3 factor variables X_2, X_3 and $(X_4)^*$ that describe availability of resources to hospitals do not change (to be exact, we do not have any data on their changes available to us), the expression (1) can be given for each j-th region as a sum of two summands. The first one is a constant $C(j)$ which is by definition equal to $b_0 + b_2 \cdot X_2 + b_3 \cdot X_3 + b_4 \cdot (X_4)^*$ where X_2, X_3, $(X_4)^*$ are variables for j–th region, $j=1,\ldots, n$. $C(j)$ value shows an expected mortality level in case there is low prevalence of active cases in j–th region when $X_1 \approx 0$. Obviously, the better available and developed are resources required by hospitals in a region, the lower $C(j)$ value is going to be. $C(j)$ value does not depend on t since ultimately parameters are estimated for (1) only once. The second summand in (1) contains a factor $X_1(j)$ which depends on t. As a result, the model (1) is given as follows after unknowns $\beta_0,\ldots,\beta_4$ have been estimated:

$$Y(j) = C(j) + b_1 \cdot X_1(j), \qquad (2)$$

where $Y(j)$ is COVID-related mortality per 1 million people;

$X_1 = X_1(j)$ is prevalence of active cases with SARS-CoV-2 calculated per 10^4 people in j-th region.

Index t is omitted are here in order to make the formulation simpler. The formula (2) can be easily used to daily estimate Y. To do that, we should take some data from a spreadsheet located on the official web-site on coronavirus for a day t; these data are overall number of infected (I), deceased (D), recovered (R); then we have to find $X_1 = 10 \cdot [I - (R+D)]/N$ where N is population number taken from Table 2; the next step is to put X_1 into (2) with using LSP-estimator b_1 for β_1 from (1) [32].

Note 2. However, if there was a change in one of variables X_2, X_3 and $(X_4)^*$ in i-th region, and a user has such information, then he (or she) should use the formula (1) instead of (2) with estimates of $b_0,\ldots, b_4$ instead of $\beta_0,\ldots, \beta_4$ (Table 1).

As a result, we detected LSP-estimates $b_0,\ldots,b_4$ for parameters (1) in early June as per the regions sampling given above; they were equal to 4.6721, 0.4494, −0.04774, −0.05668, −0.3308; σ estimate was equal to 0.03474. Significance for each factor and a free member was lower than 0.001 when calculated via «Data analysis package» in Excel menu. Determination coefficient R^2 adjusted for lack of bias turned out to be higher than 95 % and it was partially due to peculiarities related to creation of a training sampling. Regression residuals by formula (2) were distributed approximately-normally. Their normality was tested with d-statistics that has been described by L.N. Bolshev and N.V. Smirnov [40]. It is calculated as an average value of absolute deviation found as per n observations for the residuals which is taken in a ratio to a root from sample variance. This statistics is distributed approximately normally with the parameters $E(d)$, $var(d)$ according to formulas given in the book [40]. Figure values for statistics of d criterion and its parameters when calculated as per the regression residuals in (2) and the sampling $n = 40$ turned out to be the following: $d = 0.7954$, $E(d) = 0.8029$, $(var(d))^{0.5} = 0.0324$; therefore, a hypothesis on normality is not rejected since $d \approx E(d)$, and deviation from $E(d)$ is lower than ¼ of a standard for this statistics.

Results and discussion. First, let's adjust Table 1 to Note 2 outlined above. A decrease in Y value combined with growth in X_2 is given for 3 regions in it. We should note that «Aventa-M» ALV device which is considered to be rather cheap costs nearby 1.8 million rubles.

Instead of actual ALV devices number in regions available on a day t (Table 1), we took their analogue quantity required as per state standards and calculated X_2 for both cases taking data provided by Rosstat[1] into account [33, 34]. Then, having put X_2 into the formula (1) and

Table 1

Changes in *Y* occurring due to better provisions of regions with ALV devices

RF region	ALV devices, number	Ministry standard	Improvement in X_2	Decrease in *Y*	*t*
Voronezh Region	348	860	15 → 37	2.43 → 1.38	24.04
Tver Region	118	527	9.24 → 41.3	4.7 → 3.84	26.04
Rostov Region	643	1521	15.3 → 35	4.5 → 3.57	05.05

Table 2

Calculation of constant *C(j)* and mean absolute percentage error δ

Region	*C(j)* from (2)	*N(j)*,thousand people[1]	Interval as per *t*	Error δ (%), from (3)	Note
Republic of Karelia	1.060	620.3	06.05–05.07	5.0 (2.9)	0... +1
Republic of Crimea	1.163	1912.8	27.05–02.06	6.2 (2.2)	0
Republic of Tatarstan	2.164	3896.4	30.05–08.07	4.5 (3.9)	0
Arkhangelsk Region	0.120	1149.6	02.06–09.06	3.3 (2.3)	0
Vologda Region	2.074	1172.2	15.05–19.05	5.2 (3.2)	+ 1
Kurgan Region	3.191	840.1	15.05–02.07	5.3 (3.0)	+ 1… +3
Lipetsk Region	1.333	1147.1	03.06–14.06	2.3 (1.6)	+ 1
Orenburg Region	0.901	1970.4	04.05–25.05	5.6 (2.7)	0
Ryazan Region	1.541	1117.8	04.06–16.06	3.5 (2.0)	+ 4
Tambov Region	1.970	1024.7	27.05–14.06	3.0 (2.3)	+ 2
Ulyanovsk Region	1.529	1242.5	07.05–01.06	3.5 (2.2)	+ 1
Chelyabinsk Region	2.10	3484.4	18.05–27.05	1.0 (0.6)	+7…0

having preliminarily replaced $\beta_0,\ldots,\beta_4$ with $b_0,\ldots,b_4$ estimators, we estimated a probable decrease in mortality *Y* at a moment *t* due to growth in X_2. As we can see from Column 5 and calculation made as per the model, a significant decrease in *Y* is expected, from 22 % to 75 %.

The model as per the formula (1) with $b_0, \ldots, b_4$, estimators or the formula (2) can provide satisfactory precision in daily estimates of mortality caused by COVID-19 in certain regions, Table 2 contains data for 12 regions and precision achieved for them as per a sequence of days taken from a time interval as per *t*. Several regions such as Republic of Karelia, Tambov Region and Kurgan Region were not included into training sampling. All the calculations in Table 2 are made as per the formula (2) with a focus on a period of time starting from the second half of May and finishing in July. Column 5 in Table 2 contains mean percentage error (MRPE) was taken modulo:

$$\delta = \frac{100}{K}\cdot\sum_{t=1}^{K}\left|\frac{Y_t - Y_t^*}{Y_t^*}\right|, \qquad (3)$$

which is calculated when *Y* estimates obtained as per the formula (2) are compared with its smoothed true value Y_t^* (%). The calculation was made as per *K* days taken from an interval shown in Column 4, Table 2.

Sample standard deviation found out of the said sequence consisting of *K* days is given in Column 5, Table 2. At the *t*-step in this calculation Y_t estimate as per the formula (2) was compared with a smooth value Y_t^* (with its probable preliminary correction according to Column 6, Table 2; but if there was «0», then data [32] were not changed). «Upward» adjustment in COVID-19 mortality parameter is quite justified in certain regions; therefore, if Column «Note» contains a figure different from 0, it means a number of deaths added to initial data [4–7, 32, 41]. The series of graphs shows dynamics of this mortality in regions built up on data provided by the information center at the RF Public Healthcare Ministry; the graphs are given in comparison with similar ones taken from the official web-site on issues related to coronavirus [32, 41]. They are identical for 31 RF regions; 6 regions provide data with a certain lag; 19 regions sometimes understate certain data in comparison with an investigation performed by «Mediazona» Web-site; 29 regions provide data that make the graphs for them to be significantly different in many time counts. Values for δ similar to those given in Table 2 can be obtained for the remaining almost 30 regions for a time period «April – the first half of May» (they were included into the training data with earlier counting as per *t*).

This model allows obtaining precise data in Column 5, Table 2, provided that estimate of a death probability P^* has values similar to those from the training data. For example, in Ulyanovsk Region estimate P^* was equal to 0.00049 for a time series May 06 – May 17 (taking into account data given in Column 6, Table 2); and it was equal to approximately 0.0004 for a time series May 18 – June 02 for which a prediction as per the formula (2) was performed.

Let us dwell on results obtained for certain regions in greater detail. They were obtained as per the formula (2) for different time series *t*; graphs are given in Figures 1–4.

Y-axis in each graph shows mortality in j-th region *Y*. This rates is calculates as a total number of deaths per 1 million people. Figure 1 shows graphs obtained for Republic of Tatarstan. A broken line is a graph built as per the formula (2) for a day *t* form a time series (May 27, July 07); a solid line shows actual mortality[1] [32].

Then, Figure 2 shows graphs for Arkhangelsk Region[1]. A solid line shows smooth actual data; a dotted line is an exponent adjusted to *Y*; a broken line is a graph built as per the formula (2) [32].

The next Figure (3) shows graphs for Lipetsk Region. A broken line with dots is a graph built as per the formula (2). Values for a stepwise graphs were calculated as follows: we took a number of deaths, then, starting from April 17, we added one more death to them that probably remained unaccounted, then the sum was multiplied by 10^3 and divided by $N(j)$ = 1,147.1 (it is given as «+1» in Column 6, Table 2)[1] [32]. A smooth curve given in Figure 3 is MA or «moving average» and it is calculated as per points in the stepwise graph via a moving centered 7-day window.

Figure 4 shows graphs for Republic of Karelia for a time period April 16 – July 29. Dark-colored dots are obtained via putting X_k values into the formula (2). An exponential trend shown as a thin line is adjusted to these dots.

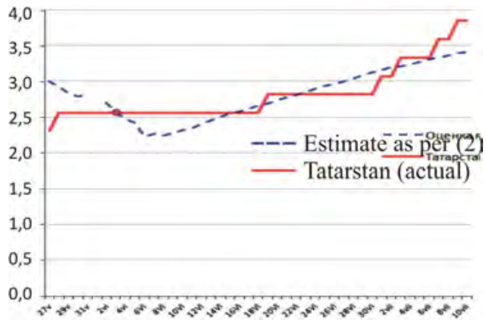

Figure 1. Dynamics in *Y* : Republic of Tatarstan

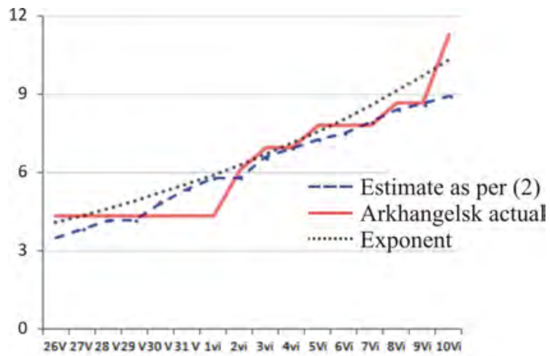

Figure 2. Dynamics in *Y* : Arkhangelsk Region

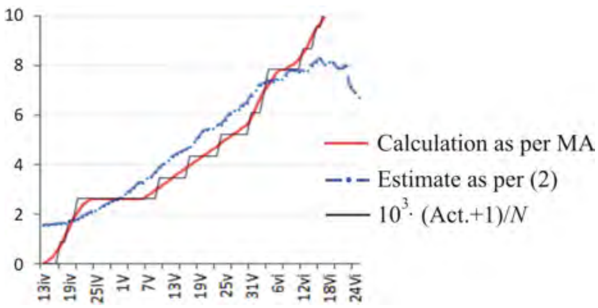

Figure 3. Dynamics in *Y* : Lipetsk Region

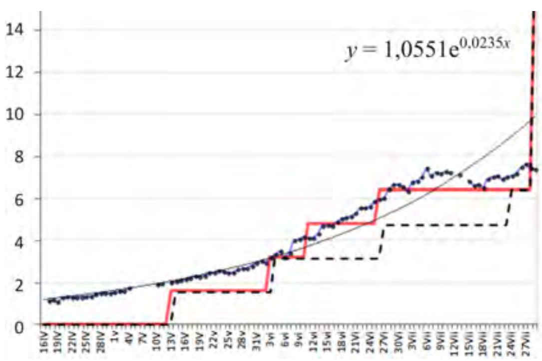

Figure 4. Dynamics in mortality *Y* in Republic of Karelia and its estimate by (2)

The constant in the formula is 1.055 and it corresponds to almost zero prevalence of active COVID-19 cases when $C(j)$ = 1.06 from

Table 2. A stepwise line (broken one) shows official mortality; a similar solid line shows *Y* adjusted as per Column 6 in Table 2. They are a bit shifted in order to avoid merging. Starting from June 11 we added one more death case when calculating an adjusted line which was probably accounted with a certain lag. This additional death case was reported by the regional authorities and it can be seen on «Mediazona» repository [7]. Shifts as per *t* in publications about death cases are also reported in other sources [6, 7, 26, 41]. We can try to logically substantiate this assumption via analyzing mortality in three regions that have a common border with Republic of Karelia, namely Leningrad Region, Vologda Region, and Arkhangelsk Region. And mortality here should be examined with close X_1, values that were detected in Republic of Karelia during the second decade of June (between values 6.8 and 9). As it can be seen from the graphs given in Figure 4, the model built with the formulas (1) and (2) gives quite reliable estimates of mortality in a time period June 06, … July 05 which is a bit adjusted «upward» (if we draw a line which is smoothed as per moving average instead of a stepwise one). The same was done for Kurgan Region. Approximately similar actions are performed by analytics in some organizations when they adjust data on mortality [5, 7], for example, in Moscow office of «Data Insight» company where specialists working at the research department are building up an index showing mortality underestimation [5].

Conclusion. Thus, we have built up a regression model and tested its precision. The model relates mortality in a given region with prevalence of active COVID-19 cases as well as with provision of hospitals with several necessary resources. It can be useful at initial stages in EP development when there are rare and insignificant growths in mortality in a region over 7–10 days and they have got Poisson distribution. Besides, the model can be useful for building up SEIR, SIRD, and some other models at a stage when mortality-related parameters are selected for them. It can also be applied when distributing resources available to public healthcare organizations.

Funding. The research was not granted any sponsor support.

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

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Received: 18.08.2020
Accepted: 23.11.2020
Published: 30.12.2020

UDC 613.6.027
DOI: 10.21668/health.risk/2020.4.03.eng

Read online

Research article

METHODICAL APPROACHES TO ASSESSING CATEGORIES OF OCCUPATIONAL RISK PREDETERMINED BY VARIOUS HEALTH DISORDERS AMONG WORKERS RELATED TO OCCUPATIONAL AND LABOR PROCESS FACTORS

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If we want to assess occupational risks predetermined by various health disorders among workers related to occupational factors and labor process factors, we need to examine whether additional methods can be applied here; these methods should allow not only quantitative determination of occupational risk but also its adequate categorizing. A procedure for risk assessment based on fuzzy sets analysis can be considered and applied for the matter.

Suggested methodical approaches to occupational risk assessment based on this procedure involve step-by-step accomplishment of the following stages: determining fuzzy figures corresponding to preset occupational risk levels; preparing initial data (numeric characteristics of occupational risk) for calculations; probabilistic assessment whether a numeric characteristic of occupational risk belongs to fuzzy numbers; and estimated probability of belonging of occupational risk numeric characteristic. A basic instrument for implementing the procedure is determining a membership function for a trapezoid fuzzy number that estimates whether determined risk assessments belong to a specific risk category.

We suggested a scale for assessing occupational risk levels, starting from negligible ($0–1\cdot10^{-4}$) to extremely high ($3\cdot10^{-1}–1$) and corresponding boundaries of trapezoid fuzzy interval (four figures that define a trapezoid number).

The procedure was tested in a situation when occupational diseases (sensorineural hearing loss), work-related diseases (arterial hypertension), and their combinations were revealed under exposure to noise equal to 85 dBA; the tests allowed establishing that membership functions were equal to 1 for all risk levels determined as per results obtained via epidemiologic research.

Key words: *occupational risk, risk categories, permissible risk, noise factor, labor process, occupational factors, fuzzy sets, trapezoid fuzzy number.*

To preserve and develop labor resources is a priority task in providing national safety and securing development of any state. Up to 2035 economy in Russia is going to develop in a situation when there is depopulation in the country and it predetermines certain peculiarities related to labor potential development and a necessity to use it more efficiently. In such conditions state policy should be aimed at mobilizing all available resources that can help

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preserve population [1]. Reduction in risks for life and health caused by work tasks performance, in other words, occupational risks, is a way to preserve employable population [2–4].

Nowadays, there is a priori (preliminary) occupational risk assessment that involves using risk categories determined as per results obtained via hygienic assessment of working conditions (working conditions categories) and a posteriori (ultimate) one performed as per medical and biological criteria[1, 2]. The most adequate results can be obtained via a posteriori assessment in case it is based on data obtained via epidemiologic research on workers' health. And here one should take into account that probably both occupational diseases and work-related ones might occur and develop.

Russian legislation defines working conditions as a set of occupational factors that influence workers' capacity and health[3]. However, methodical approaches to occupational risk assessment mostly involve analyzing risks caused by impacts exerted by specific risk factors whereas workers are usually exposed to simultaneous intensive effects produced by heterogeneous factors [5, 6]. At the same time, we should take into account that an effect produced by a given occupational factor may result in occupational risks related to several diseases, both occupational and work-related ones [7–10]. Given that, assessment of occupational risk related to different health disorders among workers and caused by a set of occupational factors and factors related to labor process requires certain study on whether it is possible to apply additional procedures that allow not only quantitative determination of occupational risks but also their adequate categorizing. Risk assessment procedure based on fuzzy set analysis can be considered as a relevant one for the matter [11].

Fuzzy logic theory (or fuzzy set theory) is a new probabilistic approach to describing processes which involve uncertainty making it difficult to apply precise quantitative procedures and approaches [12].

Use of elements taken from fuzzy set theory allows assessing conditions of multi-component negative exposure producing multiple negative effects including damage to health [13–16]. And here key parameters are estimated not with point values but with probabilistic interval ones that are characterized with a membership function showing belonging to a range of scaled parameters.

Fuzzy modeling allows including qualitative variables into analysis and operating with fuzzy initial data; modeling complicated dynamic situations quite rapidly and comparing them with preset precision. All this completely satisfies requirements to analyzing influence exerted by adverse occupational factors and working conditions on workers' health and to occupational risk assessment.

Use of fuzzy set procedures has certain advantages since in case of necessity it allows including quantitative variables in to analysis, operating fuzzy initial data and linguistic criteria, modeling complicated dynamic systems quite rapidly and comparing them with preset precision, overcoming drawbacks and limitations that can be found in existing risk assessment procedures. But still, there are certain drawbacks, primarily, a necessity to use specific software as well as a limited number of experts who are able to work with it [17].

Hygienic assessment of occupational factors, factors related to labor process, and exposure to them usually involves using both quantitative properties (for chemical or physical factors) and qualitative ones (for labor hardness and intensity). It also includes determining risk categories for calculated levels of risk

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caused by simultaneous exposure to a set of occupational factors that are able to lead to several health disorders among workers; to do that, new probabilistic procedures for occupational risk categorizing can be quite useful. And fuzzy set procedure seems quite relevant for the matter.

Our research goal was to develop methodical approaches with the use of fuzzy set theory elements to assessing occupational risks related to different health disorders and their combinations among workers caused by negative effects produced by exposure to occupational factors and factors related to labor process.

Data and methods. Suggested methodical approaches included the following stages:

– determining fuzzy figures corresponding to preset occupational risk levels;

– preparing initial data (numeric characteristics of occupational risk) for calculations;

– probabilistic assessment whether a numeric characteristic of occupational risk belongs to fuzzy numbers;

– estimated probability of occupational risk numeric characteristic belonging within a certain range.

Group occupational risk is calculated as per results obtained via epidemiologic research and is based on comparing probability of occupational and work-related diseases caused by exposure to occupational factors. To solve these tasks, it is necessary to create a test group and a reference one. Since exposure to occupational factors and factors related to labor process are determined for specific workplaces, it is assumed that all workers who work at these workplaces are exposed to factors that are thought to exist at them.

Work performed under exposure to occupational factors and ones related to labor process that differ from optimal levels is a basic criterion for including workers into test groups. In order to properly take combined exposure to occupational factors into account, a test group can be divided into sub-groups that are characterized with similar sets of occupational factors.

Work performed under exposure to occupational factors and factors related to labor process that are within permissible levels is a basic criterion for including workers into reference groups. Age and working experience of workers included into test and reference groups should be comparable with no authentic discrepancies between them.

A list of probable occupational diseases (OD) and work-related diseases (WRD) is determined for each factor; these diseases should be relevant to specific occupational factors and factors related to labor process.

After authentic cause-and-effect relations have been established as per epidemiologic criteria (RR ≥ 1.5); a number of diagnosed occupational diseases and work-related diseases is revealed in both groups, and frequency (probability) of each disease is calculated as per the following formula:

$$\mathrm{w}_{\mathrm{OD\ (WRD)}} = \frac{n_{\mathrm{OD\ (WRD)}}}{N}, \qquad (1)$$

where $\mathrm{w}_{\mathrm{OD\ (WRD)}}$ is OD (WRD) frequency;

$n_{\text{ПЗ}}$ is a number of workers in a group who have OD (WRD);

N is an overall number of workers in a group.

Then additional frequency (probability) of occupational diseases and work-related diseases is determined for a test group:

$$w^{\mathrm{add}}_{\mathrm{OD\ (WRD)}} = w^{\mathrm{test}}_{\mathrm{OD\ (WRD)}} - w^{\mathrm{ref}}_{\mathrm{OD\ (WRD)}}, \qquad (2)$$

where $w^{\mathrm{add}}_{\mathrm{OD\ (WRD)}}$ is additional frequency (probability) of occupational diseases and work-related diseases in a test group;

$w^{\mathrm{test}}_{\mathrm{OD\ (WRD)}}$ – is frequency (probability) of occupational diseases and work-related diseases in a test group;

$w^{\mathrm{ref}}_{\mathrm{OD\ (WRD)}}$ is additional frequency (probability) of occupational diseases and work-related diseases in a reference group.

Since workers are exposed to multi-factor combined influence exerted by occupational factors and factors related to labor process, it is quite possible that occupational diseases and work-related ones will develop in them simultaneously. Such a situation may result in aggravated clinical course of any disease. In this case we should calculate frequency of simultaneous OD and WRD development in test and reference groups:

$$w_{\text{OD, WRD}} = \frac{n_{\text{OD, WRD}}}{N}, \qquad (3)$$

where $w_{\text{OD, WRD}}$ is frequency of simultaneous OD and WRD development;

$n_{\text{OD, WRD}}$ is number of workers in a group with simultaneously diagnosed OD and WRD;

N is an overall number of workers in a group.

$$w^{\text{add}}_{\text{OD, WRD}} = w^{\text{test}}_{\text{OD, WRD}} - w^{\text{ref}}_{\text{OD, WRD}}, \qquad (4)$$

where $w^{\text{add}}_{\text{OD, WRD}}$ is additional frequency (probability) of simultaneous occupational diseases and work-related diseases development in a test group;

$w^{\text{test}}_{\text{OD, WRD}}$ is frequency (probability) of simultaneous occupational diseases and work-related diseases development in a test group;

$w^{\text{ref}}_{\text{OD, WRD}}$ is frequency (probability) of simultaneous occupational diseases and work-related diseases development in a reference group.

Occupational risks caused by exposure to examined occupational factors and related to occupational diseases and work-related ones ($R^{\text{occ}}_{\text{OD (WRD)}}$) are calculated as per the following formula taking gravity of these diseases into account ($g_{\text{OD (WRD)}}$)

$$R^{\text{occ}}_{\text{OD (WRD)}} = w^{\text{add}}_{\text{OD (WRD)}} \cdot g_{\text{OD (WRD)}}, \qquad (5)$$

And these occupational risks caused by exposure to examined occupational factors and related to simultaneously occurring occupational diseases and work-related ones ($R^{\text{occ}}_{\text{OD(WRD)}}$) are calculated taking combined gravity of these diseases into account ($g_{\text{OD, WRD}}$)

$$R^{\text{occ}}_{\text{OD, WRD}} = w^{\text{add}}_{\text{OD, WRD}} \cdot g_{\text{OD, WRD}}. \qquad (6)$$

Combine gravity of occupational diseases and work-related ones in case they develop simultaneously ($g_{\text{OD, WRD}}$) is calculated as per the following formula

$$g_{\text{OD, WRD}} = g_{\text{OD}} + g_{\text{WRD}} - g_{\text{OD}} \cdot g_{\text{WRD}}, \qquad (7)$$

where g_{OD} is gravity of occupational diseases;

g_{WRD} is gravity of work-related diseases.

Individual occupational health risk is assessed as per results obtained via mathematical modeling that shows dependence between probability of negative responses and working conditions, age, and working experience (creation of logistic regression models). These models (formula 8) that quantitatively determine dependence for a probability of a negative response (occupational or work-related disease) under exposure to occupational factors and factors related to labor process taking into account intensity of an influencing factor, workers' age and working experience are built for each examined group. Parameters used in a mathematical model are determined with the least square procedure and specific software for statistic data analysis (for example, Statistica 6.0). Parameters authenticity and model validity are assessed basing on one-factor dispersion analysis as per Fischer's test.

$$p_1 = \frac{1}{1 + e^{-(b_0 + b_1 x_1 \cdot x_2 + b_2 x_3)}}, \qquad (8)$$

where p_1 is a probability of a negative response (occupational or work-related disease);

x_1 is a level of exposure to noise factor, dBA;

x_2 is working experience, years;

x_3 is age, years;

b_0, b_1, b_2 are parameters used in a mathematical model.

Obtained levels of occupational risks are considered deterministic values that are assessed (assigned into a specific risk category) according to a suggested scale (Table 1).

But still, it is advisable to consider whether it is possible to apply approaches based on simultaneous use of set theory and mathematical logic when it comes to assessing occupational risks categories given multifactor combined exposure to occupational factors and factors related to labor process that are able to cause both occupational and work-related diseases.

Table 1

A scale for assessing occupational risks levels

Occupational risks levels	Occupational risk category
Less than $1 \cdot 10^{-4}$	Negligible risk
$1 \cdot 10^{-4}$–$1 \cdot 10^{-3}$	Low risk
$1 \cdot 10^{-3}$–$1 \cdot 10^{-2}$	Moderate risk
$1 \cdot 10^{-2}$–$3 \cdot 10^{-2}$	Average risk
$3 \cdot 10^{-2}$–$1 \cdot 10^{-1}$	High risk
$1 \cdot 10^{-1}$– $3 \cdot 10^{-1}$	Very high risk
$3 \cdot 10^{-1}$–1	Extremely high risk

A basic tool used to implement this procedure is determining whether deterministic risk assessments belong to specific trapezoid fuzzy intervals that characterize risk categories. A trapezoid fuzzy interval is considered as a normal fuzzy interval and its membership function may be set with a trapezoid function.

To determine exactly whether deterministic occupational risk values belong within its categories, we suggest using a scale showing trapezoid fuzzy numbers built on the basis of deterministic scale showing assessment of occupational risk levels (Table 2, Figure).

Table 2

A scale showing trapezoid fuzzy numbers for assessing occupational risk levels

Trapezoid fuzzy numbers (four numbers that set a trapezoid number)	Occupational risk category
0, 0, 0.00005, 0.00033	Negligible risk
(0.00005, 0.00033, 0.00078, 0.00325	Low risk
0.00078, 0.00325, 0.0775, 0.015	Moderate risk
0.0775, 0.015, 0.025, 0.0475	Average risk
0.025, 0.0475, 0,0825, 0.15	High risk
0.0825, 0.15, 0.25, 0.53	Very high risk
0.25, 0.53, 1, 1	Extremely high risk

Trapezoid fuzzy numbers allow determining whether a value belongs within a certain risk category, and if it belongs to the smaller base of a trapezoid number then a degree to its belonging to a relevant risk category is equal to 1; in other cases a degree of belonging is determined with a membership function.

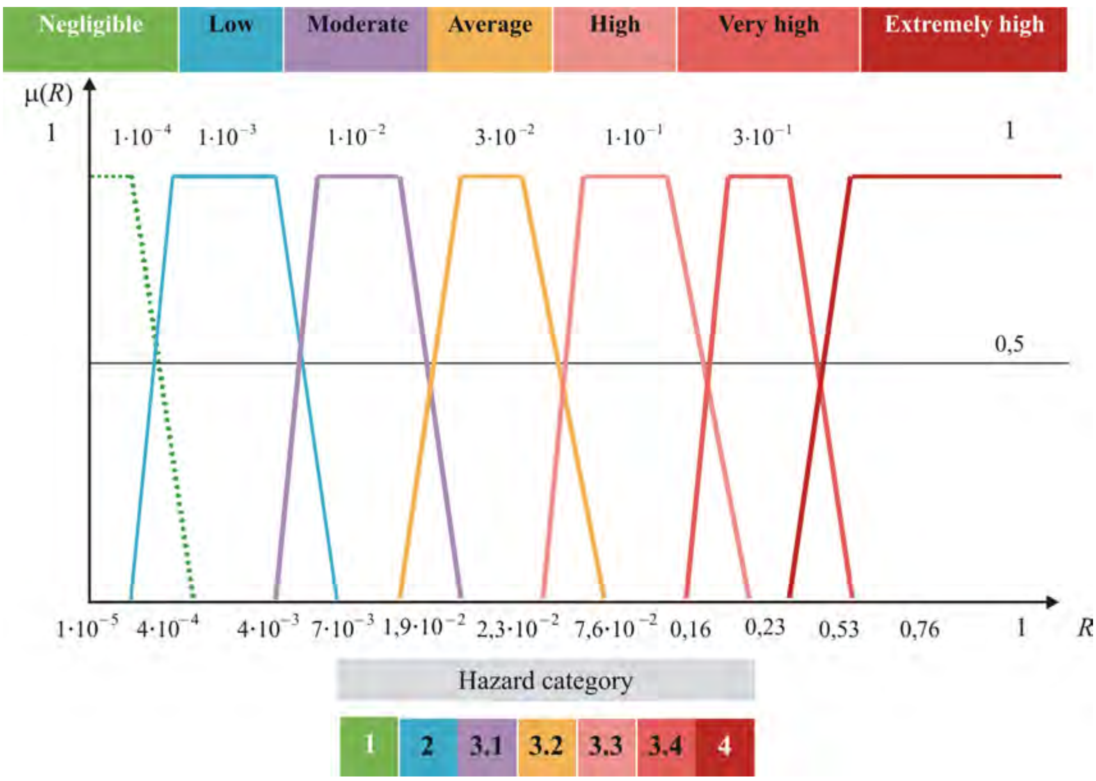

Figure. Graphic image of a scale showing trapezoid fuzzy numbers for assessing occupational risk levels

A basic tool for implementing this procedure is determining a membership function of a trapezoid fuzzy number which allows estimating whether deterministic risk assessments belong to a specific risk category. In general it is given as follows:

$$\mu(x)=\begin{cases}0, & if\, x<a_1\\ \dfrac{x-a_1}{a_2-a_1}, & if\, a_1\le x<a_2\\ 1, & if\, a_2\le x\le a_3\\ \dfrac{x-a_4}{a_3-a_4}, & if\, a_3<x\le a_4\\ 0, & if\, x>a_4\end{cases} \quad (9)$$

It is important to note that a point where two trapezoids cross means that a risk assessment equally belongs to both relevant risk categories.

Taking into account all the estimates obtained for the membership function of a trapezoid fuzzy number, adjusted risk levels (SR_k) are determined as per following formula:

$$SR_k=\sum_i q_i\cdot\mu_{ki}(R^{\mathrm{occ}}_{\mathrm{OD(WRD)}}), k=1,2,3,4,5,6, \quad (10)$$

where q_i is a weighted contribution made by risk category *i* into overall risk level;

k is a degree of risk category significance.

A weighted contribution made by risk category i into overall risk level (q_i) is calculated with Fishburne's formula:

$$q_i=\frac{2(n-i+1)}{(n-1)n}, i=1,2,3,4,5,6, \quad (11)$$

where n is a number of risk categories.

Adjusted risk levels are considered as a basis for substantiating activities aimed at occupational risk management according to its category.

The suggested approaches were tested in assessing occupational risks for workers employed at a non-ferrous metallurgy enterprise. In-plant noise was taken as a priority adverse occupational factor. Apart from it, workers' health can be also potentially influenced by such adverse occupational factors as dusts and labor hardness.

Taking working conditions into account, we created the following workers' groups. The test group was made up of 111 workers (100 % males) exposed to in-plant noise equal to 85 dBA, their average age was 35.63 ± 3.38 and their average working experience was equal to 11.40 ± 6.38 years.

The reference group included 47 workers who were not exposed to in-plane noise (100 %) males but their working conditions were similar to those of the test group. Average age was 37.36 ± 1.52 and average working experience was equal to 12.85 ± 2.30 years.

Basing on available data on prevailing damage to target organs occurring due to contacts with adverse occupational factors we substantiated and implemented a program for workers' medical examinations that included an assessment, clinical examination, and laboratory tests in the following spheres:

– a clinical examination aimed at assessing the circulatory system and hearing organs;

– diagnostics of hearing disorders with noise etiology with whisper acumetry and audiometric hearing examination (pure-tone threshold audiometry performed with «Biomedilen» 2A-02 audiometer);

– an ultrasound examination of vasomotor functions performed by brachial artery endothelium in endothelium-dependent vasodilatation test as per a procedure described and modified by D.S. Celermajer et al. (1992); the procedure was performed with «Toshiba VIAMO» ultrasound expert scanner (Japan) with 7 Hz linear device;

– an ultrasound examination of extracranial sections in brachiocephalic arteries performed as per a conventional procedure with TOSHIBA APLIOXG, model SSA-790A, ultrasound diagnostic system (Japan) with 10–14 Hz linear device;

– laboratory tests performed with unified hematologic, biochemical, and ELISA procedures that allowed estimating functional state of target organs. Laboratory parameters obtained for examined workers from the reference group were taken as assessment criteria for estimating whether laboratory parameters obtained for the test group had any deviations from normal values.

Preliminary diagnosis «sensorineural hearing loss of the 1st and 2nd degree» was put as per results obtained via clinical examination for 13 workers from the test group and 1 worker from the reference one. «Essential [primary] hypertension» was diagnosed in 14 workers from the test group and 3 workers from the reference one. 3 workers from the test group had both sensorineural hearing loss and arterial hypertension.

Sensorineural hearing loss was considered to be an occupational disease in this research work. Epidemiologic assessment of a cause-and-effect relation between arterial hypertension and working conditions revealed that relative risk parameter (RR) amounted to 5.17 (confidence intervals were 1.52–17.52). It allows considering arterial hypertension to be a work-related disease.

Additional probability that sensorineural hearing loss might occur amounted to 0.095 for workers from the test group; the same parameter in this group amounted to 0.062 for arterial hypertension. Occupational risk related to sensorineural hearing loss with its gravity being equal to 0.32 amounted to $3.1\cdot10^{-2}$ (high risk); arterial hypertension with its gravity being equal to 0.25, $1.6\cdot10^{-2}$ (average risk). Occupational risk related to combined sensorineural hearing loss and arterial hypertension with the gravity being equal to 0.49 amounted to $0.004–4\cdot10^{-3}$ (moderate risk).

We determined a membership function of a trapezoid fuzzy number for all levels of occupational risks; it allowed revealing that it was equal to 1 in all cases and adjusted occupational risk levels corresponded to those determined as per results obtained via epidemiologic research.

Funding. The research was not granted any sponsor support.

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

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Received: 10.09.2020
Accepted: 08.12.2020
Published: 30.12.2020

RISK ASSESSMENT IN HYGIENE

UDC 614.71
DOI: 10.21668/health.risk/2020.4.04.eng

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Research article

ON IMPLEMENTATION OF «CLEAN AIR» FEDERAL PROJECT IN OMSK

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The first two years of «Clean air» Federal project in Omsk have been completed and preliminary results have been estimated.

The present work deals with issues related to implementation of the Complex program aimed at reducing emissions, highlights the sanitary-epidemiologic situation related to air contamination in settlements, and describes activities aimed at optimizing a laboratory network used for monitoring over ambient air quality. It is essential to obtain maximum objective data on population health risks caused by ambient air contamination at the initial stage of the Federal project implementation.

Our research goal was to estimate intermediate results in the Federal project implementation taking into account preliminary analysis of sanitary epidemiologic welfare in Omsk related to ambient air contamination.

Our research object was ambient air quality in Omsk, potential health risks and population health parameters associated with ambient air contamination over 2009–2019.

The examination was performed in accordance with a procedure for health risk assessment under exposure to chemicals (R 2.1.10.1920-04), as well as procedures, approaches, and algorithms stipulated in the normative and methodological documents MR 2.1.6.0158-19, MR 2.1.6.0156-19, with use of geoinformation technologies and statistical procedures.

The research allowed substantiating a program for monitoring over ambient air quality taking into account all the existing monitoring systems basing on spatial distribution of total hazard quotient (S) in Omsk residential area and preliminary data obtained via aggregated calculations of ground contaminants concentrations. We suggested a list of control parameters and a procedure for their estimation in order to provide objective and timely monitoring over implementation of the Complex program aimed at reducing emissions into ambient air in Omsk. Implementation of the Complex program was estimated as per results of certain activities accomplished within it in 2019.

***Key words:** «Clean air» Federal project, ambient air contamination, emissions, priority contaminants, monitoring, health risk, population health.*

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«Clean air» Federal project, just like every national project, was started in 2017 when first activities within it were implemented. In accordance with the goals set within the Federal project a primary task in monitoring is to accomplish control over reduction in aggregated volumes of contaminants emissions that should decrease by not less than 20 % by 2024; another task is growth in a share of citizens living in large industrial centers who are satisfied with ambient air quality and this share should reach 90 %.

The Federal Service for Surveillance over Consumer Rights Protection and Human Well-being is an active participant in the Federal project responsible for its implementation; due to its declared mission and activity goals the Service can't limit its contribution only to reduction in emissions; its tasks are wider and include improvement in population health associated with ambient air quality[1]. A reduction in aggregated emissions by a preset value does not necessarily result in favorable ambient air quality in case health risks are not taken into account; consequently, it can't lead to a substantial improvement in population life quality [1, 2].

The project implementation should take place over quite a long period time, namely 5 years; in spite of that population health as an ultimate result of such activities has long-term inertia. Not long ago, on July 21 2020, the RF President issued an Order No. 474 on national goals in the state development; the Order fixed new control «indicators» that should be reached by 2030 and among them there is «a 2-time reduction in emissions of hazardous contaminants that exert the most negative influence on the environment and human health»[2]. New goals should substantially intensify activities aimed at reducing emissions, first of all, when it comes to priority contaminants. And it is advisable to include exactly those technical and organizational activities into Complex programs aimed at emissions reduction within the Federal project that will allow required wide-scale reduction in emissions of priority contaminants in future. In accordance with the Federal Law issued on July 26, 2019 No. 195-FZ on accomplishing an experiment on fixing quotas for emissions, priority contaminants are those substances which, when emitted, not only result in violated hygienic standards but also create health risks[3]. Therefore it is vital to choose relevant activities exactly at early stages in project implementation that will make for a substantial decrease in medical and demographic losses.

Our research goal was to assess preliminary results (2018–2019) achieved in the Federal project implementation taking into account preliminary analysis of sanitary-epidemiologic welfare of the population living in Omsk associated with ambient air contamination.

Data and methods. We assessed ambient air quality in Omsk, potential health risks and health indicators associated in ambient air contamination in residential areas over 2018–2019. To do that, we took data from official statistic data sources provided by federal and regional executive authorities (Rosprirodnadzor, Rospotrebnadzor, the Federal Statistics Service, the RF Public Healthcare Ministry, the RF Ministry of Natural Resources and the Environment).

Population health risks were assessed according to health risk assessment methodology applied in case of exposure to chemicals (Guide R 2.1.10.1920-04)[4]. We applied methodical approaches, procedures, and algorithms suggested by Rospotrebnadzor's scientific research organizations to analyze a sanitary-

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[1] On sanitary-epidemiologic welfare of the population in the Russian Federation in 2019: The State Report. Moscow, The Federal Service for Surveillance over Consumer Rights Protection and Human Well-being Publ., 2020, 299 p. (in Russian).

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[4] Guide R 2.1.10.1920-04 The Guide on assessing health risks under exposure to chemicals that pollute the environment. *KODEKS: an electronic fund for legal and reference documentation*. Available at: http://docs.cntd.ru/document/1200037399 (30.07.2020) (in Russian).

epidemiologic situation that characterized ambient air quality and its influence on population health, substantiation of activities aimed at reducing emissions, and creation of an updated interdepartmental monitoring and laboratory network. The approaches and procedures included those developed as methodical support for «Clean air» Federal project (Methodical Guidelines MR 2.1.6.0156-19 «Assessment of ambient air quality and health risk analysis aimed at making well-grounded managerial decisions in providing proper ambient air quality and sanitary-epidemiologic welfare of the population»; MR 2.1.6.0157-19 «Creation of programs for monitoring over ambient air quality and quantitative assessment of population exposure for fulfilling tasks within social-hygienic monitoring activities»).

We applied geoinformation technologies and statistic procedures in our research.

Results and discussion. By 2017, a year when the first activities were implemented within the Federal project, Omsk occupied the 9th rank place among cities and municipal districts in the Russian Federation where «contaminants emissions into ambient air from stationary sources»[5] were the highest.

Developed petrochemical industry with its growing production outputs, coal-powered heat-generating industries, motor transport, and autonomous heat supply units created aggregated ambient air contamination in the city that was higher than hygienic standards (maximum single concentrations) as per aromatic hydrocarbons (primarily xylene, toluene, and phenol), formaldehyde, benzpyrene, particulate matter, sulfur dioxide, nitrogen oxides, and carbon oxide. Up to 2017, practically every year formaldehyde and hydrogen chloride were registered in concentrations that were up to more than 10 times higher than single maximum MPC.

Ambient air in Omsk contains certain contaminants in concentrations that are higher than reference ones and create long-term chronic inhalation exposure; it is true for formaldehyde (concentration is 2.3 times higher than the reference level); copper (2.5 times higher); and manganese (1.4 times higher). In 2017 concentrations of $PM_{2.5}$ were 1.3 times higher than its maximum permissible average annual and average daily ones; PM_{10}, 1.4 times; formaldehyde, 1.07 times; benzpyrene, 1.9 times.

Over the whole observation period potential and actual population health in the city associated with ambient air quality was characterized with elevated carcinogenic and non-carcinogenic health risks, elevated overall mortality and morbidity, as well as unfavorable dynamics being especially negative in years prior to 2015.

Over the last 10 years individual carcinogenic risk was higher than its permissible level; according to risk levels classification[6] this risk was estimated as «alerting» and in 2017 it amounted to $2.45 \cdot 10^{-4}$.

Priority risk-creating carcinogens include formaldehyde, benzene, carbon black, benzpyrene, and some metals such as chromium, nickel, cadmium, and lead.

Population health risks in Omsk caused by non-carcinogenic effects produced by contaminants were also higher than their permissible levels over a long-term observation period; by 2017 non-carcinogenic hazard index for the respiratory organs amounted to 9.8 (high risk).

Risks related to non-carcinogenic negative effects produced on the respiratory organs to the greatest extent depend on aggregated volumes of contaminants emissions into ambient air. Their value is influenced by average daily (average annual) concentrations of most contaminants including formaldehyde (average long-term hazard quotient is equal to 2.7), par-

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[5] On the ecological situation and environmental protection in the Russian Federation in 2018: The State Report. Moscow, the RF Ministry of National Resources and the Environment; NPP «Kadastr» Publ., 2019, 844 p. (in Russian).

[6] Risk levels here and so on estimated in accordance with a classification suggested in the Methodical Guidelines MR 2.1.6.0156-19. «Assessment of ambient air quality and health risk analysis aimed at making well-grounded managerial decisions in providing proper ambient air quality and sanitary-epidemiologic welfare of the population»: methodical guidelines. Moscow, 2019 (in Russian).

ticulate matter, soot, hydrogen chloride, metals (copper, manganese, chromium, cadmium, nickel, and lead), nitrogen oxide, nitrogen dioxide, carbon oxide, ammonia, and some others.

Data taken from multiple scientific research works confirm that the said contaminants exert their influence on development of respiratory diseases that have different gravity [3–8].

Average annual hazard indexes that show possibility of non-carcinogenic systemic effects produced on a body as well as on the immune system were long within «alerting risk level» range and went down to «acceptable risks» only by 2017.

It was established that health risks were unacceptable in all 12 cities where the Federal project activities were implemented; predominantly, those risks were related to negative effects produced on the respiratory organs, blood system, development, immune system, cardiovascular system, central nervous system (CNS), and reproductive system[7].

Calculated health risks correlate well with data on actual population health. As per data provided by scientific research on territories where petrochemical industry is well developed overall morbidity among children tends to be 1.7 times higher than on average in the country; and as for its structure, respiratory pathologies among children tend to be 1.4 times higher; gastrointestinal tract diseases, 1.2 times higher; skin and subcutaneous tissue diseases, 1.7 times higher [9].

Having comparatively analyzed average long-term health indicators in Omsk region, the Russian Federation, and the Siberian Federal District (SFD), we determined priority ones that were authentically higher in Omsk region than on average in the country and, which is especially important, higher than average health indicators in the SFD as in this case there are the most similar climatic and socioeconomic conditions.

Thus, in 2017 priority health indicators included mortality caused by all reasons (1,292.0 deaths per 100 thousand people) including deaths caused by respiratory diseases (57.7 deaths per 100 thousand people), malignant neoplasms (490.6 deaths per 100 thousand people), infant mortality (6.9 deaths per 1,000 infants who were born alive), and perinatal mortality (8.01 per 1,000 infants born both dead and alive), as well as mortality among employable population.

According to the WHO documents there is conclusive evidence proving a correlation between ambient air contamination and infant mortality. Besides, when infant children are exposed to ambient air contamination, it is highly likely to result in unfavorable outcomes as they grow and in their adult life as well [3].

In 2009–2015 overall primary morbidity among population in Omsk was higher than on average in the country and in the Siberian Federal District and tended to grow; the first decrease in morbidity was detected after 2015. In 2017 priority diseases included diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (5.8 cases per 100 thousand people); diseases of the circulatory system (43.3); diseases of the digestive system (90.7); diseases of the skin and subcutaneous tissue (42.5): endocrine, nutritional, and metabolic diseases (26.7): and congenital malformations (2.6). Regional morbidity was the most apparently higher than on average in the country for endocrine diseases (90.7 %); diseases of the circulatory system (34.9 %); congenital malformations (30.0 %), and diseases of the digestive system (166.8 %).

In our opinion, these figures are not accidental at all as the gastrointestinal tract, skin, and respiratory organs are natural barriers that should prevent chemicals from entering the internal environment of a human body. Living in a zone where anthropogenic loads on the environment are high is proven to result in 78 % growth in risks of gastroenterological pathology [9].

We should note that respiratory diseases were not listed among priority ones during the

[7] On sanitary-epidemiologic welfare of the population in the Russian Federation in 2019: The State Report. Moscow, The Federal Service for Surveillance over Consumer Rights Protection and Human Well-being, 2020, 299 p. (in Russian).

whole observation period (as opposed to mortality caused by them) but morbidity with respiratory diseases among adults grew steadily up to 2017 including morbidity with chronic bronchitis. There was also a gradual increase in morbidity with asthma in all age groups, and in 2017 morbidity with asthma and status asthmaticus among adults and teenagers turned out to be the highest for the overall observation period (142.3 and 130.7 cases per 100 thousand people accordingly).

Priority diseases among infants during their 1st year of life included diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism (139.2 per 1,000 infants) including anemia (130.4) and certain diseases occurring in a perinatal period (331.3).

We comparatively analyzed average long-term morbidity among population in Omsk and rural areas in Omsk region; the analysis revealed that morbidity among urban population was considerably higher than among rural one. Thus, for example, average long-term primary morbidity among children aged 0–14 who lived in urban areas was 1.8 times higher than among their counterparts living in rural areas; as for specific diseases, morbidity with malignant neoplasms was 4.3 times higher; respiratory diseases, 1.9 times; digestive organs diseases, 2.8 times; skin and subcutaneous disuse diseases, 2.2 times.

Average long-term morbidity among infants in urban areas was also significantly higher than among infants in rural ones; overall morbidity was by 1.6 times higher; digestive organs diseases, 2.3 times; respiratory diseases, 1.9 times; specific diseases occurring in perinatal period, 1.8 times; congenital malformations, 3.5 times.

According to data obtained from research works there are certain health indicators that are associated with ambient air contamination; they are mortality caused by and morbidity with respiratory diseases, diseases of the digestive organs, circulatory system, malignant neoplasms, diseases of the blood and blood-forming organs, endocrine diseases, and neoplasms [2, 6, 9–12].

We calculated additional death cases and disease cases during 2017 caused by elevated average annual and average daily concentrations of particulate matter ($PM_{2.5}$; PM_{10}) registered at some monitoring posts[8]. Many Russian and foreign researchers state that particulate matter ($PM_{2.5}$, PM_{10}) are an important indicator showing ambient air contamination and its influence on human health [4, 5, 8, 13–17].

A growth in average annual $PM_{2.5}$ concentration equal to 0.0083 mg/m^3 resulted in additional death cases among population in Omsk; there were 9 death cases caused by cardiovascular diseases added to the background level (453.9 deaths per 100 thousand people); 40 deaths caused by all reasons for people older than 30 added to the background number (957.3 per 100 thousand people).

A growth in average annual PM_{10} concentration equal to 0.0155 mg/m^3 resulted in 7 additional deaths caused by cardiovascular diseases among people living in Omsk; 47 additional chronic bronchitis cases among adults against the background level (248.0 disease cases per 100 thousand people).

According to tasks fixed within the Federal project in Omsk a Complex program was created; the Program included activities aimed at reducing contaminant emissions into ambient air for a period up to 2024.

The Program contains environmental protection activities performed by enterprises that exert the most adverse influence on population health in Omsk and create intolerable risks. These are petrochemical enterprises and heat-and-power engineering enterprises. Hazards were identified for all industrial objects that contaminated ambient air and aggregated standardized hazard quotients were determined for each enterprise. All the enterprises were ranked as per this quotient and it allowed us to spot out

[8] Calculations were accomplished according to the Methodical Guidelines MR 2.1.6.0156-19. Assessment of ambient air quality and health risk analysis aimed at making well-grounded managerial decisions in providing proper ambient air quality and sanitary-epidemiologic welfare of the population: methodical guidelines. Moscow, 2019 (in Russian).

35 priority ones; 7 out of them took leading places as per their effects on population health leaving all the rest far behind (they were structural units belonging to HGC-11 heat generating company, Thermal power stations no. 4 and 5, Gazpromneft-Omskiy NPZ oil processing plant, Omskiy kauchuk JSC, Omsktechuglerod LLC, etc.).

According to the Complex program aggregated contaminants emissions should go down by 22.8 % in 2024 against 2017 and it amounts to 56.212 thousand tons. And this reduction is envisaged mostly for stationary sources (33.7 thousand tons) and the remaining 22.56 thousand tons are from motor transport. Therefore, emissions from stationary sources are to fall from 163.7 thousand tons in 2017 to 130.0 thousand tons in 2024; emissions from mobile sources should decrease from 87.1 thousand tons to 64.5 thousand tons mostly due to new gas-filling compressor stations built in the city and use of gas as a fuel instead of petrol in vehicles.

We analyzed data on emissions from industrial enterprises (368 objects) as per 341 substances over 2017–2018 and classified then according to related hazards. As a result we obtained an updated list of priority contaminants including those that were not examined at monitoring posts.

As this updated list of priority contaminants was being created we primarily took into account indexes showing comparative carcinogenic and non-carcinogenic hazards, residential areas density, complaints from people about ambient air contamination and their territorial distribution; any violations of hygienic standards, dynamics of average annual concentrations, and contributions made into carcinogenic and non-carcinogenic risks. Besides, we paid serious attention to recommendations given by scientific experts on lists of priority contaminants for megacities [3, 18].

The list of priority contaminants obtained due to our research included the following chemicals: sulfur dioxide, nitrogen dioxide, hydrogen sulphide, carbon oxide, benzene, hydrocarbon black (soot), dimethylbenzene (xylene), hydroxybenzene (phenol), ammonia, methylbenzene (toluene), ethylbenzene, 3,4-benzpyrene, formaldehyde, chromium-VI, nickel oxide (recalculated as per nickel), and particulate matter PM_{10}, $PM_{2.5}$. We suggest systematic hygienic assessments and health risk assessments regarding these priority contaminants.

Examinations performed in Chita allowed obtaining a similar list of priority contaminants. But in Omsk maximum comparative carcinogenic and non-carcinogenic hazard indexes are by far lower than in Chita. Considerable volumes of contaminants emissions in both cities are due to heat-and-power generating enterprises and private households using coal as an energy source and climatic peculiarities of the regions [19].

Examinations accomplished in Krasnoyarsk indicate that autonomous sources also exert certain impacts on ambient air contamination that is above hygienic standards [20].

We determined priority contaminants in Omsk that should be subject to observation in order to detect violations of obligatory hygienic requirements when control and surveillance activities are performed without any interaction with economic entities; these contaminants are manganese, acrolein, methanethiol (methyl mercaptan), kerosene, 1,2-dichloroethane, acrylonitrile, carbon disulphide, hydrogen chloride, tetrachloromethane, trichloroethylene, copper, and cadmium.

Acrolein and 1.3-butadiene (divinyl) belong to priority contaminants but are not included into control programs. These substances are contained both in emissions from enterprises and motor transport. Thus, as per data provided by leading experts in risk assessment, 1,3-butadiene accounts for 26 % of overall carcinogenic risk caused by emissions from motor transport [18].

Recent research accomplished in cities included as participants into «Clean air» Federal project allowed revealing that health risks are primarily created by the following contaminants: carbon, benzpyrene, benzene, sulfur dioxide, acrylonitrile, manganese, formaldehyde, nickel oxide, particulate matter including PM_{10} and $PM_{2.5}$, and nitrogen dioxide [21].

The established list of priority contaminants should be used as a ground for an experiment on fixing quotas as well as for assessing results and efficiency (indulging economic one) of «Clean air» Federal project implementation basing on reduction in population health risks[4].

The Complex program envisages that there should be reductions in priority contaminants emissions over 2019–2024, by 14.9 % (24,220.8 tons) overall and carcinogens by 3.3 % (24.9 tons).

Thus, for example, formaldehyde emissions should go down by 52.8 % due to activities aimed at eliminating solid communal wastes sites everywhere in Omsk and reducing emissions from stationary sources that are mostly hydrocarbons-producing enterprises; chromium-VI emissions are to go down by 12.8 % due to installing additional dust and gas traps at large chemical enterprises; benzpyrene and carbon black (soot) emissions should go down by 10.0 % and 2.6 % accordingly due to installing hybrid filters and modernizing technologic equipment at heat generating enterprises and tyres manufacturers.

At the same time, taking into account new goals on reducing emissions of priority contaminants by 2 times (that is, by 50 %) up to 2030, it is necessary to set tasks on reducing emissions of risk-creating chemicals by not less than 20–25 % up to 2024.

Enterprises operating in Omsk that emitted the largest volumes of carcinogens (54 economic entities) were given certain suggestions on activities that should allow reducing emissions as per specific contaminants. 15 enterprises out of the list that made primary contributions into carcinogenic risks presented activity programs aimed at reducing emissions of nickel, chromium, benzene, carbon black (soot), benzpyrene, and formaldehyde; it allowed preparing additional alterations that should be made into the Complex program.

We, together with environmental protection authorities, assessed a system for monitoring over ambient air quality and estimated whether it was relevant to an actual sanitary-hygienic and ecologic situation in Omsk; the assessment was performed basing on spatial distribution of aggregated hazard quotient (S) over residential areas in Omsk taking into account potential effects produced by priority emission sources (industrial enterprises) on health of people living in the city[9] (Figure). We created maps (layers) using a geoinformation system (ArcView GIS 3.2). Use of geographic information systems (GIS) allowed us to make our data more informative, and our analysis, more efficient [22].

In addition, we obtained preliminary data on aggregated calculated ground concentrations of contaminants in Omsk that took into account aggregated contaminants emissions from mobile sources (motor transport) and autonomous heat supplying sources[10]. Average daily (average annual) concentrations that were above hygienic standards were detected for benzpyrene; maximum single concentrations that were above hygienic standards were detected for 13 contaminants including those that were previously enlisted as priority contaminants, namely dimethyl benzene, hydroxybenzene, nitrogen dioxide, and sulfur dioxide; some substances were new such as dihydroperoxide, dihydrosulphide, and polyethylene polyamine. Reference concentrations that were above hygienic standards were registered at certain monitoring posts in the city center (No. 2 and 27) as per sulfur dioxide (up to 35 % higher than the standard) and benzpyrene (up to 32 % higher). Calculated average annual chromium concentrations were on average by 2 times higher than average chromium concentrations obtained via field observations and the situation was the same at all reference points that coincided with stationary posts for laboratory observations.

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[9] The examination was performed according to the Methodical Guidelines MR 2.1.6.0157-19. Creation of programs for monitoring over ambient air quality and quantitative assessment of population exposure for fulfilling tasks within social-hygienic monitoring activities. Moscow, 2019 (in Russian).

[10] Calculations were performed by «NII ATMOSFERA» JSC in accordance with a state contract (in Russian).

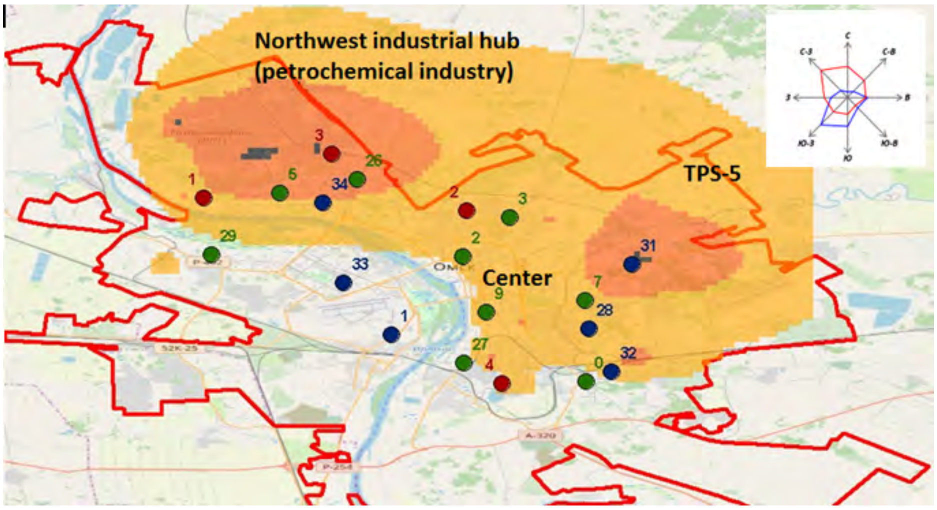

Figure. Spatial distribution of aggregated comparative hazard quotient (S) on Omsk city territory taking into account potential effects produced by industrial enterprises on residential areas in the city and predicted location of stationary posts for monitoring over ambient air quality for a period up to 2024

Symbols on the mal:

- Omsk city boundary
- Aggregated hazard quotient (S) (maximum value, the 1st level in gradation)
- Aggregated hazard quotient (S) (the 2nd level in gradation)
- Aggregated hazard quotient (S) (the 3rd level in gradation)

Predicted location of stationary posts for monitoring over ambient air quality for a period up to 2024 with their numbers

- Posts belonging to the Omsk Regional Ministry of Natural Resources and the Environment
- Posts belonging to Hydrometeorological Centre of Russia
- Posts belonging to Rospotrebnadzor

Therefore, we obtained certain arguments for preliminary substantiation of a program for monitoring over ambient air quality taking into account all monitoring systems belonging to different executive authorities responsible for environmental monitoring.

In 2019 (before optimization started) a laboratory network for monitoring over ambient air quality in Omsk included 10 stationary posts (6 posts belonged to Hydrometeorological Center of Russia and 4 posts, to the Omsk Regional Ministry of Natural Resources and the Environment), and a complete observation program was implemented at only 2 out of them. 25 chemicals were under surveillance at monitoring posts belonging to Hydrometeorological Center of Russia and 22 chemicals, at posts belonging to the Omsk Regional Ministry of Natural Resources and the Environment. Rospotrebnadzor Regional office in Omsk and Center for Hygiene and Epidemiology took air samples every month within a state program (laboratory examinations aimed at determining single concentrations) in zones influenced by the largest industrial objects. It was not sufficient bearing in mind proper health risk assessment as such samples could be used only for performing tentative hygienic assessments.

The existing monitoring network, despite minimal sufficient number of monitoring posts (10 for a city with million population) has certain drawbacks. They are as follows:

– posts are located in places that are not relevant bearing in mind intensity detected for spatial distribution of aggregated hazard quotients showing hazards caused by contaminants emitted from stationary sources taking wind rose into account: a situation in certain residential areas is not observed but these areas are influenced by petrochemical enterprises located in the northern part of the city;

– monitoring at stationary posts does not cover residential areas in scopes it should: a distance between 2 posts was longer than 5 km and monitoring covered not more than 65 % of total residential areas;

– a monitoring program implemented at monitoring posts did not correspond to hygienic tasks. On one hand, we should remember that average concentrations of certain metals such as cadmium, nickel, and chromium basically do not exceed maximum permissible ones; on the other hand, these substances have significant carcinogenic potential and when hazard are being identified thy usually take leading rank places in any lists of priority contaminants. We can't ignore this fact; therefore, a monitoring program should be altered in order to get as objective data on potential risks values as it is only possible. Thus, for example, 59 enterprises located in different parts of the city emit chromium into ambient air. Chromium occupies the 13^{th} rank place among all priority contaminants in the list obtained via hazard identification procedures but when it comes down to carcinogens it holds the 3^{rd} rank place. And preliminary aggregated calculations of ground chromium concentrations yielded higher annual average values than those obtained via field observations at all reference points. Sampling regarding chromium and other metals was performed only at 2 out of 10 monitoring posts within the existing ecological monitoring programs and examination programs were not comprehensive; single concentrations of those substances were averaged only once a month (for submitting data to Rospotrebnadzor authorities). Such priority contaminants as benzene, xylene, toluene, ethylbenzene, carbon black (soot), PM_{10}, $PM_{2.5}$, and metals either weren't examined in full scope or they were not monitored at all posts and it undoubtedly influenced health risk assessment making it less objective;

– there is no exchange of primary data obtained via laboratory examinations between Rospotrebnadzor Regional office in Omsk, the Omsk Regional Ministry of Natural Resources and the Environment, and Hydrometeorological Center of Russia.

Some researchers (V.N. Rakitskii, S.L. Avaliani, S.M. Novikov, T.A. Shashina) note that existing monitoring systems for control over quality of the environment have a specific drawback and it is their poor compatibility with requirements made by decision-makers and based on health risk analysis; it is due to existing monitoring systems not always being oriented at determining actual quantitative characteristics of population exposure and assessing related consequences for population health [23].

The performed examinations gave grounds for changes and the interdepartmental system for monitoring over ambient air quality has been substantially optimized; by 2024 it will include 19 stationary posts: 4 posts belonging to Rospotrebnadzor with 18 substances examined according to a complete observation program; 9 posts belonging to Hydrometeorological Center of Russia with 27 examined substances; 6 posts belonging to the Omsk Regional Ministry of Natural Resources and the Environment with 22 examined substances (according to the complete program at 5 posts, and according to a cut-down one at the remaining post). Location of most existing posts has been verified. We also substantiated placing additional posts in residential areas influenced by priority industrial objects, mostly in the northern-western part of the city (petrochemical production) and southern-eastern one (large coal-powered heat-generating enterprises) basing on spatial distribution of aggregated hazard quotient (S).

Taking into account preliminary data obtained via aggregated calculations on sulfur dioxide and benzpyrene concentrations exceeding their maximum daily average and reference levels, we justified placing additional monitoring posts No. 2 and 4 belonging to Rospotrebnadzor in zones influenced by main traffic highways and autonomous heating sources. When giving grounds for additional posts locations, we also took into account residential area density and absence of any posts belonging to either Hydrometeorological Center of Russia or the Omsk Regional Ministry of Natural Resources and the Environment located nearby. When this monitoring system is introduced, it will cover 98.3 % residential areas in the city.

Therefore, implemented optimization of the laboratory network for monitoring over ambient air quality will allow obtaining more objective data on ambient air quality, revealing and assessing potential health risks including those caused by emissions from specific industrial enterprises, and implementing targeted and efficient activities aimed at health risk reduction.

Another task we pursued to solve in our research was assessing results obtained via the Complex program implementation and determining a list of indicators to be monitored.

If we want to fix reasonable target indicators, we should perform comprehensive analysis of available long-term monitoring data on environmental quality and these data should be supported by results obtained via modeling and/or health risk assessment. In accordance with recommendations given by leading experts on hygiene and sanitary a list of indicators that are subject to monitoring should reflect sufficiency and efficiency of activities implemented within «Clean air» federal project as per population health criteria [23, 24].

B.A. Revich, T.L. Khar'kova, and E.A. Kvasha suggest estimating population health in cities participating in «Clean air» federal project basing on such most precise and verified indicator as mortality. This indicator can be used when assessing impacts exerted by contaminated ambient air on health together with assessing prevalence of bronchial asthma and congenital malformations among children [25].

When we rely solely on aggregated emissions, it is impossible to identify the most hazardous substances and sources of their introduction into ambient air. Contaminants concentrations should be taken as indicators which are subject to monitoring within the Federal project; otherwise, it will be impossible to assess the project efficiency [1].

In our opinion, a list of indicators which are subject to monitoring (control) should include the following:

a) ambient air quality indicators (volumes of aggregated emissions as per each substance; average annual, average daily, and single maximum concentrations of priority substances);

b) indicators of individual lifelong carcinogenic risk and risks of non-carcinogenic effects produced on critical organs (systems) and as per specific substances; a share belonging to each substance in the structure of potential risks;

c) mortality and morbidity indicators associated with exposure to contaminated ambient air (taking into account regional peculiarities and specific contaminants) as well as a rate at which these indicators go down in comparison with average rates in the country;

d) number of additional unfavorable outcomes (deaths or disease cases) related to exposure to contaminants in concentrations that are above their levels fixed by hygienic standards;

e) economic indicators that estimate medical and demographic losses in money terms;

f) number of complaints and results obtained via social questionings performed among population and aimed at determining whether people are satisfied with ambient air quality.

Progress in achieving these target indicators should be estimated as per their target values calculated for each indicator which is subject to monitoring. Hygienic standards and permissible/minimal values of potential risks taken according to conventional classifications are to be used as target indicators.

We also suggest applying «acceptable risk level» concept for assessing risks levels. Maximum permissible value of acceptable health risk is established taking into account up-to-date available technical, technological, economic, and social instruments for providing safe and/or harmless environment. Acceptable health risk can be and should be fixed directly by a federal authority responsible for the state sanitary-epidemiologic surveillance or by the RF Government basing on reliable data submitted by such an authority [26, 27].

When it comes to mortality and morbidity indicators, we can be guided by average country levels; should there be epidemiologic models «ambient air contaminant – a nosology (nosologic group or category)», then we can obtain target indicators that reflect mortality and morbidity levels under average annual contaminants concentrations that are not higher than their reference levels. It is reasonable to apply target indicators that are not lower than values stipulated by «Healthcare»[11] National project for some health indicators such as infant mortality, mortality caused by cardiovascular diseases and malignant neoplasms, and mortality among employable population.

Omsk experts performed scientific research on population health in the city and established population groups that were the most sensitive to effects produced by ambient air contamination; they were pregnant women and newborns; infant children younger than 1 year; children younger than 14. Priority health indicators include overall and particular oncologic morbidity; indicators that show health of pregnant women and newborns; prevalence of respiratory and gastric diseases[12].

Absence of additional death cases, disease cases, and admissions to hospitals caused by exposure to contaminants in concentrations higher than hygienic standards should be used as a target value for additional unfavorable outcomes.

In our opinion, target control indicators should include not only data collected for the whole city but also data on specific districts within it ranked as per an extent to which ambient air contamination influences exposed population's health.

The Table below contains an example of a report on target control indicators showing implementation of activities enlisted within the Complex plan[13] on emissions reduction and socially significant consequences as well as their assessment in dynamics taken over 2017–2019.

Year 2019 became the first one when environmental protection activities were implemented in accordance with the Complex program; preliminary results obtained in achieving target indicators were summed up.

In 2019 there were no average annual concentrations of any contaminants that were higher than hygienic standards; maximum single concentrations higher than hygienic standards were registered as per particulate matter (2 MPC), carbon oxide (1.7 MPC), nitrogen dioxide (1.4 MPC), nitrogen oxide (4.2 MPC), hydrogen sulphide (2.5 MPC), phenol (1.7 MPC), hydrogen chloride (8.8 MPC), ammonia (1.3 MPC), formaldehyde (6.3 MPC), ethylbenzene (6.5 MPC), and benzpyrene (3.6 MPC). Also in 2019 there was a growth in average annual concentrations of substances that make a considerable contribution into health risks such as benzene, formaldehyde, chromium, copper, and nickel. On the other hand, there was a decrease in annual average concentrations of such hazardous substances as benzpyrene, carbon black (soot), particulate matter, and nitrogen dioxide. A contribution made by those substances into carcinogenic and non-carcinogenic health risks went down substantially but it turned out not to be sufficient not only for risk reduction but also for preventing their growth.

Structure of carcinogenic risks determined as per substances changed with growing influence exerted by chromium and a decrease in contributions made by formaldehyde, benzene, and carbon black (soot), although aggregated specific weight of the three last contaminants still remained high (44.3 %).

Mortality caused by all reasons went down by 2.5 % over the next two years (2018–2019) and was excluded from priority indicators with their values being higher than on average in the country and the Siberian Federal District. At the same time, mortality caused by respiratory diseases in Omsk grew by 4.7 % against 2017. Infant mortality went down by 12.3 % but the target indicator value was not yet achieved.

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[11] Profile of «Healthcare» National project. Approved by the Presidium of the RF Presidential Council on strategic development and national projects (Meeting report No. 16 dated December 24, 2018). *Garant*. Available at: https://base.garant.ru/72185920/ (14.07.2020) (in Russian).

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Table

An example structure of target control indicators showing implementation of activities enlisted within the Complex plan on emissions reduction and their assessment in dynamics over 2017–2019, Omsk (a fragment of a report)

A group of indicators/ An indicator subject to monitoring*	Average long-term value (2009–2017)	Indicator taken as per years				Assessment whether a target value achieved
		2017	2018	2019		
		actual	actual	actual	Target value	
Volume f contaminants emissions into ambient air from stationary sources (tons per year)						
Overall, including:	181,070	163,700	186,500	161,390** (went down by 2,310 tons, 1.4 %)	159,800 (should go down by 3,928 tons or 2.4 %)	Not achieved
formaldehyde	12.5	10.52	10. 45	Data will be available in the 4^{th} quarter of 2020	Should go down by 8.8 % (9.6 tons)	
MPC exceeding hygienic standards						
A share of samples with contaminants in concentrations exceeding maximum single MPC	0.73 %	0.40 %	0.40 %	0.49 %	0.0 %	Not achieved; growth
Average annual contaminants concentrations obtained via environmental and social and hygienic monitoring						
Benzene	0.006	0.005	0.006	0.007	<0.03	Achieved; growth
Benzpyrene	$8.3\cdot10^{-7}$	$8.0\cdot10^{-7}$	$8.8\cdot10^{-7}$	$7.8\cdot10^{-7}$	$<1.0\cdot10^{-6}$	Achieved; growth
Formaldehyde	0.0087	0.007	0.0093	0.0095	<0.003	Not achieved; growth
Individual lifelong carcinogenic risk						
For overall population	$5.16\cdot10^{-4}$	$2.45\cdot10^{-4}$	$4.58\cdot10^{-4}$	$4.69\cdot10^{-4}$	$<1.0\cdot10^{-4}$ (acceptable level)	Not achieved; growth
Hazard index for non-carcinogenic effects for substances with similar impacts						
Respiratory organs	11.5	9.82	10.69	11.39	≤3.0 (acceptable level)	Not achieved; growth
Immune system	4.2	2.82	4.20	5.05	≤3.0 (acceptable level)	Not achieved; growth
Hazard index for non-carcinogenic effects for specific substances						
Formaldehyde	2.7	2.4	3.1	3.2	≤1.0 (acceptable level)	Not achieved; growth
Manganese	1.4	1.4	1.2	1.0	≤1.0 (acceptable level)	Achieved; decrease
Population mortality in Omsk						
Mortality caused by respiratory diseases per 100 thousand people	49.0	38.0	36.0	39.8	Average country level is 49.1	Achieved; growth
Infant mortality	5.1	5.7	5.58	5.0	4.5	Not achieved; decrease
Primary morbidity among population (per 100 thousand people from a relevant group) in Omsk						
Morbidity among children younger than 14 with asthma and status asthmaticus	143.46	134.4	98.2	205.3	Average country level**	Drastic growth
Additional unfavorable outcomes for population caused by exposure to specific contaminants						
Number of death cases caused by cardiovascular diseases under exposure to $PM_{2.5}$	–	9	0	0	0	Achieved; decrease

Note:
* means that a list of indicators is given selectively to illustrate an example and is not complete;
** means data are preliminary, they will be adjusted in the 4^{th} quarter of 2020.

Primary morbidity went down as per most nosologies over 2018–2019; endocrine diseases and diseases of the skin and subcutaneous tissue were excluded from priority nosologies. Morbidity with diseases of the blood and blood-forming organs, anemia included, went down considerably among children and teenagers. Morbidity with gastric diseases, circulatory diseases, diseases of the nervous system, and congenital malformations was still included into priority nosologies lists. Besides, in 2019 morbidity with asthma and status asthmaticus tended to grow among children younger than 14 and adults aged 18 and older. Morbidity among infants also grew including morbidity with respiratory and gastric diseases and congenital malformations.

Conclusions. At initial stages in the Federal project implementation it is important to obtain the most objective data on population health risks caused by ambient air contamination including data on specific micro-territories; these data can be obtained due to creating a laboratory observation network for monitoring over ambient air quality that is relevant for hygienic tasks, and aggregated calculations of ground concentrations based on objective reports on emission sources.

The first year when environmental protection activities were implemented in accordance with the Complex program (2019) didn't bring about a «break-through» improvement in ambient air quality. Despite average annual concentrations of some contaminants truly went down, a lot of indicators didn't achieve their target values. Obviously, a socially significant effect – real improvement in population health – can be achieved only provided there is substantial and long-term decrease in ambient air contamination in residential areas. Some researchers who focus on the first results obtained via partially implemented activities within «Clean air» Federal project in participating cities mention that emissions reductions are not efficient enough when we consider their influence on population health [1].

Bearing in mind that new target figures envisage a 2-time reduction in priority contaminants emissions by 2030 (and it can truly lead to population health improvement), it is necessary to make changes into the Complex program in 2020 including new adjusting organizational and technical activities into it; these activities will allow providing a substantial reduction in emissions of risk-creating substances that should be not less than by 20–25 % by 2024 against 2017. It will be also necessary to enhance control over implementation of activities aimed at reducing emissions of the said substances.

We believe that providing objective and timely control over implementation of activities within the Federal project will require making a list of indicators which are subject to monitoring, collecting data in due time and controlling their quality, creating a system for target indicators assessment in order to provide operative reacting and making necessary corrections. It is especially important to determine relevant lists of socioeconomic indicators (health indicators) and ways to assess them properly; these indicators should be associated with ambient air quality and take into account regional peculiarities of ambient air contamination, climatic peculiarities in a specific region and socioeconomic conditions typical for it.

Funding. The research was not granted any sponsor support.

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

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Kriga A.S., Nikitin S.V., Ovchinnikova E.L., Plotnikova O.V., Kolchin A.S., Cherkashina M.N., Vinokurova I.G., Dunaeva M.A. On implementation of «Clean air» federal project in Omsk. Health Risk Analysis, 2020, no. 4, pp. 32–46. DOI: 10.21668/health.risk/2020.4.04.eng

Received: 14.08.2020
Accepted: 09.11.2020
Published: 30.12.2020

UDC 612-06
DOI: 10.21668/health.risk/2020.4.05.eng

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Research article

TRENDS DETECTED IN CHILDREN'S HEALTH AND THEIR RELATION WITH BASIC AEROGENIC RISK FACTORS UNDER EXPOSURE TO SPECIFIC AMBIENT AIR CONTAMINATION CAUSED BY METALLURGIC AND WOOD-PROCESSING ENTERPRISES

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Industrial objects including metallurgic and wood-processing enterprises that emit hazardous chemicals into ambient air are often located within or close to residential areas; it results in poorer ambient air quality and health disorders caused by it, first of all, among children.

Our research objects were chemicals contents in ambient air in a residential area exposed to emissions from metallurgic and wood-processing enterprises (the test territory) and in an area where there were no such productions (the reference territory), and primary morbidity among children in both of them.

We determined priority chemical risk factors basing on hygienic assessment of ambient air quality and calculation of risks that non-carcinogenic effects would occur in organs and systems of children who lived in a zone exposed to the given industrial objects. These factors included aluminum oxide, particulate matter, phenol, and gaseous fluorides and their contents were up to 5.0 times higher than permissible levels. We detected negative trends in primary morbidity among children and established authentic models showing dependence between a probable growth in morbidity as per respiratory diseases, diseases of the nervous system, gastric diseases, diseases of the musculoskeletal system and connective tissue, and diseases of the urogenital system and total doses of chemicals under aerogenic exposure. All the above mentioned indicates that poor ambient air quality in a residential area can make for a growth in related morbidity as per the given nosologies.

Established and parameterized cause-and-effect relations allow predicting negative responses in critical organs and systems (as per the given nosologies) of exposed children. It provides scientific substantiation for developing relevant prevention activities aimed at reducing and preventing negative consequences for health of children living in regions where large metallurgic and wood-processing enterprises are located.

Key words: *chemical factors in ambient air, ambient air contamination, industrial objects, metallurgic and wood-processing enterprises, non-carcinogenic risks, aerogenic risk factors, critical organs and systems, primary morbidity among children.*

When industrial objects including metallurgic and wood-processing enterprises are located within residential areas or close to them, it often results in poorer quality of ambient air and occurrence of related health disorders especially among children [1]. We analyzed research works both by domestic and foreign researchers and revealed that it was not a rare case when the greatest part of a city population lived in zones exposed to chemical emissions and there were various negative responses regarding their health [2–7]. Prior-

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ity substances that create extremely high ambient air contamination in some regions where the above mentioned industries are located are nickel, copper, di-aluminum trioxide, chromium (VI), aromatic hydrocarbons, fluorides and gaseous fluorides (components that often occur in emissions from metallurgic enterprises) as well as particulate matter, methanol, phenol, etc. (components that often occur in emissions from wood-processing enterprises). All the above-mentioned substances predominantly belong to the 1–2 hazard categories and produce tropic effects on the respiratory organs, cardiovascular, musculoskeletal, nervous and endocrine systems, kidneys, and digestive organs[1] [8–12].

In some RF regions where metallurgic and wood-processing enterprises are located population morbidity with respiratory diseases is caused by ambient air being contaminated with specific chemical compounds typical for such productions. Lipetsk region, Irkutsk region, Sverdlovsk region, Krasnoyarsk region, and some others are among territories where morbidity with respiratory diseases is high; these diseases are of allergic nature, involve lymphproliferative processes, and are caused by aerogenic exposure to chemical factors which are typical for the above-mentioned industries[2]. Apart from respiratory diseases, diseases of the circulatory system are also widespread. Primary morbidity with cardiovascular diseases, predominantly functional cardiopathy, was shown to be authentically higher among people living in residential areas where particulate matter concentrations in ambient air were above hygienic standards than among people living in reference areas where hygienic standards were not violated [13]. The gastrointestinal tract is also a target organ, especially when it comes down to children, in people exposed to ambient air being contaminated with specific chemicals. Morbidity with gastric diseases among children living in contaminated areas is usually 2–4 times higher than it is in areas where there are no such industrial objects outlined above [14]. Thus, children exposed to aromatic hydrocarbons more frequently suffer from inflammatory-dystrophic diseases of the gastrointestinal tract such as chronic gastritis and gastroduodenitis. Such substances as phenol and ethylbenzene have hepatotoxic properties and are able to produce direct effects on cellular structures via doing damage to membrane hepatocytes transportation, distorting biological processes in liver cells, and freeing their own metabolites out of them [15]. Diseases that involve functional disorders in the central nervous system and endocrine system are more frequent among children living in industrially developed regions than among children living on reference territories [16]. A basic mechanism for effects produced by aerotechnogenic chemical risk factors on the hormone, nervous, and immune system is activation or suppression of hypothalamo-pituitary-adrenal axis that can result in hormonal imbalance [17, 18]. Neuroendocrine impacts on the immune system functioning are related to the nervous system being able to perform direct or indirect control over various hormones secretion; they are also related to «inverse» influence exerted by hormones on neuromediators [18, 19]. When certain chemicals (chromium, lead, phenol, copper oxide, etc.) are introduced with ambient air via inhalation, there is an increase in morbidity with diseases of the kidneys. Being nephrotoxic, these substances can both directly influence renal parenchyma or exert indirect impacts via changes in hemodynamics and acid-base balance in the internal environment [20]. Renal functional disorders occur as a decrease in glomerular filtration, tubular reabsorption inhibition, and weaker renal plasma flow[3]. Analy-

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[1]HS 2.1.6.3492-17. Maximum permissible concentrations (MPC) of contaminants in ambient air in urban and rural settlements. KODEKS: an electronic fund for legal and reference documentation. Available at: http://docs.cntd.ru/document/556185926 (03.11.2020) (in Russian).

[2] On sanitary-epidemiologic welfare of the population in the Russian Federation in 2019: The State Report. Moscow, The federal Service for Surveillance over Consumer Rights Protection and Human Well-being Publ., 2020, 299 p. (in Russian).

[3] Pathological kidney physiology: a manual. In: E.N. Kuchuk, F.I. Vismont eds. Minsk, BSMU Publ., 2011, 41 p. (in Russian).

sis of morbidity among children who lived in residential area exposed to emissions from both metallurgic and wood-processing enterprises revealed that primary morbidity with diseases of the musculoskeletal system was up to 2.0 times higher among them than on average in the country [21]. Given all the above mentioned, we can conclude that in such areas there is elevated risk of disability among children and poorer life quality.

Therefore, all these data indicate that chemical factors that are components in emissions form metallurgic and wood-processing enterprises make a significant contribution into ambient air contamination and increased prevalence of diseases associated with it practically as per all basic nosology categories.

Our research goal was to reveal and assess trends in occurring health disorders and their relations with basic aerogenic risk factors given specific ambient air contamination by metallurgic and wood-processing enterprises.

Data and methods. Our research objects were chemicals contents in ambient air and primary morbidity among children living on a territory where metallurgic and wood-processing enterprises were located (the test territory) and children living on a territory without such enterprises (the reference territory).

Ambient air samples were taken on the examined territories at seven observation points and analyzed during 2014–2017 by experts from the Center for Hygiene and Epidemiology. Obtained results were assessed via analyzing contents of the examined chemical components and their conformity with hygienic standards fixed by the HS 2.1.6.3492-17.

Health risks for children under chronic inhalation exposure to chemical factors were assessed in accordance with the Guide on health risk assessment under exposure to chemicals that pollute the environment involving calculation of hazard quotient and hazard index (HQ, HI) that were determined taking into account organs and systems being critical under aerogenic exposure[4].

Our initial data for analyzing morbidity among children were taken from state statistical reports such as Form No. 12 «Data on a number of diseases registered among patients living on a territory where a medical organization renders its services» over 2014–2018. To analyze morbidity among children living on the test and reference territories basing on data obtained from state statistical reports, we calculated primary morbidity in each analyzed year and calculated average values over the whole observation period (2014–2018). Data on morbidity are given as a number of disease cases per 1,000 people from a corresponding age group. To describe dynamics of morbidity, we calculated its growth (decrease) rates in 2018 against 2014 (in %).

Mathematical modeling within «a dose of a chemical inhaled with ambient air – morbidity among children» system was performed basing on data on population applying for medical aid in 2014–2018.

Results and discussion. We performed hygienic assessment of ambient air quality in residential areas influenced by metallurgic and wood-processing enterprises as per data provided by the Center for Hygiene and Epidemiology over 2014–2017. The assessment revealed that hygienic standards were violated as per contents of certain chemicals in ambient air such as aluminum and its compounds (up to 2.00 average daily MPC); particulate matter (up to 3.01 average daily MPC); phenol (up to 1.1 average daily MPC), gaseous fluorides (up to 1.7 average daily MPC) (Table 1).

Over the same period, ambient air in residential areas on the reference territory contained particulate matter in concentrations that were up to 1.2 times higher than hygienic standards. Hygienic standards on the reference territory were not violated as per aluminum, benzene, phenol, manganese, nickel, chromium, lead and its compounds, and fluorides.

[4] G 2.1.10.1920-04. Guide on health risk assessment under exposure to chemicals that pollute the environment. Moscow, The Federal Center of the State Sanitary Epidemiologic Surveillance, RF Public Healthcare Ministry Publ., 2004, 143 p. (in Russian).

Table 1

Average contaminants concentrations in ambient air in residential areas influenced by metallurgic and wood-processing enterprises detected at observation posts belonging to the Center for Hygiene and Epidemiology in 2014–2017, shares of MPCav.d.

A chemical	MPCav.d., mg/m^3	2014	2015	2016	2017	Average over 2014–2017
Aluminum and its compounds	0.01	–	–	2.00	–	2.00
Benzene	0.1	–	–	–	–	–
Particulate matter	0.15	–	–	3.01	–	3.01
Phenol	0.006	0.21	1.50	1.59	–	1.10
Manganese	0.001	–	–	0.07	–	0.07
Methanol	0.5	–	–	0.01	–	0.01
Nickel	0.001	–	–	0.03	–	0.03
lead	0.0003	–	–	0.33	–	0.33
Poorly soluble non-organic fluorides	0.03	–	–	0.06	–	0.06
Gaseous fluorides	0.005	0.74	1.55	2.89	–	1.73
Chromium $^{6+}$	0.0015	–	–	0.01	–	0.01

Table 2

Hazard quotients (HQ) and hazard indexes (HI) under chronic inhalation exposure for children living on a territory exposed to metallurgic and wood-processing enterprises

No.	Chemical	Hazard quotient (HQ)									
		Blood and blood-forming organs	Cardiovascular system	Nervous system	Respiratory organs	Reproductive system	Hormone system	Kidneys	Liver	Immune system	Skeletal system
1.	Aluminum and its compounds	–*	–*	5.4	5.4	–*	–*	–*	–*	–*	5,4
2.	Benzene	0.41	0.41	0.41	–*	0.41	–*	–*	–*	0.41	–*
3.	Particulate matter	–*	5.3	–*	5.3	–*	–*	–*	–*	–*	–*
4.	Manganese	–*	–*	1.8	1.8	–*	–*	–*	–*	–*	–*
5.	Nickel oxide	2.0	-*	2.0	2.0	-*	-*	-*	-*	2.0	
6.	Lead and its compounds	0.26	–*	0.26	–*	0.26	0.26	0.26	–*	–*	–*
7.	Phenol	–*	0.98	0.98	0.98	–*	–*	0.98	0.98	–*	–*
8.	Poorly soluble fluorides	–*	–*	–*	0.18	–*	–*	–*	–*	–*	0,18
9.	Gaseous fluorides	–*	–*	–*	1.98	–*	–*	–*	–*	–*	1,98
10.	Chromium (VI)	–*	–*	–*	0.2	–*	–*	0.2	0.2	–*	–*
	Hazard index (HI)	**2,67**	**6.69**	**10.86**	**17.84**	0.67	0.26	**1.44**	**1.18**	**2.41**	**7.56**

Note: 1 * means a substance does not influence a critical system under such introduction (when inhaled).

We assessed non-carcinogenic risks of diseases caused by aerogenic exposure to chemicals; the assessment revealed hazard quotients being higher than permissible levels (HQ > 1) for children living on the test territory as regards aluminum and its compounds (HQ = 5.4), particulate matter (HQ = 5.3), manganese (HQ = 1.8), nickel oxide (HQ = 2.0), and gaseous fluorides (HQ = 1.98) (Table 2).

We established that hazard indexes for children exceeded their permissible levels under chronic inhalation exposure to chemicals regarding the respiratory organs (17.8 times), nervous system (10.9 times), skeletal and cardiovascular systems (6.7–7.6 times), blood and blood-forming organs and immune system (2.4–2.7 times), kidneys and liver (1.2–1.4 times).

Basic contributions into intolerable non-carcinogenic risks of respiratory diseases were made by aluminum (30.2 %), particulate matter (29.7 %), nickel oxide (11.2 %), and gaseous fluorides (11.0 %); diseases of the nervous system, aluminum (49.7 %), nickel (18.4 %), and manganese (16.6 %); blood and blood-forming organs, nickel oxide (74.9 %); immune system, nickel oxide (82.9 %); cardiovascular system, particulate matter (79.2 %); skeletal system, aluminum (71.4 %), and gaseous fluorides (26.2 %). We didn't establish any hazard quotients exceeding their hygienic standards as per aluminum, manganese, nickel, and gaseous fluorides on the reference territory when assessing chronic aerogenic exposure.

The existing aerogenic exposure that occurs due to increased contents of emissions from metallurgic and wood-processing enterprises in ambient air can make for a growth in morbidity with the diseases of respiratory organs, digestive organs, musculoskeletal system and connective tissue, and genitourinary system. It is confirmed by analysis of primary morbidity dynamics among children in 2014–2018 as per certain nosologies (Table 3).

Overall, primary morbidity among children living on the test territory changed insignificantly over the analyzed period; however, there was significant growth as per certain nosologies. Thus, growth in primary morbidity among children over 5 analyzed years was established for the following nosologies: diseases of the digestive organs (118.18 %); diseases of the musculoskeletal system and connective tissue (43.58 %); diseases of the genitourinary system (44.97 %).

We analyzed primary morbidity among children as per specific nosologies; the analysis revealed the greatest growth as per the following ones: osteopathy and chondropathy (190.06 %); glomerular, tubulointerstitial kidney diseases, other diseases of the kidneys and ureter (71.72 %). The greatest decrease rates were revealed for chronic bronchitis, unspecified bronchitis and emphysema (73.33 %); asthma (52.38 %).

Comparative analysis of primary morbidity revealed that average primary morbidity among children was 2.2–41.9 times higher practically as per all nosologic groups on the test territory than on the reference one. Endocrine diseases were the only exclusion from the comparison as there were no such diseases detected among children living on the reference territory.

Table 3

Primary morbidity among children (aged 0–14) living on the test territory influenced by metallurgic and wood-processing enterprises taken as per basic nosologic categories over 2014–2018

Nosologic category (as per ICD-10)	Test territory		Reference territory	
	Average value over 2014–2018	Growth rate against 2014, %	Average value over 2014–2018	Growth rate against 2014, %
J00-J99 Diseases of the respiratory system	2,370.35	–54.97	1,094.18	2.1
K00-K93 Diseases of the digestive system	174.62	118.18	64.78	–47.7
M00-M99 Diseases of the musculoskeletal system and connective tissue	50.22	43.58	1.2	–
G00-G99 Diseases of the nervous system	40.61	–1.09	5.93	179.5
N00-N99 Diseases of the genitourinary system	54.98	44.97	5.60	–100.0
E00-E90 Endocrine, nutritional, and metabolic diseases	30.84	9.27	–	–

Table 4

Parameters used in models showing «a dose of a chemical from the environment – morbidity among children» dependence (as per data provided by the Regional Fund for Obligatory Medical Insurance over 2014–2018)

Nosology group	A chemical contained in ambient air	Model parameters				
		b_0	b_1	F	R^2	p
Diseases of the respiratory system	Nickel	–0.023	6,938.462	72.2	0.29	0.0001
Diseases of the nervous system	Lead	–4.639	17,177.6	143.2	0.52	0.0001
	Manganese	–3.058	0.867	19.1	0.16	0.0001
Diseases of the musculoskeletal system and connective tissue	Gaseous fluorides	–3.241	71.353	18.3	0.14	0.0001
Diseases of the genitourinary system	Lead	–3.094	6,078.919	52.9	0.28	0.0001
	Phenol	–2.824	31.241	70.2	0.31	0.0001

We built a mathematic model showing «exposure – response» dependence; it allowed us to establish the following authentic direct cause-and-effect relations: an increase in morbidity with «Diseases of the respiratory organs» and total doses of nickel ($R^2 = 0.29$; $b_0 = –0.023$; $b_1 = 6{,}938.462$; $p = 0.0001$); «Diseases of the nervous system» and total doses of manganese and lead ($R^2 = 0.16–0.56$; $–3.058 \leq b_0 \geq –4.639$; $0.867 \leq b_1 \geq 17{,}177.6$; $p = 0.0001$); «Diseases of the musculoskeletal system and connective tissue» and total doses of gaseous fluorides ($R^2 = 0.14$; $b_0 = –3.241$; $b_1 = 71.353$; $p = 0.0001$); «Diseases of the genitourinary system» and total doses of lead and phenol ($R^2 = 0.28–0.31$; $–2.824 \leq b_0 \geq –3.094$; $31.241 \leq b_1 \geq 6{,}078.919$; $p = 0.0001$) (Table 4).

Conclusion. We analyzed the results obtained via hygienic assessment of ambient air quality and non-carcinogenic risks of diseases occurrence in critical organs and systems of children who lived on a territory exposed to metallurgic and wood-processing enterprises. The analysis allowed establishing priority chemical risk factors (di-aluminum trioxide, particulate matter, phenol, and gaseous fluorides) that were up to 5 times higher than their permissible levels. Unfavorable hygienic situation involving poor ambient air quality in residential areas can lead to a growth in associated morbidity with diseases of the musculoskeletal system and genitourinary system; this conclusion is confirmed by a growth in primary morbidity among children as per these nosologies and authentic cause-and-effect relations between probabilities of growth in morbidity and total doses of chemicals under aerogenic exposure.

Despite there is a descending trend in primary morbidity with diseases of the respiratory system and nervous system over the analyzed period, we established a relation between an increase in morbidity and risk factors (nickel, manganese, and lead). Obtained dependence can indicate that a prognosis is unfavorable as these diseases can develop among children in future.

Therefore, established and parameterized cause-and-effect relations allow predicting negative responses in critical organs and systems (as per specific nosologic groups) among exposed children. These results can be used for developing scientifically substantiated and relevant prevention activities aimed at reducing and preventing negative consequences for health of children living in regions where both metallurgic and wood-processing enterprises are located.

Funding. The research was not granted any sponsor support.

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

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Received: 30.09.2020
Accepted: 03.12.2020
Published: 30.12.2020

UDC 614.1: 614.7
DOI: 10.21668/health.risk/2020.4.06.eng

Read online

Research article

METHODICAL ASPECTS IN ASSESSING RISKS OF COMORBID PATHOLOGY OCCURRENCE UNDER EXPOSURE TO CHEMICAL ENVIRONMENTAL FACTORS

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Risk assessment methodology is a promising trend in examining effects produced by environmental factors on population health. However, at present little attention has been paid to issues related to comorbid pathologies occurrence under chronic exposure to toxicants.

Our research goal was to improve methodic approaches to assessing risks of co-morbid pathology occurrence under exposure to multi-component chemical factors in the environment.

Data and methods. To develop an algorithm for establishing a probability that comorbid pathology would occur, we analyzed scientific publications that focused on effects produced by technogenic chemicals on a body and health risk assessment methodology. Methodic approaches were tested with epidemiologic hygienic analysis techniques and statistical processing of data obtained via profound medical and biological examination of children living in Perm region where chemical enterprises were located.

Results. We suggested a systemic approach to assessing risks of co-morbid pathologies caused by complex exposure to chemical environmental factors; the approach includes reference groups creation; determining responses in critical organs and systems via stage-by-stage modeling within «chemical factor – exposure marker – marker parameter – disease» system; determining population and individual risks of environmentally induced comorbid diseases. The performed analysis allowed establishing marker parameters of bronchial asthma and comorbid pathologies occurrence in children living on a territory with multi-component contamination of ambient air predominantly with saturated spirits, aldehydes, and particulate matter. It was shown that a number of additional comorbid diseases that were probabilistically related to increased chemicals contents in the examined children's blood could amount up to 15 ‰, and a contribution made by the examined chemicals into comorbid pathology occurrence would reach 14.2–23.4 %.

Implementation of mathematical analysis procedures outlined in the present work will make for higher efficiency of activities aimed at managing and minimizing health risks for people living under combined exposure to chemical environmental factors.

Key words: *chemical factors, risk assessment, exposure marker, biomarker of an effect, comorbid pathology, cause-and-effect relations, medical and biological examinations.*

Contemporary changes in the living environment and negative trends detected in morbidity among population in the Russian Federation require comprehensive research on factors that influence human health; it is especially vital for industrially developed regions [1–4]. According to data obtained via clinical and epidemiological examinations performed on territories where ecological situation is rather adverse, prevalence of morbidity with respiratory diseases, diseases of the cardiovascular and nervous system, gastric and endocrine diseases is 1.2–2.6 times higher than on reference territories and functional deviations in critical organs or systems are 1.2–1.4 times more frequent. Poor quality of the environment was shown to be a leading factor in making life expectancy shorter [2, 4–10]. Not

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coincidentally, issues related to providing sanitary-epidemiologic welfare of population, raising life quality, and health protection are among key targets in the state social policy implemented in the country.

Health risk assessment is a significant component in prevention medicine. Establishing probability of undesirable effects related to impacts exerted by environmental factors underlies environmental quality management and population health preservation [11–19]. We should note that studies on assessing risks of negative effects on health primarily focus on specific diseases and don't always take into account complex impacts exerted by chemical factors [4, 6, 17]. Another problem is selecting relevant indicators for risk assessment. An interesting and promising aspect here is getting an insight into pathogenetic mechanisms that cause functional disorders in several organs or systems under exposure to a set of chemical environmental factors that might be rather long-term [8, 16, 20–23].

Recently, a lot of attention has been paid to assessing risks of comorbid pathology. It was shown that comorbid pathology was a multifactor phenomenon developing due to several factors such as hereditary predisposition, metabolic disorders, chronic infections, social causes, and environmental factors as well. When several diseases develop in a combination, it changes pathophysiological clinical course and clinical signs of each of them thus aggravating a patient's state; it can result in death at more mature age[1] [24–28]. Over the last decades different scales have been suggested for detecting comorbid pathology predominantly among adult population; they are used in clinical practice for determining gravity of a disease and predicting unfavorable outcomes [25]. So far there have not been enough studies focusing on influence exerted by environmental factors on comorbid states development and assessing risks of comorbid pathology associated with impacts exerted by toxicants.

Our research goal was to develop methodical approaches to assessing risks of comorbid pathology development under multicomponent exposure to a set of chemical environmental factors.

Data and methods. To develop an algorithm for determining a probability that comorbid pathology might develop, we examined literature data on how technogenic chemicals influenced a human body and on methodology for assessing health risks under negative influences exerted by environmental factors. Methodical approaches were tested with epidemiologic and hygienic analysis procedures and statistical processing of data obtained via profound medical and biological examination of children living in Perm region where chemical enterprises manufacturing products with organic synthesis technologies were located. A reference territory was a territory where there were no industrial enterprises.

Results and discussion. In accordance with basic documents health risk assessment involved a systemic examination of all aspects in impacts exerted by an adverse factor on human health that included four stages; these stages allowed revealing probability of certain negative effects that might occur under exposure to a chemical detected in environmental objects.

Hazard identification stage involved determining a list of adverse chemicals that might produce effects resulting in health disorders among population and detecting critical organs and systems that were susceptible to negative effects produced by established risk factors taking exposure scenarios into account. Contamination sources were revealed and environmental objects quality was assessed as per data obtained via analyzing statistical reports (Form No. 2, TP-Air), results obtained via social and hygienic monitoring performed by Rosgidromet and Rospotrebnadzor's regional office, and data obtained via field observations that allowed assessing quality of the environment. It was

[1] Isaeva R.B. Peculiarities of comorbid chronic pathology in children in areas near the Aral sea where ecological situation is adverse: the thesis of the dissertation … for the Doctor of Medical Sciences degree. Moscow, 2007, 48 p. (in Russian).

established that over a 5-year observation period hygienic standards for ambient air quality were violated on the test territory as per contents of formaldehyde (13.3 average daily MPC), benzene (up to 7.7 average daily MPC), phenol (up to 3.5 average daily MPC), and particulate matter (up to 4.2 single maximum MPC). Besides, one third of samples contained methanol (up to 0.06 single maximum MPC).

The next stage, namely exposure assessment, involved calculating and analyzing risks of negative effects occurring under multi-component and multi-environment exposure to chemicals (hazard quotient and index) and it allowed identifying priority chemical factors that created unacceptable health risks for exposed population and establishing critical organs and systems that were damaged by them. Unacceptable risk levels were detected on the test territory for respiratory diseases (HI chronic is up to 13.3) associated with long-term exposure to particulate matter (HQ chronic is up to 9.6); pathology of the central nervous system (HI chronic is up to 6.4) and cardiovascular system (HI chronic is up to 5.1) caused by chronic exposure to benzene (HQ chronic is up to 4.25) and phenol (HQ chronic is up to 1.7); immune pathology (HI chronic is up to 7.6) caused by long-term exposure to benzene and formaldehyde (HQ chronic is up to 3.3).

We performed structural-dynamic analysis of morbidity and mortality among population basing on data obtained from official statistic reports (The Federal Statistic Observation report Form No. 12 «Data on a number of diseases registered among patients who live on a territory where a medical organization renders its services») and data on people applying for medical aid obtained from the Territorial Fund for Obligatory Medical Insurance. This analysis allowed us to reveal whether a health risk found its actual realization as a specific disease. Relative risk is a qualitative parameter showing a correlation between morbidity and influencing chemical risk factors. Dynamic analysis of statistical data obtained over the observation period on the test territory revealed that a growth in primary morbidity as per «Diseases of the respiratory organs» nosologic category among children amounted to 30.5 %, and primary morbidity with cardiovascular pathology increased by 6.4 times (up to 14.79 ‰). A number of children suffering from bronchial asthma and allergic rhinitis that were first diagnosed in them grew by 1.2–42.8 times. Performed epidemiologic analysis allowed establishing a cause-and-effect relation between impacts exerted by the examined chemical environmental factors and respiratory diseases (OR = 1.97), gastric diseases (OR = 1.7), and pathology of the nervous system (OR = 3.6).

We performed a profound examination of reference groups in order to establish and quantitatively assess a probability of comorbid pathology among population living in residential areas exposed to a set of chemical factors. At an initial stage in the research we substantiated exposure markers via building non-linear logistic regression models[2] taking into account obtained authentic correlations between concentration of a chemical on blood and inhalation exposure to it in ambient air:

$$p = \frac{1}{1+e^{-(b_0+b_1 a)}}, \qquad (1)$$

where p is a probability that contents of an examined chemical in blood deviate from the standard;

a is a dose of a chemical introduced with ambient air, mg/(kg·day);

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

b_0, b_1 are parameters applied in a mathematical model.

We revealed that contents of benzene, phenol, formaldehyde, and methanol in examined children's blood had statistically significant cause-and-effect relations with doses of the said chemicals introduced with ambient air ($R^2 = 0.18–0.30$; $31.97 \le F \le 99.71$; $p = 0.0001–0,0005$); subsequently, it allowed

[2] Chetyrkin E.M. Statistical forecasting methods. Moscow, Statistika Publ., 1977, 356 p. (in Russian).

us to consider elevated concentrations of these chemicals to be exposure markers.

Medical and biological examination involves obligatory assessment of critical organs and systems susceptible to negative effects produced by established chemical risk factors. Diseases are diagnosed basing on results obtained via clinical-functional and laboratory research techniques. In case a correlation between a nosology and exposure to a chemical is revealed, one should only take into account those diagnoses that occur much more frequently than among non-exposed people ($p \leq 0.05$) and correspond to functional disorders in damage organs or systems in a body.

When substantiating biomarkers of an effect, we took into account laboratory and functional parameters that reflected disorders in critical organs and systems and had significant deviations from physiological standards and from average parameters revealed in the reference group with frequency of occurrence exceeding 5 %. Subsequently, a correlation between a factor and a biomarker was established with a logistic model:

$$p_J^Z = \frac{1}{1+e^{-(b_0+b_1x_I)}}, \qquad (2)$$

where p_J^Z is a probability that j-th biomarker will deviate from physiological standards under impacts exerted by i-th factor;

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

b_0, b_1 are parameters applied in a mathematical model;

x_i is a value of i-th chemical factor.

Besides, we determined a correlation between a biomarker and a disease that is given with the following formula:

$$p_J^Y = \frac{1}{1+e^{-(b_0+b_1z_I)}} \qquad (3)$$

where p_J^Y is a probability that k-th disease will occur depending on a value of j-th biomarker;

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

b_0, b_1 are parameters applied in a mathematical model;

z_j is a value of j-th biomarker.

Under exposure to a set of factors a probability that j-th biomarker will deviate from the standard is given as:

$$p_j^Z = 1 - \prod_i (1 - p_{ij}^Z), \qquad (4)$$

where p_j^Z is a probability that j-th biomarker will deviate from standard.

Complex influence exerted by biomarkers on a probability that k-th disease might occur was given as:

$$p_k^Y = 1 - \prod_j (1 - p_j^Z p_{jk}^Y), \qquad (5)$$

where p_k^Y is a probability that k-th disease will occur.

Overall, when relationships are modeled sequentially within «exposure marker – laboratory / functional parameter of a response (biomarker) – disease» system, it allows revealing regularities in occurrence of diseases in respiratory organs and comorbid pathology (Figure).

Subsequently a probability p^Y that comorbid pathology would occur was determined as per the following formula:

$$p^Y = \prod_k p_k^Y. \qquad (6)$$

At the final stage we used (4) and put (5) into (6) thus obtaining an overall formula for determining a probability that comorbid pathologies might occur:

$$p^Y = \prod_k (1 - \prod_j (1 - (1 - \prod_i (1 - p_{ij}^Z)) p_{jk}^Y)). \qquad (7)$$

Regression analysis involved testing the obtained models in order to determine their relevancy and authenticity; to do that, we applied one-factor dispersion analysis and took into account Fischer's test value with 95 % significance, determination coefficient (R^2) and Student's t-test for significance being $p \leq 0.05$.

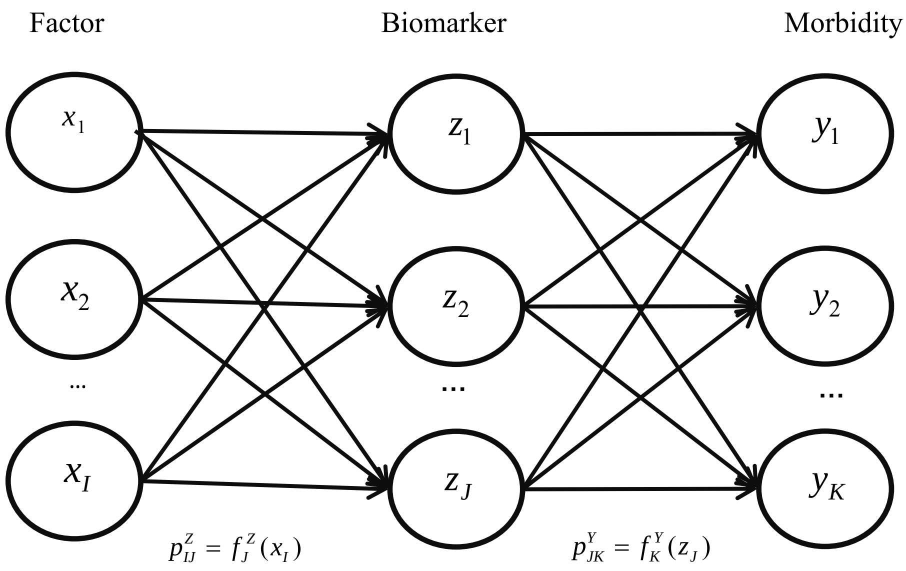

Figure. A graphic image showing results obtained via analyzing relations between comorbid pathology parameters

To establish biomarkers of an effect that were responses to increased concentrations of technogenic chemicals and that created pathogenetically justified relations, we comparatively analyzed internal relations within «exposure marker – laboratory / functional parameter of a response» system separately for exposed and non-exposed population.

Data obtained for the examined territory via performed sequential modeling allowed establishing biomarkers and cause-and-effect relations that characterized dependence between comorbid pathology development and deviations in markers under exposure to elevated concentrations of organic saturated alcohols, aldehydes, and particulate matter. We revealed several markers that predicted such negative effects as bronchial asthma (P^y = 0.13–0.29) and comorbid asthenoneurotic syndrome (P^y = 0.38–0.47) on the test territory where ambient air was contaminated with multi-component mixture of chemicals predominantly containing saturated alcohols, aldehydes, and particulate matter. Those markers included allergization index pathogenetically related to increased formaldehyde contents in blood (R^2 = 0.52; F = 193.67; p = 0.0001); increased contents of ionized calcium that was caused by increased phenol contents in blood (R^2 = 0.52; F = 193.67; p = 0.0001), creatine phosphokinase activity related to increased phenol and formaldehyde concentrations in blood (R^2 = 0.59–0.69; $533.28 \leq F \leq 1,028.48$; p = 0.0001); activity of C-reactive protein related to increased benzene contents in blood (R^2 = 0.42; F = 233.0; p = 0.0001); lower superoxide dismutase activity caused by increased formaldehyde, benzene, and phenol contents in blood (R^2 = 0.38–0.69; $188.63 \leq F \leq 287.67$; p = 0.0001) and average daily contents of particulate matter in ambient air (R^2 = 0.53; F = 291.03; p = 0.0001); a decrease in lungs vital capacity detected via spirography and depending on elevated methanol concentration in blood (R^2 = 0.41; F = 108.64; p = 0.0001), and a decrease in maximum volume velocity at FEF25 caused by increased benzene and phenol contents in blood (R^2 = 0.48–0.65; $324.95 \leq F \leq 613.16$; p = 0.0001); increased average systolic blood pressure in the lung artery related to increased phenol concentration in blood (R^2 = 0.83; F = 793.33; p = 0.0001) and average daily contents of particulate matter in ambient air (R^2 = 0.25; F = 42.13; p = 0.0001); and an increase in the range shown by heart rate study related to increased phenol concentration in blood (R^2 = 0.58; F = 485.6; p = 0.0001). We established that additional cases of these comorbid pathologies that were probabilistically related to increased methanol, formaldehyde, benzene, and phenol contents in blood and increased contents of particulate matter in ambient air could reach 14 %, and a contribution made by the examined chemicals into comorbid pathology development might be as high as 23.4 %.

So, markers predicting bronchial asthma (P^y = 0.13–0.29) and functional pathology in the gastrointestinal tract (P^y = 0.58–0.77) associated with aerogenic contamination with organic saturated alcohols, aldehydes, and particulate matter include elevated allergization index, ionized calcium contents, creatine phosphokinase and C-reactive protein activity, systolic blood pressure in the lung artery, the range in heart rate, lower superoxide dismutase activity, lower lung vital capacity and maximum volume velocity at FEF25. Apart from them, we should also mention an increase in total bilirubin contents related to elevated benzene, phenol, formaldehyde, and methanol concentrations in blood (R^2 = 0.32–0.61; $58.93 \leq F \leq 517.70$; $p = 0.0001$). A number of additional bronchial asthma cases and comorbid functional pathology in the gastrointestinal tract that are probabilistically associated with increased methanol, formaldehyde, benzene, and phenol contents in blood and increased contents of particulate matter in ambient air can amount to 15 %, and a contribution made by the examined chemicals into comorbid pathology development might be as high as 14.2 %.

All the obtained data allow developing individual prevention programs based on established common pathogenetic mechanisms explaining how bronchial asthma and comorbid asthenoneurotic syndrome and functional pathology in the gastrointestinal tract develop simultaneously.

Conclusions. Suggested methodical approaches to assessing risks of comorbid pathologies occurrence under multi-component exposure to environmental factors have great practical value as they allow establishing correlation within «environment – population health» system, predicting population and individual risks of environmental diseases; all this is an obligatory component in giving evidence that damage was done to health during sanitary-epidemiologic investigations, inspections, and examinations.

When comorbid diseases formation under exposure to adverse multi-component chemical factors is examined with the suggested algorithm for risk assessment, it allows spotting out key components in pathogenesis of these diseases occurrence; it can give grounds for developing relevant medical and prevention programs.

Overall, use of suggested mathematical analysis procedures is aimed at making health risk management more efficient and minimizing health risks existing on territories where people live under combined exposure to various adverse chemicals that contaminate the environment.

Funding. The research was not granted any sponsor support.

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

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Received: 12.08.2020
Accepted: 05.11.2020
Published: 30.12.2020

UDC 613; 614
DOI: 10.21668/health.risk/2020.4.07.eng

Read online

Research article

EMERGENCE AND VARIABILITY OF INFLUENCE EXERTED BY WEATHER AND CLIMATIC FACTORS ON LIFE EXPECTANCY IN THE RUSSIAN FEDERATION TAKING INTO ACCOUNT DIFFERENTIATION OF RF REGIONS AS PER SOCIOECONOMIC AND SANITARY-EPIDEMIOLOGIC DETERMINANTS

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The present research focuses on estimating influence exerted by weather and climatic factors on life expectancy (LE) in the Russian Federation taking into account socioeconomic and sanitary-epidemiologic determinants. To estimate influence exerted by this factor on LE, a mathematic model was applied; the model was based on neuron networks and allowed taking into account emergence and variability of influence exerted on changes in LE by a set of heterogeneous factors including weather and climatic ones.

It was established that over 2010–2018 climate changed in most RF regions as there was a growth in average monthly temperatures (temperature deviated from its long-term average monthly values by +1.2 ºC in July, and by +1,5 ºC in January),and changes in precipitations (deviations amounted to -1.9% in July and +13.0 % in January). It was established that «average monthly temperature in July» exerted the greatest direct influence on LE; thus, if this parameter grows by 1 %, it results in additional 1.7 days of LE.

«Average precipitations quantity in January» turned out to be the most significant factor leading to a decrease in LE; a 1 % growth in this parameter resulted in LE decrease by 0.12 days. It was shown that mathematical expectancy of LE loss variability in RF regions obtained basing on 85 scenarios of weather and climatic conditions ranged from -4.2 days to 348.7 days. Overall in the RF climate-associated losses in LE taken as weighted average as per population number amounted to 191.7 days. It was established that climate-associated losses in LE were authentically lower in North Caucasian regions than in regions located in temperate zone with Atlantic-continental and continental climate (by 1.6 and 1.8 times accordingly). We also comparatively analyzed losses in LE due to influence exerted by climate in RF regions distributed into different groups (clusters) as per socioeconomic parameters; the analysis revealed authentic differences between the second and the fourth cluster (p=0.01), and between the third and the fourth ones (p=0.006). We didn't reveal any authentic differences in climate-associated losses in LE among clusters as per sanitary-epidemiologic parameters.

Key words: *life expectancy, climate, weather-climatic factor, global climatic change, artificial neuron networks, factor analysis, RF population, demographic policy in the RF.*

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Research on consequences that result from global climatic change performed worldwide and by Russian scientific experts as well highlights substantial influences exerted by this change on people's health. And publications tend to present a considerable number of facts confirming both direct and indirect, but predominantly negative, impacts exerted by these examined processes on human health.

Basic theses contained in reports issued by the Intergovernmental Panel on Climatic Change (IPCC) state that over a period slightly longer than 100 years global temperature has risen by approximately 1.0 °C; an increase in average sea level is caused by the World Ocean getting warmer and glaciers and snow melting; the latter also leads to depletion of drinking water resources. Experts believe a primary reason for global warming is worldwide increase in greenhouses gases emissions due to industrialization that is taking place in many countries; basic predictions for this century are limited to a temperature rise equal to 1.5–2.0 °C [1, 2].

The issue is vital for all countries in the world, including the RF; given that, in 2004 the country ratified the Kyoto Protocol and in 2016 the Paris Agreement was signed (has not yet come into force)[1, 2, 3] [3]. These international treaties are based on the United Nations Framework Convention on Climate Change with its primary goal being reduction in greenhouse gases emission as it will allow stabilizing the climatic system on the planet thus reducing overall health risks for the mankind[4].

As for the Russian Federation, there is the Climatic doctrine in the national legislation with its primary goal being «…to provide safe and sustainable development of the RF including institutional, economic, ecological, and social, including *demographic*, aspects under changing climatic conditions…»[5]. Apart from the Climatic doctrine, there are several ecological projects that are now implemented in the RF and are aimed at finding solutions to issues related to climatic change. In particular, «Ecology» National project declares among its goals a 22 % reduction in aggregated emissions volumes by 2024 in large industrial centers and it will allow minimizing health risks and reducing medical and demographic losses[6].

According to the Report made by Rosgidromet on climatic risks existing on the RF territory climate in the country is warming significantly faster (by 2.5 times) than on average in the world; the process in the most intense in the Arctic and sub-Arctic zones in the RF. Apart from temperature growth in the ground atmosphere there is also change in quantity of precipitations, especially in winter and spring, in eastern and northern regions in the country where we can expect a significant increase in them in this century[7].

The report also dwells on a growing threat related to hazardous weather and climatic phenomena that cause up to 90.0 % of the most noticeable economic losses. According to statistic data provided by the document, a number of such phenomena grew considerably from 150–200 in 1990–2000 to 250–300 in later years and this number tended to only grow. Floods, droughts, and other hazardous natural phenomena become more and more frequent, and moreover, their intensity grows resulting in even greater economic and demographic burden caused by climatic factors.

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[1] The Paris Agreement. The United Nations Organization (UNO), 2015, 19 p.

[2] The Kyoto Protocol to the United Nations Framework Convention on Climatic Change. *The United Nations Organization (UNO)*, 1997. Available at: https://www.un.org/ru/documents/decl_conv/conventions/kyoto.shtml (30.09.2020) (in Russian).

[3] On ratifying The Kyoto Protocol to the United Nations Framework Convention on Climatic Change: The Federal Law issued on November 4, 2004 г. No. 128-FZ. Laws, codes, and regulatory acts in the Russian Federation, 2004. Available at: https://legalacts.ru/doc/federalnyi-zakon-ot-04112004-n-128-fz-o/ (30.09.2020) (in Russian).

[4] The United Nations Framework Convention on Climatic Change. *The United Nations Organization (UNO)*, 1992. Available at: https://www.un.org/ru/documents/decl_conv/conventions/climate_framework_conv.shtml (30.09.2020) (in Russian).

[5] On the Climatic doctrine of the Russian Federation: The RF President Order issued on December 17, 2009 No. 861-rp. *KonsultantPlus*, 2009. Available at: http://www.consultant.ru/document/cons_doc_LAW_94992/ (30.09.2020) (in Russian).

[6] The profile of «Ecology» National project. Approved by the Presidium of the RF Presidential Council on strategic development and national projects (The meeting report dated December 24, 2018 No. 16), 2018, 48 p. (in Russian).

[7] The report on climatic risks existing on the Russian Federation territory. Saint-Petersburg, 2017, 106 p. (in Russian).

Besides, we can expect overall increase in heat waves duration with simultaneous fall in cold waves.

Conclusions on influence exerted by weather and climatic factors on people's health tend to be rather uncertain and allow only approximate estimates since most climate-related changes in the environment reflect only its indirect influence on human health. The only certainty here can be found regarding direct losses caused by natural disasters that result in thousands deaths annually as well as more intense phenomena such as heat waves that lead to an increase in number of deaths among people who suffer for cardiovascular and respiratory diseases, especially elderly people and urban population [4].

Indirect causes that result in increase in morbidity and mortality among population associated with weather and climatic factors include the following: a threat to food security (droughts, hail, and floods), growing areas where infectious agents are active and longer seasons when transmissible infections (malaria) can be caught, poorer drinking water quality and depletion of its reserves (diarrhea), climatic migration, etc [5]. This burden is going to be especially grave in developing countries where public healthcare systems will be unable to cope with the imminent danger. According to estimates made by the World Health Organization climatic changes occurring over 2030–2050 will raise an annual number of climate-related deaths up to 250 thousand, 38 thousand of them being due to impacts exerted by heat on susceptible population groups; 108 thousand, due to malaria and diarrhea; 95 thousand, due to hunger among children [4].

Conclusions made by experts are validated with results obtained via scientific research performed both in Russia and abroad and focusing on climatic change and related population health risks. Experts are starting to pay greater attention to impacts exerted by heat and cold waves on population mortality.

H. Achebak et al. accomplished a national examination in Spain and revealed that too high or too low temperatures created an elevated relative risk (RR) of deaths due to circulatory system diseases. The authors noted there were certain age and sex related peculiarities in such mortality; thus, women ran higher risks than men when the weather was hot and the same was true for people older than 90 against those aged 60–74 [6].

Research performed by M. Medina-Ramon and J. Schwartz involved examining a large sampling of cities in the US; the authors revealed that extreme temperatures (heat and cold) resulted in increased mortality due to myocardial infarction; and though mortality caused by respiratory diseases went down due to higher temperatures, this effect was negligible bearing in mind growing heat-related mortality caused by other diseases [7].

L. Zhang et al. state in their research work that there is a tight correlation between a socio-economic situation existing on a specific territory where heat waves occur and an increase in morbidity among population, especially among elderly people [8]. Research performed in China revealed that heat waves resulted in losses on potential years of life (YLL[8]), and it was true both for sub-tropical and moderate-continental climatic zones. Besides, a cumulative effect produced by heat waves is higher than a single impact and it is much more apparent among elderly people [9, 10].

Several researchers state that an increase in mortality occurring against global climatic change will be due to not only weather and climatic factors but also related increase in ozone and particulate matter (PM) contents in ambient air [11–14]. There are also data on probable influence exerted by the climatic factor on life expectancy (LE) that indicate that LE has gone down by 0.12–0.39 years on average in Europe, and some countries are expected to face a considerably greater decrease in LE [15].

B.A. Revich and D.A. Shaposhnikov focused on examining impacts exerted by popu-

[8] YLL – years of life lost (years of life lost due to untimely deaths).

lation health on territories in the RF where climate was extremely continental. They revealed that there was an authentic increase in risks of elevated mortality due to all natural death causes, especially due to strokes caused by heat waves (RR = 1.44 for people older than 65). Impacts exerted by cold waves were less apparent but they were also characterized with authentic values (RR = 1.11) [16]. Similar results were obtained for other weather-related criteria such as wind and cold index, efficient air temperature, and universal thermal climate index[9] [17].

Having generalized scientific data and experts opinions on impacts exerted by weather-climatic factors on population health, we can conclude that most of them indicate that there are wide-scale and sometimes even catastrophic effects related to increased mortality and, consequently, a decrease in life expectancy. But at the same time global warming that becomes apparent via average temperatures rising by 1–2 °C can make a climate in certain regions a bit milder; in its turn, it can cause a slight decrease in effects produced by extreme natural phenomena.

Experts from Rosgidromet are inclined to make similar conclusions; they state that «…there can be certain positive outcomes brought about by climate change in Russia; overall, one can mention better climatic conditions for agriculture, increase in water supply, and longer navigation along the Northern Sea Route. An existing trend for the heating season to become shorter and a rise in its average temperature (up to

0.8 °C/10 years in the central Yakutia) raises heat efficiency of buildings and constructions and creates conditions for reduction in energy consumption…»[10] [18]. Predicted improvements in various branches caused by climatic change can also become apparent via population health improvement and reduction in medical and demographic risks.

Since most RF regions are located in zones where climatic conditions are rather harsh, a direct transfer of most scientific conclusions is not substantiated, and the issue requires additional research. Moreover, scientific research practically never covers such tasks as assessing a contribution made by existing weather and climatic factors on population health taking into account socioeconomic, sanitary-epidemiologic, and other living conditions.

Our research goal was to assess emergence and variability of impacts exerted by weather and climatic factors on life expectancy in the Russian Federation taking into account socioeconomic and sanitary-epidemiologic conditions.

Data and methods. To assess impacts exerted by weather and climatic conditions on life expectancy among the RF population taking into account socioeconomic and sanitary-epidemiologic factors, we examined a system of cause-and-effect relations between parameters that described all the spheres and living conditions that were included into 6 groups (determinants): «public healthcare», «sanitary-epidemiologic welfare on a given territory», «economic situation», «socio-demographic parameters», «weather and climatic conditions on a given territory».

The examination involved applying system analysis procedures and relied on official statistical data provided by the Federal Statistic Service. Cause-and-effect relations were analyzed with a created mathematical model based on neural networks.

When creating the model, we took weather and climatic conditions as our initial (independent) parameters; apart from them we also took parameters that described socioeconomic and sanitary-epidemiologic situa-

[9] Shartova N.V., Shaposhnikov D.A., Konstantinov P.I., Revich B.A. Universal thermal climate index applied to determine thresholds of temperature-related mortality. *Health Risk Analysis*, 2019, no. 3, pp. 83–93. DOI: 10.21668/health.risk/2019.3.10.eng

[10] The second estimate report made by Rosgidromet on climate change and its outcomes on the RF territory. Section 6. Impacts exerted by climate change on economic entities and population health. Ways to adapt to these impacts. Moscow, Federal Service for Hydrometeorology and Environmental Monitoring Publ., 2014, pp. 43–56. (in Russian).

tion as well as parameters related to lifestyle that were examined in detail in previous research works[11,12]. Average monthly temperatures and precipitations quantity in July and January were taken as weather and climatic conditions as well as their deviations from average long-term values in a given RF region over 2010–2018[13]. Life expectancy in RF regions was a dependent variable in our model and was estimated basing on data provided by the Federal State Statistic Service over 2010–2018[14].

We modeled cause-and-effect relations basing on all the collected data that reflected spatial and time distribution of all the examined parameters. As there were too many variables included into the model and multiple internal correlations, we reduced initial data dimensions via factor analysis; as a result, our initial scheme that included 148 parameters (socioeconomic, sanitary-epidemiologic, and weather and climatic ones) was transformed into one containing 33 common factors.

Cause-and-effect relations were modeled basing on creating a neural network model that took into account multiple and non-linear relationships between separate parameters. The neural network was trained basing on common factors values calculated for each RF region and LE parameter.

We applied the trained neural network model for cause-and-effect relations that showed impacts exerted by a set of parameters on life expectancy to solve two analytical tasks; the first one was to assess parameters as per intensity of their impacts exerted on LE; the second task was to assess a contribution made by existing weather and climatic conditions into loss of LE years.

To solve the first task, we made model calculations of changes in life expectancy under sequential 1 % increase in each analyzed parameter in comparison with average country levels. This examination allowed obtaining averaged comparative assessments of changes in life expectancy for each parameter that were used as a criterion for ranking.

A contribution made by weather and climatic factors into life expectancy was determined basing on series of numerical experiments that reflected probable changes in LE in RF regions in case of changes in independent variables. To do that, we sent signals on the input layer in the neural network that were actual and scenario values of sanitary-epidemiologic, socioeconomic, and weather and climatic conditions transformed into common factors via factor analysis. Difference in predicted LE values calculated with scenario and actual values of variables was used as a measure for probable changes in life expectancy associated with changes in the examined factors (1):

$$\Delta LE_j^k = F(\widetilde{X}_j^k) - F(\widetilde{X}_j^0), \qquad (1)$$

where ΔLE_j^k is a change in life expectancy in j-th RF region under k-th scenario impacts exerted by factors, days;

$F(\widetilde{X}_j^k)$ is in life expectancy in j-th RF region assessed as per the neural network model in accordance with k-th scenario impacts exerted by factors, days;

$\widetilde{X}_j^k$ is a vector of initial variables into the neural network model corresponding to the j-th RF region according to k-th scenario impacts exerted by factors after factor transformation has been completed;

$F(\widetilde{X}_j^0)$, $\widetilde{X}_j^0$ are values corresponding to zero scenario which means all the variables were given actual values determined in a given region.

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[11] Zaitseva N.V., Onishchenko G.G., Popova A.Yu., Kleyn S.V., Kiryanov D.A., Glukhikh M.V. Social and economic determinants and potential for growth in life expectancy of the population in the Russian Federation taking into account regional differentiation. *Health Risk Analysis*, 2019, no. 4, pp. 14–29. DOI: 10.21668/health.risk/2019.4.02.eng

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

[13] Russian statistical annual bulletin. 2019: Statistical data collection. *Rosstat*. Moscow, 2019, 708 p. (in Russian).

[14] RF regions. Socioeconomic parameters. 2019: P32 Statistical data collection. *Rosstat*. Moscow, 2019, 1204 p. (in Russian).

Each scenario in a numeric experiment involved fixing all the variables except parameters reflecting weather and climatic conditions; values of the latter were sequentially equated with values existing in a given RF region. Overall, we developed and examined 85 scenarios (number of regions).

An RF region with the greatest LE losses was determined in each of 85 models showing climatic conditions which was conditionally considered to be the most «prosperous» in an analyzed scenario: when weather and climatic conditions were applied in the model, their influence resulted in maximum decrease in LE in it thus showing that this region had «better» weather and climatic parameters against model ones regarding losses in life expectancy. This «prosperous» region was used as a reference one in a given scenario and losses in LE caused by weather and climatic model parameters in other RF regions were determined in comparison with it. Losses in life expectancy for each region were assessed as per difference between calculated changes and values obtained for a conditionally «prosperous» region (2):

$$\delta LE_j^k = \min_j(\Delta LE_j^k) - \Delta LE_j^k, \qquad (2)$$

where δLE_j^k is losses in life expectancy in j-th RF region under k-th scenario impacts exerted by factors, days.

To get ultimate assessment, we averaged all values obtained as per 85 scenarios (3):

$$\overline{\delta LE_j} = 1/K \sum_k \delta LE_j^k, \qquad (3)$$

where $\overline{\delta LE_j}$ are averaged losses in life expectancy in j-th RF region as per k-th scenario impacts exerted by factors, days;

Regional assessments of LE losses were generalized for the country as a whole basing on weighted averaging where resident population number was used as a weight coefficient (4):

$$\overline{\delta LE_{Р\Phi}} = \frac{\sum_j N_j \overline{\delta LE_j}}{\sum_j N_j}, \qquad (4)$$

where $\overline{\delta ОПЖ_{Р\Phi}}$ is average weighted losses in life expectancy in the RF, days;

N_j is population number in j-th RF region, people.

Cause-and-effect relations between the examined parameters were modeled and subsequent calculations were performed within RStudio medium («neural net» package) with neural networks instruments.

We assessed climate-related losses in life expectancy in RF regions classified as per socioeconomic and sanitary-epidemiologic parameters basing on the results obtained via our previous research which allowed us to distribute RF regions into several clusters according to these determinants[9,10].

Results and discussion. According to official state statistic data most RF regions (68 to be exact) are located in moderate climatic zones with Atlantic-continental and continental climate with 84.9 % RF population living there. 6 RF regions are located in Arctic and sub-Arctic zones with arctic and sea climate types combined (2.4 % RF population). 10 RF regions have mountain climate that is typical for the North Caucasus, Altai, and the Sayan Mountains (8.6 % RF population)[15].

We comparatively analyzed the examined weather and climatic factors and revealed that over 2010–2018 average deviations from average long-term temperatures in January and July on average grew by 1.7 °C in January (from –1.0 °C to 3.3 °C) and by 1.3 °C in July (from –0.7 °C to 2.3 °C), several regions excluded. Deviations exceeded climatic average monthly standard and it confirmed predictions as regards global warming. Besides, there were changes in average deviations from average long-term precipitations (more than ± 20.0 % from the standard) that fell in January and July

[15] Russian regions. Basin characteristics of the RF regions. 2019: Statistic data collection. *Rosstat*. Moscow, 2019, 766 p. (in Russian).

in 33 RF regions: the most substantial deviations were registered in January as average deviation from average long-term average monthly value was equal to 13.0 % (from -47.8 % to 146.6 %); the same deviation in July amounted to (–1.9 %). We also analyzed absolute temperatures averaged over 2010–2018; the analysis revealed the following RF regions with the warmest weather in January: Crimea (+1.4 °C), Krasnodar region (+0.8 °C), and Adygei Republic (+0.5 °C). Regions with the coldest weather in July were Chukotka (+10.1 °C), the Nenets Autonomous Area (+11.7 °C), and Kamchatka (+13,3 °C). Astrakhan region has the hottest weather in July with average long-term temperature there being equal to +26.8 °C in this month.

While building a neural network model based on a set of the examined weather and climatic parameters of the RF regions we managed to select an optimal network structure that consisted of two internal layers containing 8 and 3 neurons accordingly and was characterized with the maximum determination coefficient R^2 = 0,78.

We assessed how intensely the examined parameters influenced life expectancy; the assessment revealed that socioeconomic and social-demographic parameters were priority ones as they occupied the first 15 rank places; for example, if there was a 1 % growth in «Working hours per 1 employed on average per 1 week» parameter, LE grew by 6.1 days; a 1 % growth in «A share of employable population, %» parameter resulted in 5.1 additional days; a 1 % growth in «A share of employable population aged 15–72 with higher education, %» parameter, 4.8 additional days; etc.

As for weather and climatic conditions, the greatest influence on life expectancy was exerted by «average monthly temperature in July». Thus, on average in the country a 1 % growth in the parameter led to LEB growing by 1.7 days. Apart from this parameter, a 1 % growth in other parameters in July, such as «deviation from average long-term precipitations rate in July», «deviation from average long-term temperature in July», and «average long-term precipitations in July» resulted in calculated LE growth by 0.4 days, 0.18 days, and 0.16 days accordingly. «Average long-term precipitations in January» turned out to be the most significant parameter resulting in LE decrease as 1 % growth in it led to LE reducing by 0.12 days. An increase by 1 % in the remaining analyzed weather and climatic factors in January («average monthly temperature in January», «deviation from average long-term temperature in January», «deviation from average long-term precipitations rate in January») also caused a decrease in life expectancy, excluding «average monthly temperature in January» since growth in the latter resulted in LE growth (Table 1). All these estimations are made for the country on average and do not take regional peculiarities into account. Given that, all obtained results can be applied and interpreted within limits imposed by federal generalization and limits of a neural network model application.

Scenario modeling that took regional parameter values into account allowed us to obtain differential estimations for emergent influence exerted by weather and climatic factors on life expectancy in specific regions. Figure 1 shows results obtained via regional estimates of life expectancy losses caused by impacts exerted by weather and climatic factors and obtained via scenario modeling as per 85 climatic models.

Our study that included 85 weather and climatic scenarios for each RF region allowed revealing that losses in life expectancy caused by climatic factors influence varied substantially in different regions, from –4 days to –349 days (Figure 1).

Spotting out specific clusters on the RF territory as per losses value (Figure 1) clearly demonstrates that they tend to grow in north-eastern direction; it correlates with a well-known phenomenon which is called «northern-eastern gradient of growth in mortality» in scientific literature [19, 20]. And it should be noted that weather and climatic conditions also change in this direction, so we can tentatively conclude that future warming will probably result in climate becoming milder in most RF regions and, consequently, in certain growth in life expectancy.

Table 1

Averaged changes in life expectancy of RF population caused by changes in the examined weather and climatic factors given in relevant measurement units (Celsius degrees, millimeters), by 1 %

Parameter	Changes in LE (in days) given:		Neural network model application limits, range:	
	A 1 % increase in the parameter	An increase by 1 measurement unit (Celsius degrees, millimeters)	from	to
Average monthly temperature in July, °C	1.68	8.83	7.2	29.2
Average monthly precipitations in July, mm	0.16	0.22	3.0	319.0
Deviation from average long-term temperature in July, °C	0.18	16.82	–4.2	5.8
Deviation from average long-term precipitation rate in July, %	0.35	0.35	4.0	359.0
Average monthly temperature in January, °C	0.08	0.64	–39.4	3.5
Average monthly precipitations in January, mm	–0.12	–0.33	2.0	169.0
Deviation from average long-term temperature in January, °C	–0.04	–2.8	–7.4	8.9
Deviation from average long-term precipitation rate in January, %	–0.08	–0.07	7.0	350.0

Figure 1. Averaged losses in life expectancy in RF regions caused by influence exerted by weather and climatic factors and obtained basing on 85 climatic models, days

Averaged weighting of all the obtained results revealed that overall LE losses due to weather and climatic factors in the RF amounted to 191.7 days. Basic factors that determine this value include average monthly temperature in July (approximately 76 %), deviation from average long-term precipitation rate in July (15.8 %), and deviation from average long-term temperature in July (8.1 %).

We also analyzed averaging results as per regions located in different weather and climatic zones; the results are given in Figure 2.

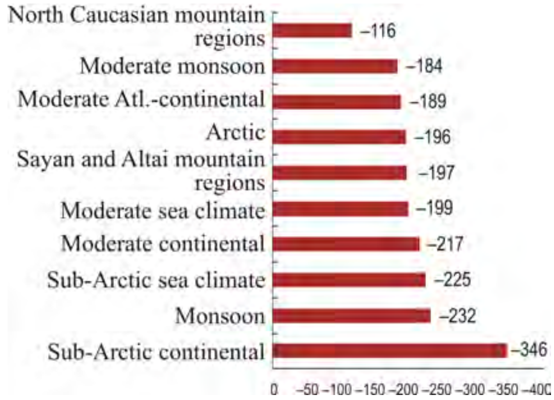

Figure 2. Averaged LE losses caused by weather and climatic factors taken as per average weighted value according to population number in RF regions distributed into groups as per climatic zone they are located in, days

This analysis allowed detecting certain peculiarities that occurred due to impacts exerted by a set of parameters being specific and variable.

Variability and emergence of impacts exerted by climatic factors had its influence on LE losses associated with these factors in RF regions located in different climatic zones (latitude zoning). Thus, LE losses in regions located in moderate zones with Atlantic-continental climate (50 regions) on average amounted to –189 days (varying from –244 in Karelia to –4 days in Kalmyk Republic) (Figure 3). Variability of climate-associated LE losses is caused by aggregated impacts exerted by multidirectional climatic factors but to a greater extent it is determined by temperatures in January (varying from –16.7 °C to +1.6 °C; average value in the zone is (–8.5 °C); in the RF, (–12.0 °C)) and July (varying from +11.7 °C to +26.8 °C; average value in the zone is (+20.2 °C); in the RF, (+19.2 °C)), precipitations in January (varying from 16.3 mm to 92.1 mm; average zone value is 43.7 mm; in the RF, 35.7 мм) and July (varying from 18.6 mm to 93.6 mm; average value in the zone is 66.9 mm; in the RF, 72.4 mm).

Climate-associated LE losses in zones with moderate continental climate (12 RF regions) amounted to –217 days on average (the range was from –283 days in Krasnoyarsk region to –133 days in Buryatia). LE losses in this climatic zone are due to comparatively low temperatures in January (–20.6 °C; in the RF, –12.0 °C) and July (+17.5; in the RF, +19.2 °C); at the same time precipitations in January are comparatively lower (18.6 mm; in the RF, 35.7 mm), and in July, comparatively higher (78.4 mm; in the RF, 72.4 mm) than on average in the country.

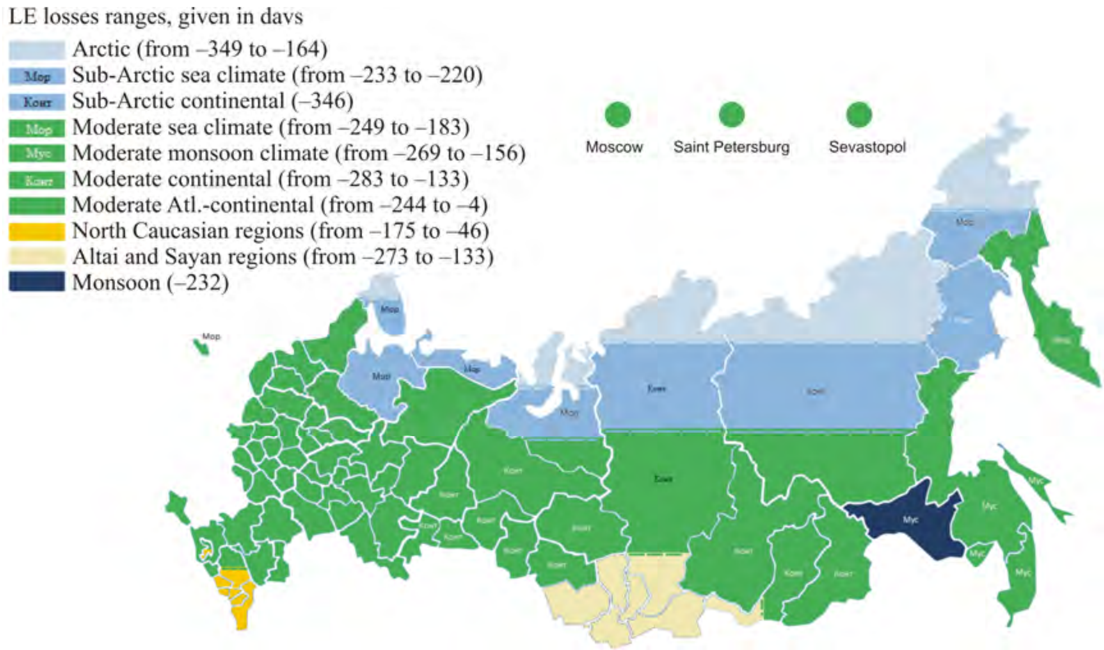

Figure 3. A map showing climatic zones and climate types in RF regions and occurring climate-associated LE losses, days (if a regions has several climatic zones they are shaded with a respective color)

The greatest climate-associated LE losses occur in Magadan region located in a sub-Arctic zone with continental climate; LE losses there amounted to –346 days (Figures 1 and 3). Substantial LE losses in the region are caused by low temperatures in January (–27.2 °C; in the RF, –12.0 °C) and July (13.9 °C; in the RF, 19.2 °C) as well as relatively low precipitations in July (61.8 mm; in the RF, 72.4 mm).

The smallest LE losses caused by weather and climatic factors are detected in RF regions located on territories with mountain North Caucasian climate (5 RF regions); average losses there amounted to –119 days with their range varying from –175 in North Ossetia to –46 days in Kabardino-Balkaria (Figures 1 and 3). Low LE losses in regions located in this climatic zone are mostly due to higher temperatures in January (–1.87 °C; in the RF (–12.0 °C)) and in July (+22.9 °C; in the RF, +19.2 °C) as well as lower precipitation in January (26.9 mm; in the RF, 35.7 mm).

These data indicate that climate-associated losses in life expectancy are substantial in most RF regions and it requires developing and implementing compensatory activities, including those aimed at improving socioeconomic parameters and providing support for population living in regions located in zones with adverse weather and climatic conditions.

Comparative analysis of LE losses in different climatic zones revealed authentic discrepancies (as per Mann-Whitney test) between regions located in North Caucasian mountain zones and regions located in moderate zones with Atlantic-continental climate ($p = 0.002$) and with continental climate ($p = 0.003$).

Results obtained via the analysis allowed making a hypothesis on probable mutual or one-directional influence exerted by socioeconomic, sanitary-epidemiologic, and weather and climatic factors. To prove it, we performed preliminary calculations of average LE losses for regions distributed into specific groups (clusters) as per socioeconomic and sanitary-epidemiologic parameters described in our previous works[9,10].

We comparatively analyzed LE losses caused by weather and climatic factors in clusters with different socioeconomic situation in RF regions. The analysis revealed that the greatest LE losses occurred in the 1st cluster that included 2 RF regions. Regions included into this cluster are located in an Arctic zone and a zone with moderate Atlantic-continental climate. Average climatic-associated LE losses in the cluster amounted to –236 days (The Yamal-Nenets Autonomous Area, –237 days; the Nenets Autonomous Area, –164 days). Certain economic parameters were high in the cluster including investments into capital assets and gross regional product per capita. But at the same time criminal rate, alcohol consumption, and a share of dilapidated housing were also high in the cluster and it could potentiate negative impacts exerted by weather and climatic factors and created additional risks of greater LE losses. Thus, the cluster included regions that were among those with the lowest temperatures in July (12.5 °C; in the RF, 19.2 °C) and the lowest precipitations in July (37.1 mm; in the RF, 72.4 mm) as well as with comparatively more significant deviation from average long-term temperature in July (1.5 °C; in the RF, 1.1 °C).

The second cluster occupies the 2nd rank place following the descending order in climate-associated LE losses. Economic parameters are relatively high there, unemployment rate is low, and public healthcare is qualitative; but at the same time, alcohol sales per capita, divorce rate, and crime rate are rather high. Averaged weighted LE losses amounted to –208 days (the range varied from –349 days in Chukotka to –164 in Yakutia). The cluster includes 6 RF regions located in zones with Arctic, sub-Arctic continental, moderate Atlantic-continental, and continental climate. Climate-associated LE losses in these regions are caused by relatively low temperatures in January (on average (–21.5 °C); in the RF (–12.0 °C)) and July (14.5 °C; in the RF 19.2 °C), lower precipitations in July (63.3 mm) than on average in the country (72.4 mm), and lower deviation from average long-term temperature in July (0.9 °C; in the RF, 1.1 °C).

Regions included in the 3rd cluster had the following specific features: most analyzed socioeconomic parameters there corresponded to average country levels; registered unemployment was low; consumption of basic food products was close to recommended levels; high divorce and crime rates; high share of population older than employable age (25.5 %). Average LE losses in these regions amounted to –203 days with the range varying from –283 days (Krasnoyarsk region) to –137 days (Krasnodar region). Regions included into this cluster (31 overall) are located in zones with moderate Atlantic-continental, continental, and sea climate and tend to have lower temperatures in July (on average 18.6 °C; in the RF, 19.2 °C) and January (–12.7 °C; in the RF (–12.0 °C), higher precipitations in January (37.2 mm; in the RF, 35.7 mm), and greater deviation from average long-term precipitations rate in July (100.4 %; in the RF, 98.0 %).

The 4th cluster turned out to have the lowest LE losses due to weather and climatic factor with average cluster value being –175 days; it varied from –273 days (Khakassia) to –4 (Kalmyk Republic). Socioeconomic parameters in the cluster include low crime rate, low divorce rate, low share of dilapidated housing, and the lowest alcohol sales per capita among all clusters. But still, some economic parameters such as share of housing equipped with centralized water supply, sewage, and heating and public healthcare quality are also rather low. Regions included into this cluster are located in zones with moderate Atlantic-continental climate and continental climate as well as in zones with North Caucasian mountain climate, Altai and Sayan mountain climate. Diverse climatic conditions in the region caused variability in climate-associated LE losses. Climate-associated LE losses were relatively low in the cluster due to the following factors: relatively low precipitations (71.2 mm; in the RF, 73.3 мм), more substantial deviation from average long-term precipitation rate in January (118.2 %; in the RF, 116.8 %); factors that led to growth in LE included relatively high temperatures in January (–10.0 °C; in the RF, (–11.2 °C)) and July (+20.4 °C; in the RF, +19.7 °C).

Our comparison between clusters that were determined basing on socioeconomic differentiation of RF regions allowed us to reveal authentic discrepancies (as per Mann-Whitney test) in climate-associated LE losses between the 2nd and the 4th cluster ($p = 0.01$), as well as between the 3rd and the 4th cluster ($p = 0.006$) (Figure 4a).

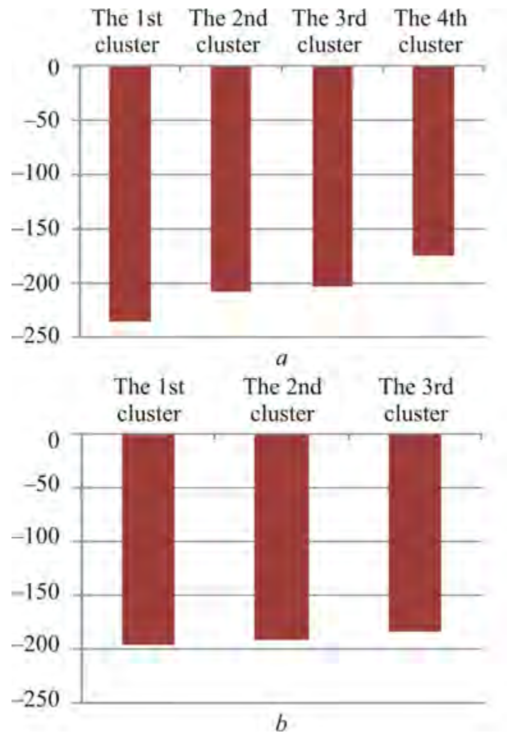

Figure 4. Averaged LE losses caused by weather and climatic factors given in averaged weighted values as per population number in RF regions distributed into several clusters with different socioeconomic (a) and sanitary-epidemiologic (b) parameters, days

We comparatively analyzed LE losses caused by weather and climatic factors in clusters with different sanitary-epidemiologic situation in regions included into them; the analysis didn't reveal any significant discrepancies. Climate-associated LE losses averaged weighted as per population number amounted to –196 days in the 1st cluster; –191 days and –184 days in the 2nd and the 3rd clusters accordingly (Figure 4b)[10]. The results indicate that weather and climatic parameters exert the same impacts (LE losses) on regions with different sanitary-epidemiologic situation and they are similar to average country level.

Accomplished preliminary analysis allowed revealing combined emergent and variable influence exerted by weather and climatic conditions and socioeconomic determinants on

LE: the phenomenon requires more profound examining and assessing. Basing on the results obtained via the present research we can only conclude that effects produced by these factors can either mutually enhance or weaken each other and they should be taken into account when planning and implementing programs aimed at improving socio-demographic situation in RF regions bearing regional differentiation in mind.

Given that we can't manage weather and climatic factors and our ability to adapt to them is rather limited as well as a significant contribution made by them into changes in LE, we can conclude that these factors should be given special attention and taken into account when implementing programs aimed at improving socio-demographic situation in RF regions.

Conclusions. Basing on the accomplished research work we can conclude the following:

1. Over the last decades climate changed in many RF regions, especially in arctic and subarctic zones and in the eastern part of the country as well; as per the last estimates, changes occurred at a rate 2.5 times higher than on average in the world. Ground air temperatures and precipitations underwent the greatest changes (average deviations from average long-term temperatures in July over 2010–2018 amounted to +1.2 °C, in January +1.5 °C; the same deviations in precipitations quantity amounted to –1.9 % in July and +13.0 % in January).

2. Global processes related to climate change indicate that weather and climatic conditions tend to become milder in most RF regions; in its turn, it can result in living conditions becoming more comfortable and consequent health improvement and longer life expectancy in these regions. Our research on a system of cause-and effect relations between socioeconomic, sanitary-epidemiologic, and weather and climatic indicates that it is necessary to study multidirectional consequences of global warming in greater detail. The research results revealed that provided that there are mo drastic climatic changes life expectancy is likely to grow in RF regions in case average temperature increases. Thus, regularities obtained for the country in general show that an increase in average temperature in July results in LE growing by 8.83 days and by 0.64 days in case in increases in January. These results are limited by a model definition range: from +7.2 °C to +29.2 °C in July; from –39.4 °C to +3.5 °C in January; they do not take extreme changes in climatic and weather conditions into account.

3. Most people in the RF live in climatic zones with conditions that are far from being optimal; it causes losses in life expectancy associated with weather and climatic factors. Our estimations revealed that climate-associated LE losses amounted to –191.7 in the RF on average but losses in regions varied from –4 days (in Kalmyk Republic) to –349 days (in Chukotka).

Basic factors that cause LE losses include socioeconomic conditions as they occupy 15 first rank places among all the parameters. Average temperature in July exerts the most significant impacts as it accounts for approximately 76 % LE losses on average in the country.

4. We comparatively analyzed LE losses caused by emergence of weather and climatic factors as per climatic zones. The analysis revealed that climate-associated LE losses in regions located in the North Caucasian mountain zones were authentically lower than in regions located in moderate zones with Atlantic-continental and continental climate (by 1.6 and 1.8 times accordingly). Thus, LE losses varied from –283 to –4 days in zones with moderate climate where most RF population lived (84.9 %); they were on average caused by high precipitations in January (38.4 mm; in the RF, 35.7 mm) and deviations from average long-term temperatures (1.6 °C; in the RF, 1.5 °C) and precipitations (115.0 mm; in the RF, 113.4 mm) in January. LE losses varied from –175 days to –46 days in the North Caucasian mountain climatic zones where 4.5 % RF population lived; these losses were determined by on average relatively higher temperature in January (–1.87 °C; in the RF, –12.0 °C) and July (+22.9 °C; in the RF, +19.2 °C) as well as lower precipitations in January (26.9 mm; in the RF, 35.7 mm).

5. The research allowed revealing effects produced by combined exposure to weather-climatic and socioeconomic factors and it requires more profound examination in future research works.

6. It is extremely important to implement national and regional programs aimed at prolonging life expectancy as it will improve demographic situation in the country; given that, impacts exerted by unmanageable factors, including weather and climatic ones, should be taken into account as significant components in achieving targets fixed within such programs.

In future works the authors plan to continue studying combined, share, and mutual impacts exerted by weather and climatic, socioeconomic, and sanitary-epidemiologic determinants on population health in the Russian Federation.

Funding. The research was not granted any sponsor support.

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

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Received: 02.09.2020
Accepted: 03.12.2020
Published: 30.12.2020

UDC 617.753.2-053.5:681.3
DOI: 10.21668/health.risk/2020.4.08.eng

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Research article

LONG USE OF DIGITAL DEVICES AS A RISK FACTOR THAT CAUSES MYOPIA OCCURRENCE IN SCHOOLCHILDREN

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Use of digital devices results in much higher health risks for children caused by greater visual and static loads, low physical activity, intensified intellectual activity, and psychological discomfort.

The article focuses on results obtained in examining reasons why schoolchildren from the 1st, 5th, 9th, and 11th grade use various digital devices, how frequently they do it and for how long they use mobiles, PC, pads, or laptops. All schoolchildren use digital devices, most frequently, mobile phones and PC. Almost ¾ children in the 1st grade use a mobile phone; half of them, a PC, 1/3 use a pad; and each fifth schoolchild uses a laptop. Practically all 5th grade children use a mobile phone; two thirds, a PC; half of them, a laptop or a pad. Also practically all senior schoolchildren use a mobile phone; three quarters, a PC; one third, a laptop; pads are used much less frequently. A number of used digital devices per 1 person grows with age, from 1.8 for 1st grade children to 2.6 for 5th grade children and 2.3 for senior schoolchildren. Average duration of digital devices use per day also grows from 3 hours for 1st grade children to 8.1 hours for senior schoolchildren.

Most schoolchildren tended to have diseases of the eye, namely refraction and accommodation disorders; accommodation disorders prevailed among 1st grade children, and myopia was more frequent among 5th grade children and senior schoolchildren. A number of children with myopia grows by 2.1 times during school years. Relative risk calculation revealed that if digital devices are in use for 6 hours or longer, it results in 1.8 times higher risks of myopia.

Key words: *schoolchildren, questioning, digital devices, duration of use, eyesight disorders diagnostics, diseases of the eye, myopia, relative risk.*

Electronic digital devices play a significant positive role in our everyday life as they have become our irreplaceable assistants in many spheres [1]. In this era of information technologies children start using various digital devices in early childhood [2–5]. With their parents' permission children get acquainted with information technologies in their childhood years and impacts exerted by IT on children's life become more and more intense as they grow up [2]. On the one hand, when children master digital skills, it makes for development of intellectual component in their human potential. Children who use digital appliances tend to have better developed thinking skills, memory, attention, imagination, and digital competences [1–2]. On the other hand, computers, laptops, pads, mobile phones, and smartphones do not bring only benefits; they can also produce negative effects on human health, especially when it comes to a growing person [6–9]. At present there are practically no wide-scale national studies that focus on the issue.

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Digital environment brings about a substantial increase in health risks for children related to greater visual and static loads, low physical activity, intensified intellectual activities, and psychological discomfort [6, 10–12]. Lifestyle pursued by children nowadays differs significantly from that of previous generations as it is characterized with low physical activity, shorter amounts of time spent outdoors, and a lot of study [11]. All this, together with active use of gadgets and digital devices, effects produced by new hygienic factors, and permanent exposure to electromagnetic radiation creates risks of mental and physical health disorders [12]. Uncontrollable use of digital devices often results in bad body posture, poorer eyesight, headaches, increased blood pressure, poorer attention concentration, psychoemotional strain, and gadget-dependency [13–18]. Use of laptops during lessons in primary school does not provide a possibility to maintain a proper working posture for a child even if furniture conforms to all safety requirements related to pupils' height. It results in greater risks of visual disorders and disorders of the musculoskeletal system [19].

Duration and correct use of digital devices in educational process at schools is standardized and children are involved in different kinds of activities during a lesson; this diversity helps reduce negative effects on health [19–22]. There are safety parameters for schoolchildren work with electronic resources fixed in relevant regulations [19]. There is an integral hygienic assessment procedure used for assessing a child's working posture when he or she works with a PC and a procedure for determining whether visual fatigue has occurred in a schoolchild [19, 21]. But such activities are not regulated at all when children use digital devices at home during their free time [2–3].

If we want to assess effects produced by digital devices on children's health, we have to analyze time spent by them using such devices and try to determine whether children from different age groups use such devices for different periods of time. A.A. Shabunova and A.V. Korolenko established that the highest health index values occurred in children who used a PC or a smartphone rather rarely and it indicates that it is necessary to control frequency and periods of time spent by children on use of digital devices [2].

In a contemporary society eye disorders in children are considered to be one of the most significant medical and social problems. At present, «myopia epidemic» concept is widely used in Russia. When children start school, 2.4 % of them are already short-sighted. By the 5th grade a share of short-sighted children grows by 8 times, reaching 19.7 %. By the 11th grade, myopia frequency among schoolchildren is close to European levels and amounts to 36.8 % [14]. There are a lot of research works on risks of myopia development in childhood and a great amount of them are published by foreign authors [14, 17–18]. Some experts have examined effects produced by digital devices, PC or a mobile phone in particular, on children's eyesight [6–7, 14, 17–18]. When parents pay attention to visual activities performed by their children, it can result in significantly lower risks of myopia development. Control over use of electronic digital devices leads to a more than 2-time decrease in risks of myopia development for children [14].

Our research goal was to characterize use of various digital devices and determine risks caused by their long use and related to eye diseases occurrence in children during their school years.

Data and methods. We questioned 140 first-grade pupils, 170 fifth-grade students, and 204 senior schoolchildren (9–11 grades) who attended secondary schools in Ivanovo; questioning was aimed at determining frequency, duration, place and purpose of using various digital devices. We also performed certain examinations in order to diagnose visual disorders in these schoolchildren; our examinations involved autorefractometry, visual acuity test, and non-direct ophthalmoscopy. Data were statistically processed with conventional variation statistics procedures using licensed applied software packages «Microsoft Office 2010» and «Statistica for Windows 6.0». Discrepancies were considered to be statistically authentic at $p < 0.05$. We used licensed

«OpenEpi 303» software program to calculate relative risk (RR). Relative risk is used to compare probability of an outcome depending on a risk factor occurrence. RR is used in studies when examined groups are made up depending on whether a risk factor is present or absent. In case a RR value exceeds 1, a conclusion is made that a risk factor increases frequency of an outcome (a direct relation).

Results and discussion. Questioning revealed that all the first-grade pupils frequently used digital devices. A mobile phone (71.4 %) and a PC (51.4 %) were used more frequently than a pad (35.6 %) and a laptop (18.6 %) (Table 1).

45.7 % first-grade pupils used a mobile phone every day; 18.6 %, 2–3 times a week; 5.7 %, once a week; 1.4 %, less than once a week. 18.6 % first-grade pupils used a mobile phone for less than 1 hour during a day; 25.7 %, for 1 hour; 24.3 %, for 2–4 hours; 2.9 %, for longer than 6 hours. All children stated that they used a mobile phone at home; beside that, 5.7 % used it at school and 4.3 % at other places. First-grade pupils most frequently used a mobile for games (78 %); watching short clips (51 %); communication (30 %); searching for information (20 %); painting (18 %); reading (6 %); modeling and animation (6 %). 28.6 % first-grade students didn't use a mobile phone at all.

Half of first-grade pupils (51.4 %) used a PC; 12.9 % out of them did it every day; 18.5 %, 2–3 times a week; 7.1 %, once a week; 12.9 %, less than once a week. 24.3 % first-grade pupils used a PC for less than 1 hours a day; 15.7 %, for 1 hour; 10.0 %, for 2–4 hours; 1.4 %, for more than 6 hours. All children stated that they used a PC at home; besides, 1.4 % children sued it elsewhere. First-grade pupils used a PC most frequently for watching movies or short clips (58.3 %) and games (55.6 %); less frequently for painting (25 %), searching for information (22.2 %), communication (5.6 %), information input (5.6 %), modeling and animation (2.8 %), and creating presentations (2.8 %). 48.6 % first-grade pupils didn't use a PC at all.

One third of first-grade pupils (35.6 %) used a pad; 15.7 % out of them did it every day; 7.1 %, 2–3 times a week; 1.4 %, once a week; 11.4 %, less than once a week. 11.4 % first-grade pupils used a pad for less than 1 hours a day; 11.4 %, for 1 hour; 10.0 %, for 2–4 hours; 1.4 %, for more than 6 hours. 96 % first-grade pupils stated that they used a pad at home; besides, 4 % children sued it elsewhere. First-grade pupils used a PC most frequently for games (92 %), watching movies or clips (40 %), and painting (40 %); less frequently for searching for information (28 %), communication (8 %), modeling and animation (8 %), reading (4 %), and information input (4 %). 64.4 % first-grade pupils didn't use a PC at all.

First-grade pupils used a laptop much less frequently than other digital devices (18.6 %). There were no first-grade pupils who used a laptop every day; 5.7 % used it 2–3 times a week; 4.3 %, once a week; 8.6 %, less than once a week. 10.0 % first-grade pupils used a laptop for less than 1 hour a day; 8.6 %, 1 hour. 92.3 % children stated they used a laptop at home, and 7.7 % did it elsewhere. First-grade pupils used a laptop most frequently for watching movies or short clips (69.2 %) and games (38.5 %); less frequently, for searching for information (23.1 %), painting (23.1 %), communication (7.7 %), and reading (7.7 %). 81.4 % first-grade pupils didn't use a laptop at all.

Table 1

Frequency of digital devices use by schoolchildren (%)

Digital device	1 grade (*n* = 140)		5 grade (*n* = 170)		9–11 grades (*n* = 204)	
	use	don't use	use	don't use	use	don't use
Mobile phone	71.4	28.6	97.6	2.4	98.1	1.9
PC	51.4	48.6	69.1	30.9	77.4	22.6
Pad	35.6	64.4	48.2	51.8	18.6	81.4
Laptop	18.6	81.4	49.4	50.6	33.7	66.3

Fifth-grade students used digital devices more intensely than first-grade ones ($p < 0.001$). They also used a mobile phone (97.6 %, $p < 0.001$) and a PC (69.1 %, $p < 0.05$) more frequently than a pad (48.2 %, $p > 0.05$) or a laptop (49.4 %, $p < 0.001$).

80.0 % fifth-grade students used a mobile phone every day; 12.9 %, 2–3 times a week; 4.7 %, once a week. 7.1 % fifth-grade students used a mobile phone for less than 1 hour during a day; 22.4 %, for 1 hour; 42.3 %, for 2–4 hours; 5.8 %, for 4–6 hours; and each fifth student (20 %) used it for longer than 6 hours a day. 95.2 % fifth-grade students stated that they used a mobile phone at home; beside that, more than half of them (56.6 %) used it at school and 47 % at other places. Fifth-grade students most frequently used a mobile for games (75.9 %); communication (74.7 %); searching for information (73.5 %); watching short clips (62.7 %); less frequently, for reading (45.8), painting (22.9 %); information input (18.1 %), creating presentations (16.9 %), and modeling and animation (8.4 %). 2.4 % fifth-grade students didn't use a mobile phone at all.

Two thirds of fifth-grade students (69.1 %) used a PC; each forth of them (25 %) did it every day; each fifth (20.2 %), 2–3 times a week; 10.7 %, once a week; 13.1 %, less than once a week. 17.6 % fifth-grade students used a PC for less than 1 hours a day; 27 %, for 1 hour; 16.5 %, for 2–4 hours; 5.9 %, for 4–6 hours; 2.4 %, for more than 6 hours. Most fifth-grade students (93.2 %) stated that they used a PC at home; besides, 25.4 % children used it at school and 3.4 % at other places. Fifth-grade children used a PC most frequently for searching for information (72.9 %), watching movies or short clips (54.2 %), games (49.2 %), and creating presentation (40.7 %); less frequently, for reading (27.1 %), communication (23.7 %), painting (15.3 %), information input (13.6 %), and modeling and animation (5.1 %). One third of fifth-grade (30.9 %) students didn't use a PC at all.

Half of fifth-grade students (48.2 %) used a pad; 23.5 % out of them did it every day; 8.2 %, 2–3 times a week; 7.1 %, once a week; 9.4 %, less than once a week. 9.4 % fifth-grade students used a pad for less than 1 hours a day; 20 %, for 1 hour; 15.3 %, for 2–4 hours; 3.5 %, for more than 6 hours. 95.1 % fifth-grade students stated that they used a pad at home; 12.2 % did it elsewhere. Fifth-grade children used a pad most frequently for games (78 %) and searching for information (51.2 %); less frequently, for reading and painting (29.3 % each activity), communication (22 %), watching movies and short clips (19.5 %), information input (7.3 %), and creating presentations (2.4 %). 51.8 % fifth-grade students didn't use a pad at all.

Also half of fifth-grade students (49.4 %) used a laptop. 4.7 % out of them did it every day; 17.6 %, 2–3 times a week; 11.8 %, once a week; 15.3 %, less than once a week. 16.5 % fifth-grade students used a laptop for less than 1 hours a day; 20 %, for 1 hour; 8.2 %, for 2–4 hours; 3.5 %, for 4–6 hours; 1.2 %, for more than 6 hours. Most fifth-grade students (97.6 %) stated that they used a laptop at home; 2.4 % did it at school and 4.8 %, elsewhere. Fifth-grade children used a laptop most frequently for searching for information (61.9 %), watching movies and short clips (52.4 %), games (45.2 %), and creating presentations (40.5 %); less frequently, for reading (21.4 %), communication and information input (19 % each activity), and painting (14.3 %). 50.6 % fifth-grade students didn't use a laptop at all.

Senior students attending 9–11 grades also used a mobile phone (98.1 %) and a PC (77.4 %) more frequently, but they used a laptop and a pad significantly less frequently than fifth-grade students (33.7 %, $p < 0.05$ and 18.6 %, $p < 0.001$, accordingly). Practically all senior schoolchildren used a mobile phone every day (92.3 %); 4.9 %, 2–3 times a week; 0.9 %, once a week. 1.9 % senior schoolchildren used a mobile phone for less than 1 hour during a day; 5.9 %, for 1 hour; one third (30.1 %), for 2–4 hours; 26.2 %, for 4–6 hours; and one third (34 %) used it for longer than 6 hours a day. As opposed to first-grade pupils and fifth-grade students, senior schoolchildren used a mobile phone everywhere; 95.1 % did it at home, 80.2 % at school and elsewhere. Senior schoolchildren most frequently used a mobile for searching for information (92.1 %), communication (86.1 %), and watching short clips

(66.3 %); less frequently, for reading (57.4 %), games (43.6 %), information input (43.6 %), creating presentations (11.9 %), painting (5 %), and modeling and animation (2.9 %). 1.9 % senior schoolchildren didn't use a mobile phone at all.

Two thirds of senior schoolchildren (77.4 %) used a PC; more than one third of them (39.2 %) did it every day; each fifth (20.6 %), 2–3 times a week; 4.9 %, once a week; 12.7 %, less than once a week. 16.5 % senior schoolchildren used a PC for less than 1 hours a day; 10.7 %, for 1 hour; one forth (25.2 %), for 2–4 hours; 12.6 %, for 4–6 hours; and 12.6 %, for more than 6 hours. Most senior schoolchildren (93.6 %) stated that they used a PC at home; besides, 26.5 % used it at school and 12.7 % at other places. Senior schoolchildren used a PC most frequently for searching for information (89.8 %), creating presentations (67.1 %), watching movies or short clips (65.8 %), and communication (60.8 %); less frequently, for games (50.6 %), information input (35.4 %), reading (30.4 %), modeling and animation (7.6 %), and painting (2.5 %). 22.6 % senior schoolchildren didn't use a PC at all.

One third of senior schoolchildren (33.7 %) used a laptop; 10.8 % did it every day; 14.9 %, 2–3 times a week; 3 %, once a week; 5 %, less than once a week. 9.7 % senior schoolchildren used a laptop for less than 1 hours a day; 7.8 %, for 1 hour; 11.7 %, for 2–4 hours; 1.9 %, for 4–6 hours; and 3.9 %, for more than 6 hours. All senior school-children stated that they used a laptop at home; besides, 17.6 % used it elsewhere. Senior schoolchildren used a laptop, just like a PC, most frequently for searching for information (85.8 %), watching movies or short clips (58.8 %), communication (55.9 %), and creating presentations (41.2 %); less frequently, for games (35.3 %), information input (20.6 %), reading (17.6 %), and painting, modeling and animation (5.9 % each activity). Two thirds of senior schoolchildren (66.3 %) didn't use a laptop at all.

Senior schoolchildren used a pad much less frequently (18.6 %); 6.9 % did it every day; 5.9 %, 2–3 times a week; 0.9 %, once a week; 4.9 %, less than once a week. 4.9 % senior schoolchildren used a pad for less than 1 hours a day; 3.9 %, for 1 hour; 5.8 %, for 2–4 hours; 0.9 %, for 4–6 hours; and 2.9 %, for more than 6 hours. All senior school-children stated that they used a pad at home; besides, 15.8 % used it at school and 21.1 % elsewhere. Senior schoolchildren used a pad most frequently for searching for information (57.9 %), communication (47.4 %), reading and games (42.1 % each activity); less frequently, for watching movies or clips (31.6 %), creating presentations (10.5 %), and information input (5.3 %). Most senior schoolchildren (81.4 %) didn't use a pad at all.

Therefore, when it comes to a specific digital device, school children use a mobile phone or a PC more frequently than a laptop or a pad. Almost ¾ first-grade pupils use a mobile phone, and half of them use a PC; each fifth also uses a laptop. On average each first-grade pupil uses 1.8 digital devices, predominantly a mobile phone, and an average time spent by a child on using digital devices amounts to 3 hours a day. Practically all fifth-grade students use a mobile phone; two thirds, a PC, half of them, a laptop or a pad. On average each fifth-grade student uses 2.6 digital devices, and average time spent by him or her on using various digital devices amounts to 6.3 hours a day. Practically all senior schoolchildren also use a mobile phone; ¾ teenagers use a PC; one third, a laptop; a pad is rather rare. On average each senior schoolchild uses 2.3 digital devices and average time spent by him or her on using various digital devices amounts to 8.1 hours a day. A number of used digital devices grows with age, from 1.8 for first-grade pupils to 2.6 for fifth-grade students and 2.3 for senior schoolchildren. Average time spent on using digital devices per day also grows from 3 hours for first-grade pupils to 8.1 hours for senior schoolchildren.

Complex ophthalmologic examination revealed that diseases of the eye and adnexa were rather frequent among schoolchildren (Table 2).

100 % first-grade pupils had diseases of the eye and adnexa. Refraction and accommodation disorders were the most frequent (98.4 %) with

Table 2

Frequency of detected diseases of the eye and adnexa among schoolchildren (%)

Diseases of the eye and adnexa	ICD-10 code	1 grade (n = 126)	5 grade (n = 168)	9–11 grades (n = 198)	p_{1-3}
		1	2	3	
Inflammation of eyelids (blepharitis)	H 01.0	–	1.2	–	
Lacrimal gland disorders	H 04.1	–	1.2	2.0	
Heterophoria	H 50.5	–	1.2	–	
Refraction and accommodation disorders including:	*H 52*	*98.4*	*84.4*	*93.0*	
– hypermetropia	H 52.0	12.7	13.1	1.0	$p = 0.0015$
– myopia	H 52.1	17.4	32.1	36.5	$p = 0.0098$
– astigmatism	H 52.2	14.3	8.3	20.2	$p > 0.05$
– anisometropia and aniseikonia	H 52.3	1.6	8.3	3.0	$p > 0.05$
– accommodation disoredrs	H 52.5	52.4	22.6	32.3	$p = 0.0111$
Visual disturbances including:	*H 53*	*1.6*	*10.8*	*3.0*	
– amblyopia ex anopsia	H 53.0	–	–	1.0	
– subjective visual disturbances	H 53.1	1.6	10.8	2.0	$p > 0.05$
Total with pathologies		**100**	**98.8**	**98.0**	
Without pathologies		**–**	**1.2**	**2.0**	

prevailing accommodation disorders (52.4 %). Besides, 17.4 % children had myopia; 14.3, astigmatism; 12.7 %, hypermetropia; 1.6 %, anisometropia and anisekonia. 1.6 % first-grade pupils had visual disturbances, in particular, subjective visual disturbances.

98.8 % fifth-grade students had diseases of the eye and adnexa. They also most frequently suffered from refraction and accommodation disorders (84.4 %) with prevailing myopia (32.1 %). 22.6 % fifth-grade students had accommodation disorders: 13.1 % suffered from hypermetropia; 8.3 %, from astigmatism, and 8.3 % from anisometropia and aniseikonia. Besides, 1.2 % fifth-grade students had inflammation of eyelids (blepahritis); 1.2 %, lacrimal gland disorders; 1.2 %, heterophoria; 10.8 %, subjective visual disturbances.

98 % senior schoolchildren had diseases of the eye and adnexa. As it was the case with first-grade students and fifth-grade ones, refraction and accommodation disorders were the most frequent (93 %) with prevailing myopia (36.55). 32.3 % senior schoolchildren had accommodation disorders; 20.2 %, astigmatism; 3 %, anisometropia and aniseikonia; 1 %, hypermetropia. Besides, 2 % senior schoolchildren had lacrimal gland disorders; 3 % had visual disturbances such as amblyopia ex anopsia (1 %) and subjective visual disturbances (2 %).

Therefore, a number of children with myopia grew by 2.1 times during school years ($p = 0.0098$), hypermetropia frequency went down by 12.7 times ($p = 0.0015$), and accommodation disorders frequency, by 1.6 times ($p = 0.0111$). Dynamics revealed in diseases of the eye and adnexa frequency among fifth-grade students was a bit ambiguous against first-grade pupils and senior schoolchildren. Astigmatism was 1.7 times less frequent in the 5th grade than in the 1st one; however, it became 2.5 times more frequent among senior schoolchildren. Accommodation disorders frequency followed the same trends as it fell by 2.3 times among fifth-grade students in comparison with first-grade ones and then grew by 1.4 times among senior schoolchildren. Anisometropia and aniseikopenia frequency, in its turn, grew by 5.3 times among fifth-grade students and fell by 2.7 times among those attending 9–11 grades. Hypermetropia fell one-way and myopia frequency grew one-way from the 1st grade to 9–11th.

Bearing in mind that senior schoolchildren spend 2.7 times more tome using digital devices than first-grade pupils ($p = 0.044$), a period of time during which various digital devices are used can be considered a risk factor that causes myopia occurrence in schoolchildren. Relative risk (RR) calculation revealed that in case digital devices are used for 6 hours a day or longer, there is 1.8 times higher risk of myopia occurrence (RR 1.8; 95 % CI 1.21–3.61, $p < 0.05$).

Conclusions.

1. All schoolchildren use digital devices quite intensely, PC and mobile phones being the most frequently used ones. A number of used digital devices grows with age, from 1.8 per a 1 first-grade pupil to 2.6 per a fifth-grade student and 2.3 per a senior schoolchild. Average time spent on using digital devices per day also grows from 3 hours for first-grade pupils to 8.1 hours a day per senior schoolchildren.

2. Most schoolchildren suffer from diseases of the eye and adnexa, in particular refraction and accommodation disorders; accommodation disorders prevail among first-grade pupils where as myopia is the most widely spread disease among fifth-grade students and senior schoolchildren. A number of children with myopia grows by 2.1 times from the 1st grade to senior school.

3. Use of digital devices for 6 hours a day or longer results in a 1.8 times higher risk of myopia.

Funding. The research was not granted any sponsor support.

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

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Received: 17.06.2020
Accepted: 24.11.2020
Published: 30.12.2020

UDC 614.72
DOI: 10.21668/health.risk/2020.4.09.eng

Read online

Research article

MARKERS SHOWING ALLERGIC REACTIONS IN CHILDREN CAUSED BY AEROGENIC EXPOSURE TO MANGANESE AND NICKEL COMPOUNDS

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High prevalence of allergic diseases among children and their close relation with quality of the environment require new approaches to organizing diagnostic and prevention activities.

Our research objects were 247 children attending pre-school children facilities (PSCF).

It was detected that children who permanently lived and/or attended a pre-school facility for not less than three years under long-term chemical aerogenic exposure to manganese and nickel compounds in low doses (0.17–0.23 MPC average daily) had contents of these metals in their blood that were 1.9–2.0 times higher than the same parameter in children from the reference group and 1.7–2.1 times higher than background level in the region. Pre-school children with their biological media being contaminated with nickel and manganese compounds suffered from atopic dermatitis, allergic rhinitis, and bronchial asthma 1.3–4.5 times more frequently ($0.23 \leq R^2 \leq 0.73$; $59.2 \leq F \leq 388.1$; $p \leq 0.001$).

Allergic diseases associated with aerogenic exposure to chemicals with sensitizing power have certain pathogenetic peculiarities such as active overall inflammatory reaction; sensitization in 54–86 % children (the parameter is 1.5–4.3 times higher than in the reference group); cellular metabolism disorder; depletion of antioxidant protection resources in 72 % children; deficient activity of phagocytic and humoral section in immunity (1.2 times lower than in the reference group); cytokine regulation disorders (2.4–2.5 time difference); reduced expression of a receptor that induces activation apoptosis; stronger sympathetic influence on heart rate modulation in 26.0 % children. Basing on statistical analysis and model making, we determined markers that showed occurring allergic reactions caused by aerogenic exposure to manganese and nickel compounds. These markers are targets for prevention activities; they include growth in allergic pathologies prevalence; these pathologies occurring together with chronic inflammatory-proliferative diseases and disorders in the vegetative nervous system; increased contents of leukocytes, eosinophils, and immunoglobulin E specific to nickel in blood; a decrease in phagocyte number and contents of IgM, IgA in blood serum ($0.07 \leq R^2 \leq 0.74$; $19.3 \leq F \leq 713.2$; $p \leq 0.0001$).

Key words: *allergic diseases, pre-school children, ambient air, chemicals with sensitizing power, manganese, nickel, markers.*

According to data obtained via multiple epidemiologic research both in Russia and abroad allergic diseases are among the most widely spread pathologies occurring in children [1–5]. It has been established that morbidity with certain allergic nosologies is 4.5 times higher among children living in large industrial centers where metallurgic and civil engineering enterprises and power industry are located and where traffic is intense than among children living on territories where sanitary-epidemiologic situation is relatively favorable. A leading factor that causes high prevalence of allergic pathologies among chil-

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dren living in cities with developed industries is ambient air being contaminated with chemicals that have sensitizing properties (lead, manganese, nickel, and chromium) as well as negative reactions summating or mutually potentiating each other [6–11].

Results obtained via monitoring over ambient air quality in large industrial centers indicate that certain metals (manganese and nickel compounds) persist in ambient air in them in concentrations that either adhere to the fixed hygienic standards or exceed them [12–15].

Being predominantly haptens, inhaled chemicals with sensitizing properties oxidize due to metabolism and combine with proteins thus creating specific complex antigens; these antigens induce releasing local inflammation mediators and histamine liberation [16]. Initially negative environmental factors act as triggers or primers that stimulate pathogenic processes in critical organs and systems together with destabilization in adaptation processes and damage done to resistance mechanisms [17–20].

It is necessary to develop new approaches to spotting out target population groups and determining relevant medical and preventive activities taking into account adverse effects occurring when biological media are contaminated with technogenic chemicals that have sensitizing properties. It will allow preventing high growth rates detected for morbidity with allergic diseases.

Our research goal was to determine markers that indicated allergic reactions occurrence in children associated with aerogenic exposure to nickel and manganese compounds.

Data and methods. Our test group included 107 children aged 5–7 who permanently lived and/or attended a pre-school children facility (PCF) on a territory where nickel and manganese compounds were contained in ambient air in concentrations equal to 0.17–0.23 average daily MPC. Our reference group was made up of 240 children attending a PCF who were not exposed to chemicals with sensitizing properties contained in ambient air. Both groups were comparable in terms of age and sex ($p > 0.05$).

Medical examinations were performed in conformity with the ethical principles stated in Helsinki Declaration (1964; last edited in October 2013). Prior to any examinations, parents or legal representatives gave their informed voluntary consent on medical intervention and personal data processing.

Nickel and manganese compounds contents were quantitatively determined in children's blood as per methodical guidelines 4.1.3230-14[1].

Medical and sociological data were obtained via questioning with parents participating in it.

Morbidity was analyzed as per data taken from medical documentation (Form No. 026/u-2000) and results obtained via medical examinations (performed by allergologists, otorhinolaryngologists, pediatricians, and neurologists).

Laboratory diagnostics included examining integral hematologic parameters, immunologic and metabolic status, non-specific resistance, sensitization, and oxidation-antioxidant processes.

Vegetative regulation was assessed via analyzing heart rate modulation performed with «Poly-Spectr-8/EX» program (Neurosoft, Ruissia).

Data were analyzed with Statistica 6.0 software package and specific software products that were compatible with MS-Office. We applied two-sample Student's t-test to compare both groups as per quantitative parameters. Dependence between parameters was assessed via one-factor dispersion analysis and correlation-regression analysis. To quantitatively determine closeness of correlations between parameters, we calculated odds ratio (OR) and its confidence interval (CI). Discrepancies between obtained results were considered statistically significant at $p \leq 0.05$.

Results and discussion. We performed chemical and analytical examination of ambi-

[1] MG 4.1.3230-14. Measuring mass concentrations of chemical elements in biological media (blood and urine) with mass spectroscopy with inductively coupled plasma. *KODEKS: an electronic fund for legal and reference documentation*. Available at: http://docs.cntd.ru/document/495856222 (12.09.2020) (in Russian).

ent air quality on territories where PCF were located (2014–2018); it revealed that nickel and manganese compounds persisted in ambient air on the test territory in quantities equal to 0.17–0.23 average daily MPC. Average nickel and manganese compounds contents amounted to 0.00014 ± 0.000029 mg/m^3 and 0.00019 ± 0.00004 mg/m^3 and it was higher than the same parameters on the reference territory (0.000012 ± 0.000002 mg/m^3 and 0.000025 ± 0.000005 mg/m^3, $p \leq 0.0001$).

Having analyzed technogenic chemicals contents in children's blood, we established that nickel and manganese compounds contents were 1.9–2.0 times higher in blood of children from the test group than in blood of those from the reference one (0.0047 ± 0.0013 against 0.0025 ± 0.0006 µg/cm^3 and 0.022 ± 0.012 against 0.011 ± 0.001 µg/cm^3 accordingly, $p \leq 0.0001$) and 1.7–2.1 times higher than the regional background level ($p \leq 0.001$). A share of blood samples with elevated nickel and manganese compounds contents was 2.5–2.6 times higher in the test group than in the reference one (72.7 % against 28.8 % and 57.1 % against 22.1 %, $p \leq 0.0001$–0.001; $4.6 \leq \text{OR} \leq 6.44$; $2.53 \leq \text{CI} \leq 12.2$; $0.0001 \leq p \leq 0.001$).

Sociologic research didn't reveal any statistically significant discrepancies between the analyzed groups as per social, medical-biological ($p > 0.05$) and other factors (including peculiarities related to surrounding plants and periods when they give pollen) that were able to cause similar health disorders in children.

We comparatively analyzed data taken from medical documentation (Form No. 026/u) and data obtained via medical examinations; the analysis revealed that pre-school children with high sensitizing chemicals contents in blood suffered from atopic dermatitis (L20.8, L20.9) 1.3 times more frequently (48.6 and 36,7 %, $p = 0.04$); allergic rhinitis (J30.3, J30.4), 1.4 times more frequently (25.0 and 18.4 %, $p = 0.04$); bronchial asthma (J45), 4.5 times more frequently (9.0 and 2.0 %, $p = 0.003$) than children from the reference group. A share of children with combined respiratory and skin allergies was 1.5 times higher among children from the test group (47.0 against 32.0 %, $p = 0.007$). We established an authentic correlation between higher morbidity among children with predominantly allergic asthma (J45.0), mixed asthma (J45.8), and atopic dermatitis (L20.8, L20.9) and increased manganese concentration in blood ($0.23 \leq R^2 \leq 0.52$; $59.2 \leq F \leq 279.5$; $p \leq 0.001$). A contribution made by nickel into predominantly allergic asthma (J45.0), allergy, unspecified (T78.4), and atopic dermatitis (L20.8, L20.9) can amount to 37.0–73.0 % ($130.6 \leq F \leq 388.1$; $p \leq 0.001$).

Respiratory diseases and certain immune disorders occurred accordingly in 94.0 % and 67.0 % children from the test group and it was 1.6 times more frequent than among children from the reference group (57.1 % and 41.0 % accordingly, $p \leq 0.001$). We established that aerogenic exposure to nickel and manganese compounds resulted in 2.9–11.0 times more frequent occurrence of diseases from these nosologic groups (ICD-10) (OR = 2.9–11.0; CI = 1.64–29.50; $p \leq 0.0001$). We comparatively analyzed frequency of specific respiratory nosologies and revealed that children from the test group suffered from chronic diseases of tonsils and adenoids (J35.0, J35.1, J35.2, J35.3, J35.8, J35.9) 3.0 times more frequently than children from the reference group (42.0 against 14.0 %, $p \leq 0.0001$). We established dependence between chronic diseases of tonsils and adenoids and nickel and manganese compounds contents in blood ($0.18 \leq R^2 \leq 0.73$; $45.03 \leq F \leq 713.2$; $p \leq 0.0001$). As for diseases of the nervous system, the most significant discrepancies between the examined groups were revealed for «Disorder of autonomous nervous system, unspecified» nosology (G90.9) as it was diagnosed in 19.0 % children from the test group and only 10.0 % children from the reference one ($p = 0.02$). A contribution made by nickel into autonomous nervous system disorders amounted to 44.0 %; by manganese, 74.0 % ($F = 214.3$–757.9; $p \leq 0.0001$).

We assessed changes in hematologic parameters and overall inflammation reactions in a body; the assessment revealed authentic discrepancies between contents of leukocytes ($7.50 \pm 0.33 \cdot 10^9/dm^3$), monocytes ($7.75 \pm 0.34$ %), and thrombocytes ($326.68 \pm 11.98 \cdot 10^9/dm^3$) in children from the test group and physiological standards ($p < 0.001$) as well as the same parameters in children from the reference group ($7.07 \pm 0.26 \cdot 10^9/dm^3$, 7.02 ± 0.24 %, $293.62 \pm 9.60 \cdot 10^9/dm^3$ accordingly, $p = 0.000–0.05$). A share of blood samples with elevated monocytes, leukocytes, and thrombocytes contents amounted to 89.7 %, 90.7 %, and 48.6 % accordingly in the test group and it was 1.2–1.6 times higher than the same parameters in the reference group (73.8 %, 45 %, 30.6 %, $p = 0.001–0.007$). We established a direct correlation between concentrations of nickel and its compounds in blood and monocytosis ($r = 0.12$, $p = 0.04$). There was also an authentic correlation between a probable increase in leukocytes contents in blood and elevated manganese concentration in blood with its contribution being equal to 26 % ($F = 97.2$; $p \leq 0.0001$).

Children with their biological media being contaminated with metals had elevated relative eosinophils contents in blood (4.38 ± 0.58 %) and their eosinophilic-lymphocytic index was also higher (0.108 ± 0.016 arb. units) than the physiological standard ($p < 0.0001$) and the same parameters in the reference group (3.17 ± 0.36 % and 0.07 ± 0.01 arb. units accordingly, $p \leq 0.001$). It indicated that specific regain cellular forms participated in inflammation. Primering effects produced by these chemicals on hyper-reactivity occurrence are confirmed by established dependence between eosinophilia intensity and manganese ($R^2 = 0.25$; $F = 93.2$; $p \leq 0.0001$) and nickel ($R^2 = 0.32$; $F = 126.9$; $p \leq 0.0001$) concentrations in blood.

Alkaline phosphatase tended to be less active in children from the test group (342.88 ± 12.41 against 366.84 ± 10.26 U/dm^3, $p \leq 0.001$) and it was probably due to membrane-toxic effects produced by manganese and active metabolic consumption occurring during biotransformation. Protein-forming functions performed by the liver were reduced in children with elevated chemicals with sensitizing properties in blood as it was indicated by lower overall protein (70.96 ± 0.89 g/dm^3) and albumins (42.40 ± 0.93 g/dm^3) contents in blood serum against the same parameters in the reference group (72.54 ± 0.59 g/dm^3 and 43.6 ± 0.59 g/dm^3, $p = 0.01–0.03$). We revealed an inverse correlation between nickel concentration and albumins contents in blood ($r = -0.162$, $p = 0.008$).

Antioxidant protection was depleted and it became apparent via lower plasma antioxidant activity (AOA) in 72 % children from the test group and it was 1.3 times higher than the same parameter in the reference group (53 %, $p = 0.001$). Average group AOA value was lower for children living under aerogenic exposure to manganese and nickel compounds than for children from the reference group (34.002 ± 1.09 against 35.911 ± 0.66 %, $p \leq 0.001$) and lower than the bottom limit of the physiological standard ($p < 0.0001$). Antioxidant reserves depletion was 2.3 times more probable among children from the test group than among those from the reference one (OR = 2.26, CI = 1.27–4.10; $p = 0.009$).

Th-1-dependent response tended to be inhibited in children with their biological media being contaminated with metals; it was characterized with a decrease in gamma-interferon as the most significant atopic processes regulator; its level was 2.4 times lower among children from the test group than in those from the reference one (3.26 ± 2.91 against 7.84 ± 3.25 pg/mL, $p = 0.03$).

Average VEGF protein contents was 2.5 times higher in children from the test group than in those from the reference one (172.88 ± 51.47 and 67.95 ± 20.10 pg/mL, $p < 0.0001$); this protein promotes allergic inflammation due to its ability to increase vascular permeability.

Despite there were no discrepancies in quantitative parameters showing overall immunoglobulin E (IgE) production in children from the examined groups (101.51 ± 35.12 and 78.84 ± 31.09 IU/mL, $p = 0.25$), elevated specific IgE levels were more frequently revealed in pre-school children from the test group as 53.6 % children had IgE specific to cat fur with its value being higher than the physiological standard (it was 2.3 times higher than the same parameter in the reference group, 23.1 %, $p < 0.0001$; OR = 3.08, CI = 2.09–7.07; $p < 0.0001$); 85.7 % children had IgE specific to Aspergillusniger (1.4 times higher than in the reference group, $p < 0.0001$; OR = 3.9, CI = 2.01–7.95; $p < 0.0001$). Average group values of IgE specific to *Dermatophagoides pteronissimus* and to *Aspergillus niger* were also authentically 2.5–4.3 times higher among exposed children than among those from the reference group (0.4 ± 0.14 against 0.16 ± 0.06 a.u. and 0.26 ± 0.09 against 0.06 ± 0.03 a.u., $p < 0.0001$). These detected peculiarities are related to technogenic chemical factors initially acting as primers and inducing sensitization. Immunoglobulin E specific to nickel was authentically 1.5 times higher in pre-school children from the test group than the same parameter in children from the reference one (0.28 ± 0.05 against 0.18 ± 0.02 IU/cm^3, $p < 0.0001$). We detected a statistically authentic cause-and-effect relation between IgE specific to nickel and nickel contents in blood ($R^2 = 0.49$; $F = 71.13$; $p \leq 0.0001$).

Children with their biological media being contaminated with manganese and nickel compounds tended to have hypofunction of the humoral section in the immunity as 64.2–72.5 % of them had lower immunoglobulin M (1.21 ± 0.04 g/dm^3) and G (10.16 ± 0.29 g/dm^3) contents in their blood serum than the physiological standard ($p < 0.0001$). IgM contents was 1.2 times lower among them than in children from the reference group (1.21 ± 0.04 g/dm^3 and 1.4 ± 0.06 g/dm^3, $p < 0.0001$), and a decrease in IgM contents was 4.0 times more probable in the test group (OR = 4.01, CI = 2.25–7.34; $p = 0.00$). We established an inverse correlation between nickel contents in blood and IgM concentration ($r = -0.133$, $p = 0.03$). We also established that children from the test group had lower IgA contents in their blood serum than their counterparts from the reference group (1.39 ± 0.07 against 1.49 ± 0.11 g/dm^3, $p < 0.0001$) and it was due to effects procured by nickel ($R^2 = 0.35$; $F = 144.75$; $p < 0.001$).

We analyzed non-specific resistance as per overall phagocytosis parameters and revealed that pre-school children from the test group had up to 1.2 times lower phagocytic index (1.82 ± 0.04 a.u.) and phagocytic number (0.88 ± 0.06 a.u.) than children from the reference group (2.06 ± 0.09 and 1.05 ± 0.11 a.u. accordingly, $p \leq 0.001$–0.01). 49.5 % children from the test group had lower phagocytic number and it was 1.6 times higher than the same parameter in the reference group (30.6 %, $p = 0.001$). A decrease in phagocytic number was 2.2 times more probable in children from the test group than in those from the reference one (OR = 2.2, CI = 1.25–3.96; $p = 0.01$). We established an authentic decrease in phagocytic number in case manganese contents in blood were elevated ($R^2 = 0.07$; $F = 19.3$; $p = 0.0001$).

65.0 % children who had sensitizing chemicals in their blood in quantities up to 2.1 times higher than the regional background level had lower expression of activation apoptosis induction receptor among CD95 + lymphocytes against the reference group (14.65 ± 2.45 against 23.95 ± 3.52 % and 0.43 ± 0.08·10^9/L against 0.68 ± 0.14·10^9/L, $p \leq 0.001$–0.002). A decrease in relative CD3+CD95+-lymphocytes contents was 7.2 times more probable and a decrease in their absolute quantity was up to 17.0 times more probable in children from the test group than in those from the reference one ($7.25 \leq OR \leq 17.36$; $3.92 \leq CI \leq 50.68$; $p < 0.0001$).

Non-specific mechanisms play a significant role in allergic reactions occurrence; in particular, we can mention imbalance between sympathetic and parasympathetic sections in the nervous system. Greater sympathetic influence on heart rate modulation was detected in each forth child from the test group (25.7 %) and it was 2.3 times more frequent than in the reference one (11.0 %, $p = 0.03$). Sympathetic regulation prevalence was 2.7 times more probable among pre-school children from the test group than among those from the reference one (OR = 2.7; CI = 1.3–6.05; $p = 0.01$).

We performed statistical analysis of data obtained via sanitary-hygienic, clinical-laboratory, and functional examinations; assessed dependence between parameters; built and analyzed relevant models. All this allowed us to establish markers and peculiarities of pathogenetic mechanisms responsible for negative effects occurrence such as allergic reactions in pre-school children living under long-term aerogenic exposure to chemicals contained in ambient air in low doses.

Key pathogenetic sections in allergic diseases occurrence under aerogenic exposure to technogenic chemicals with sensitizing properties (manganese and nickel compounds) include the following: a decrease in protein-forming function performed by the liver (↓albumins; $r = -0.162$, $p = 0.008$), inhibited humoral section in the immune response (↓IgM, IgA; $R^2 = 0.35$; $F = 144.75$; $p < 0.001$; $r = -0.133$, $p = 0.03$), and specific sensitization (↑IgE specific to nickel; $R^2 = 0.49$; $F = 71.13$; $p \leq 0.0001$) for nickel; lower phagocytic activity (↓ phagocytic number compounds; $R^2 = 0.07$; $F = 19.3$; $p = 0.0001$) for manganese; there are also sections related to nickel and manganese compounds contents in blood such as non-specific sensitization (↑eosinophils; $0.25 \leq R^2 \leq 0.32$; $93.2 \leq F \leq 126.9$; $p \leq 0.0001$), overall inflammation reaction activity (↑monocytes and leukocytes; $r = 0.12$, $p = 0.04$; $R^2 = 0.26$; $F = 97.2$; $p \leq 0.0001$).

Therefore, allergic reactions associated with aerogenic exposure to nickel and manganese compounds have the following markers: a 1.5 times increase in prevalence of combined allergic pathologies; comorbidity with chronic inflammatory-proliferative diseases (up to 3.0 times higher), disorders of the autonomous nervous system (up to 1.9 times higher); apparent non-specific (leukocytosis is 1.1 times higher) and immune (monocytosis is 1.3 times higher) inflammation; inhibited humoral section (IgM and IgA) and 1.2 times lower phagocytic activity (phagocytic number); specific sensitization (1.5 times higher IgE specific to nickel); non-specific sensitization (1.5 times higher eosinophilia); depleted antioxidant protection (1.1 times lower AOA).

Established markers are target ones for diagnostic and preventive activities. Basic preventive activities aimed at reducing or eliminating allergic reactions caused by aerogenic exposure to chemicals with sensitizing properties should include the following: a decrease in chemicals contents in a body; sanitation of chronic infection foci such as ENT organs; reduction in inflammation processes activity; recovery of antioxidant protection and vegetative homeostasis; immune response modulation.

Conclusions:

1. Atopic dermatitis, allergic rhinitis, and bronchial asthma were diagnosed 1.3–4.5 times more frequently among children from the test group than among children from the reference group ($0.23 \leq R^2 \leq 0.73$; $59.2 \leq F \leq 388.1$; $p \leq 0.001$) since children from the former group lived under long-term aerogenic exposure to nickel and manganese compounds in low doses (0.17–0.23 average daily MPC) and had these compounds in their blood in contents 1.7–2.1 times higher than the regional background level.

2. Pre-school children with elevated nickel and manganese compounds in their blood had certain pathogenetic peculiarities detected in their bodies regarding allergic diseases such as overall inflammatory reaction activity (60.7–89.7 % children); sensitization (53.6–85.7 % children); depleted antioxidant reserves (72.0 % children); cellular metabolism disorders and disorders of the humoral and phagocytic sections in the immunity (49.5–72.5 % children); apoptosis regulation disorders (65.0 %); intra-cellular interaction disorders and vegetative imbalance (25.7 % children).

3. We established markers of allergic reactions associated with aerogenic exposure to chemicals with sensitizing properties (nickel and manganese compounds) that were target ones for preventive activities. They included humoral section (IgM, IgA) inhibition and spe-

cific sensitization (IgA specific to nickel) caused by effects produced by nickel ($0.35 \leq R^2 \leq 0.49$; $71.13 \leq F \leq 144.75$; $p \leq 0.001$); lower phagocytic activity (phagocytic number) caused by exposure to manganese ($R^2 = 0.07$; $F = 19.3$; $p = 0.0001$); non-specific sensitization (eosinophils) and inflammation (leukocytes) caused by exposure to nickel and manganese ($0.25 \leq R^2 \leq 0.32$; $93.2 \leq F \leq 126.9$; $p \leq 0.0001$).

Funding. The research was not granted any sponsor support.

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

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Received: 29.09.2020
Accepted: 21.11.2020
Published: 31.12.2020

UDC 604.6: 613.2
DOI: 10.21668/health.risk/2020.4.10.eng

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Research article

ANALYSIS OF GMO CONTENTS AS A COMPONENT IN RISK-ORIENTED SURVEILLANCE OVER FOOD PRODUCTS SAFETY

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Control over use of genetically modified products is a vital task within a risk-oriented model for surveillance over food safety products all over the world including the Russian Federation.

Our research goal was to examine domestically manufactured food products in order to determine whether they contained certain regulatory sequences typical for genetically modified organisms.

We applied polymerase chain reaction with hybridization-fluorescent detection in real time mode to examine 77 food products samples; the task was to determine whether they contained DNA enhancer (E-35S) and promoter (P-35S) of S35 sequence belonging to cauliflower mosaic virus, terminator of nopaline synthase gene from Agrobacterium tumefaciens (T-NOS), 35S enhancer (E-FMV) and promoter (P-FMV) of Figwort mosaic virus, as well as vegetable DNA inducing soya DNA.

When analyzing the extracted DNA, we didn't detect transgenic elements in any samples; however, there were vegetable components reveled in them including 68.8 % samples with soya DNA. We established that some sausages were falsified as they contained vegetable elements. In 15.6 % cases data on a product structure turned out to be false because soya DNA was not listed on consumer package. Our research on determining soya DNA and transgenic elements in food products indicates that soya ingredients have been added into food products in spite of their absence in relevant documents as recipe components.

All the obtained results taken into account, we assume it is necessary to improve control procedures for detecting genetically modified and vegetable components used as ingredients in food products as their falsification can make for changes not only in their consumer properties but also damage consumers' health.

Key words: *genetically modified organisms, enhancers, promoter, terminators, polymerase chain reaction, DNA soya, vegetable DNA, falsification, food products safety.*

Genetic engineering has been developing intensely over recent years and it has resulted in creation of new selection technologies based on targeted modification in plant genome [1]. Every year plants with genetically modified hereditary properties are produced in larger quantities and more widely applied in agriculture [2]. Genetic modification gives them spe-

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cific properties that increase their resistance to adverse climatic factors, pests, pesticides, and diseases [3, 4]. According to the latest data genetically modified cultures are grown on almost 200 million hectares worldwide [5]. New lines of transgenic plants are created every year in spite of all concerns related to insufficiently examined impacts exerted by genetically modified organisms (GMO) on human health and the environment [6–8]. We should note that at present, according to data provided by the International Service for the Acquisition of Agri-biotech Applications (ISAAA), there are 526 genetically modified (GM) lines of 32 plant species registered all over the world [9]. 27 GM-cultures out of them are allowed to be used in the Russian Federation (15 corn lines, 10 soya lines, 1 beetroot line, and 1 rice line); however, GM-plants can be grown only on test land spots [10][1]. Nevertheless, we can run across food products on the market, both domestically produced and imported ones, that are made from GMO-containing ingredients [11, 12].

Issues related to GM-products safety and control over their application are being discussed all over the world [13–15]. Thus, a threshold level for food GM-products marking in Japan amounts to 5 %; in Australia and New Zealand, 1 %; and in the EU countries, 0.9 % [16–18]. The RF legislation also stipulates that population should be informed about GMO contents in products [19]. In Russia alterations into the Technical Regulations on food products marking came into force on December 26, 2018. Should such products be manufactured with the use of GMO, then a «GMO» sign is made on their package close to a unified sigh for products allowed to be distributed on the Eurasian Economic Union market; both signs are to be of the same size and shape. This special GMO marking is to be put on all products with GM-components in them exceeding 0.9 %[2].

Meat and food products made of processed meat are an essential part in food rations consumed by people in Russia. GM-soya is a frequently occurring source of genetically modified components in meat products as there is hardly an enterprise that makes sausage and manages without it. However, not the fact itself that vegetable protein has been added is important but absence of any data on it. Surveillance over adherence to scientifically substantiated recipes that involves determining raw components in finished meat products often reveals falsifications, both regarding their contents and their quality as well [20, 21].

A most vital task related to providing proper quality and safety of food products is to develop, implement, and update systems for control over raw materials and finished products using highly efficient analysis techniques. Polymerase chain reaction (PCR), including that performed in real-time mode, is among such techniques applied within controlling procedures and GMO safety assessment [22, 23].

Our research goal was to examine domestically produced food products and determine whether they contained regulatory sequences typical for genetically modified organisms; the research was aimed at improving risk-oriented surveillance over food products safety.

Data and methods. Overall, we selected 77 food products for determining genetically modified ingredients in them; they were 73 meat products (sausage, ham, and pate); 2 soya products (soya milk and soya cheese), 1 soya texture that was a component in a dressing for instant macaroni product made of dried vegetables, and 1 bread sample that contained soya flour. All the examined samples were homogenized. DNA was extracted out of homogenized samples with «DNK-sorb-S-M» kits (Rospot-

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rebnadzor's Scientific Research Center, Russia) and «MagnoPrime FITO» (NekstBio LLC, Russia).

PCR with hybridization-fluorescence detection was performed in real time mode on Rotor-Gene Q (Qiagen, Germany) and CFX96 (Bio-Rad, the USA) amplifiers. We performed our research with reagent kits produced by Rospotrebnadzor's Scientific Research Center; «AmpliSens GM Plant-1-FL» kit was used to determine DNA fragments of an enhancer (E-35S) and promoter (P-35S) in a sequence belonging to 35S cauliflower pattern virus; gene terminator of nopaline-synthase from Agrobacterium tumefaciens (T-NOS); enhancer (E-FMV) and promoter (P-FMV) of 35S fig-wort pattern virus. «AmpliKvant GM soya-FL» was used to quantitatively determine GM-soya lines that had an enhancer (E-35S) or promoter (P-35S) in a sequence belonging to 35S cauliflower pattern virus in their genome. Besides, performing an analysis with «AmpliSens GM Plant-1-FL» test system, we determined plant endogenous control, that is, a gene that was specific for plant genome (both transgenic and non-transgenic); it was the evidence that plant DNA occurred in an examined sample. «AmpliKvant GM soya-FL» kit allowed revealing soya DNA occurrence basing on use of soya endogenous control.

Amplification was performed with Rotor-Gene Q device as per the following procedure: 95 °C for 15 minutes, 1 cycle; 95 °C for 10 seconds, 59 °C for 1 minute, 45 cycles. The procedure for CFX96 device was as follows: 95 °C for 15 minutes, 1 cycle; 95 °C for 15 seconds, 59 °C for 1 minute, 42 cycles. FAM, HEX, ROX и Cy5 phosphors were used as fluorescent compounds applied for determining specific sequences. We analyzed accumulation curves for fluorescent signals as per each detection channel using program software installed on the devices. Results were interpreted basing on occurrence (or absence) of an intersection between fluorescence curve on a relevant channel with threshold curve that determined occurrence (or absence) of threshold cycle Ct value for this sample. The test was considered valid in case correct results were obtained for controls of DNA extraction and amplification. Data wee statistically processed with Microsoft Excel 2010.

Results and discussion. We analyzed 77 domestically produced food products. Meat products accounted for the biggest share of them, 94.8 %. Having examined marking on 77 food products, including meat and soya ones, we didn't manage to find any data on GMO occurrence in any of them. Having analyzed extracted DNA, we revealed that all samples didn't contain any fragments of enhancer (E-35S) or promoter (P-35S) in a sequence belonging to 35S cauliflower pattern virus, gene terminator of nopaline-synthase from Agrobacterium tumefaciens (T-NOS), as well as enhancer (E-FMV) or promoter (P-FMV) 35S of 35S fig-wort pattern virus that frequently occurred in GM-plants. Threshold cycle values were not determined as per three channels (Cy5, FAM, and ROX). But still, vegetable components were detected in all samples. The Figure below shows accumulation curves for fluorescent signal obtained for five food product samples as per HEX channel; these curves allow us to state that the samples contain plant DNA (Figure).

At the next stage we examined food products in order to reveal soya DNA and regulatory sequences that were typical for GMO. To do that, we used «AmpliKvant GM soya-FL» reagent kit that allowed determining both GM-components and falsification with soya ingredients. Having analyzed the selected food products, we didn't find any transgenic constructions in them. But still, 68.8 % analyzed samples contained soya DNA. However, data on soya additives was absent in 15.6 % cases and it means such products were falsified. Their manufacturers used soya raw materials which were not listed on their labels as components in a finished product. We should note that all such non-conformities were revealed for sausages.

Conclusion. Our examination performed on food products didn't reveal any plant GMO but instead we found plant DNA fragments

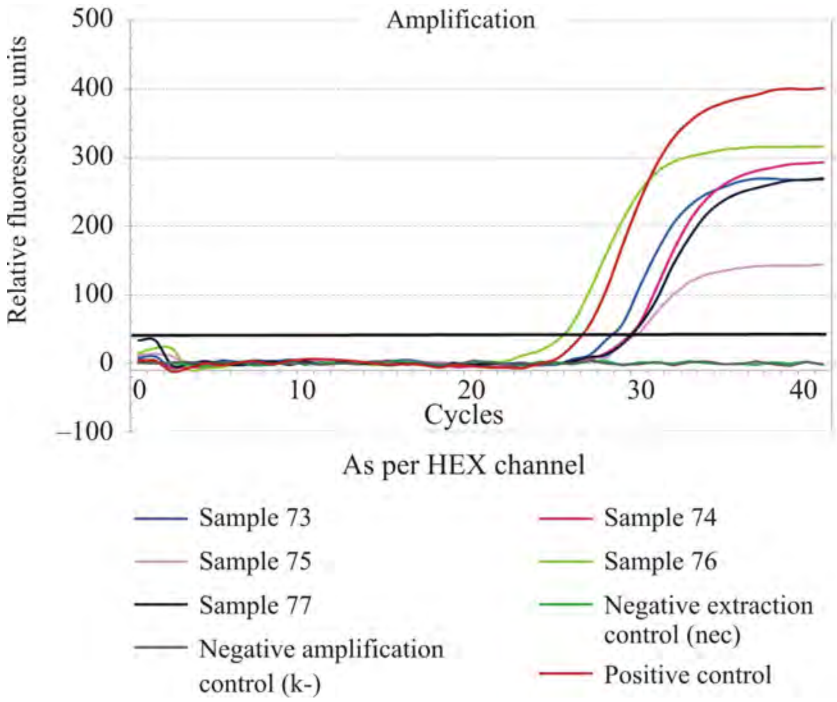

Figure. Accumulation curves for fluorescent signal obtained for food products samples No. 73–77 as per HEX channel with CFX96 device

including 68.8 % samples that contained soya DNA. Soya was not listed among components on consumer package in 15.6 % cases and it is informational falsification. Results obtained via determining DNA soya contents and transgenic construction elements in food products indicate that additional soya ingredients were included into them without being declared in relevant documents as recipe components.

Therefore, our analysis allowed revealing that data listed on food products labels are not always credible as regards ingredients. These cases are crude violation of the Federal Law «On consumer rights protection» as regards providing customers with reliable data. Absence of data on components which are included into a food product on its label does not conform to requirements fixed in the Customs Union Technical Regulations TR TS 022/2011 «Food products and their marking». Taking these results into account, it is necessary to improve control over occurrence of GMO and plant components used as ingredients in food production since food products falsification can lead not only to changes in their consumer properties but also cause damage to consumers' health.

Funding. The research was not granted any sponsor support.

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

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Received: 14.05.2020
Accepted: 11.11.2020
Published: 30.12.2020

UDC 613.6 (576.651)
DOI: 10.21668/health.risk/2020.4.11.eng

Read online

Research article

WORKING CONDITIONS AND WORK-RELATED PATHOLOGIES AT ENTERPRISES LOCATED IN CHUKOTKA AUTONOMOUS AREA

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For many years, morbidity with work-related diseases has been higher in Chukotka Autonomous Area (ChAA) than on average in Russia.

Our research objects were working conditions and morbidity with work-related diseases. Our research goal was to examine reasons for work-related pathology occurrence, its structure, and prevalence in ChAA in 2008–2018. We examined data obtained via social-hygienic monitoring in 2008–2018 in Chukotka, paying close attention to a section entitled «Working conditions and work-related pathology».

We established that noise (17.4 %) and cooling microclimate (11.8 %) were the most widely spread hazardous occupational factors in ChAA. 20.1 % workers were exposed to a combination of hazardous factors. 13.5 % workers were employed at industrial objects that belonged to the 1st surveillance group (the highest risks); 31.9 % worked at economic entities from the 3rd surveillance group (average risks). In 2008–2018 216 work-related diseases were first diagnosed in Chukotka, mostly among workers employed at mining enterprises (81.5 %). Sensorineural hearing loss / noise effects in the internal ear (35.2 %) and respiratory diseases (31.9 %) prevailed in their structure. 73.6 % diseases were detected due to patients applying for medical aid themselves. In 2008–2015 there was a steady growth in work-related morbidity (from 1.94 to 13.5 per 10,000 workers), but there was a decrease in it in 2016–2018 (down to 5.11 per 10,000 workers) with considerable fluctuations in numbers of first diagnosed diseases. Risks of work-related pathology occurrence were higher in Chukotka in 2018 than in 2008: OR=2.37; CI 1.82–3.09; χ^2=43.8; $p<0.001$.

To prevent work-related pathology in Chukotka, it is necessary to continue activities aimed at working conditions improvement, in particular, reducing exposure to noise and aerosols with predominantly fibrogenic effects in mining industry in the region.

Key words: *social-hygienic monitoring, working conditions, work-related morbidity, Chukotka Autonomous Area (ChAA), occupational factors, noise, cooling microclimate.*

According to the RF President Order issued on May 02, 2014 No. 296 (last edited on May 13, 2019) the Chukotka Autonomous Area (ChAA) that is located in the in the north-east of the country is included into the Arctic zone of the Russian Federation. The region has some specific features such as extreme climatic conditions, low population number (49.3 thousand people in 2018) and density (0.07 person per 1 square kilometer), and poorly developed social and economic infrastructure. Basic economic activities in ChAA are mining (black and brown coal, gold, and silver), construction, energy production and distribution [1, 2]. It is well known that workers employed in mining, a leading branch in ChAA, are among those occupational groups that run elevated risks of occupational pathology occurrence [3–5]. Arctic climatic conditions make an additional contribution into probability of health disorders [6, 7]. Such disorders are caused by overall and local exposure to cold, high humidity, apparent seasonal photoperiodicity, strained ion-magnetic re-

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gime, and other factors [8–10]. It is proven that combined exposure to these factors creates a so called «northern or arctic stress» that results in untimely decrease in adaptive resources of a body or even their depletion [10, 11].

In 2008–2018 ChAA was among RF regions with occupational morbidity levels being higher than on average in the country; they varied from 1.92 (2008) to 13.5 (2015) cases per 10 thousand people[1, 2]. Arctic zones are usually poorly inhibited and labor resources there are scarce; therefore, when people cease their working activity too early due to occupational diseases while still being of employable age, it creates additional social and economic problems for regional development [12, 13]. The document entitled «The Basics of the RF State Policy in the Arctic zone for a period up to 2020 and further on»[3] set a task that scientists have to solve, namely, to achieve proper functioning of life support systems and occupational conditions in Arctic regions. A part of this task is to examine influence exerted on a human body by adverse environmental factors, including occupational ones. Industrial objects in ChAA are located far away from cities where medical theory and practice are most developed and it makes examining health of workers employed at hazardous productions in remote districts in the Polar zone even more vital.

Our research goal was to examine reasons, structure, and prevalence of occupational pathology in ChAA.

Data and methods. We examined data obtained via «Working conditions and occupational pathology» social and hygienic monitoring program in ChAA in 2008–2018. All the data were provided by the Federal Center for Hygiene and Epidemiology of the Federal Service for Surveillance over Consumer Rights Protection and Human Well-being (Moscow).

We processed research data with Microsoft Excel 2010 and Epi Info, v. 6.04; we also calculated Student's t-test for independent samplings, relative risk (RR), 95 % confidence interval (CI), and test of fit χ^2. Numeric data were given as simple mean and error of the mean ($M \pm m$). Critical significance of a zero hypothesis was taken as 0.05.

Results and discussion. In 2008–2018 several adverse occupational factors prevailed at workplaces at most industrial enterprises (each having a share that exceeded 7 %) and workers were exposed to them; they included elevated noise levels, cooling microclimate, aerosols with fibrogenic effects, labor hardness being higher than permissible levels, overall vibration, non-ionizing electromagnetic fields (EMF) and electromagnetic radiation (EMR). More than one fifth of workers were exposed to more than one adverse factor. Attention should be paid to drastic (2 times and higher) annual fluctuations in number of workers exposed to aerosols with fibrogenic effects, labor hardness, unfavorable lighting environment, and other adverse occupational factors. And there were both rises and falls in their levels without any apparent regularities (Table 1).

As compared with 2008, in 2018 there was greater risks of workers being exposed to elevated local vibrations (RR = 2.15; CI 1.82–2.54; $\chi^2 = 83.6$; $p < 0.001$), labor intensity (RR = 1.45; CI 1.20–1.75; $\chi^2 = 15.3$; $p < 0.001$), non-ionizing EMF and EMR (RR = 1.22; CI 1.12–1.34; $\chi^2 = 19.4$; $p < 0.001$), unfavorable lighting environment (RR = 3.15; CI 2.71–3.66; $\chi^2 = 249.9$; $p < 0.001$), and several adverse factors combined (RR = 1.91; CI 1.80–2.02; $\chi^2 = 514.9$; $p < 0.001$). And on the contrary, in 2008 as opposed to 2018, there was greater probability of exposure to aerosols with fibrogenic effects (RR = 2.33; CI 2.11–2.58;

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$\chi^2 = 293.7$; $p < 0.001$), noise (RR = 1.19; CI 1.12–1.26; $\chi^2 = 33.7$; $p < 0.001$), chemical factors (RR = 2.42; CI 2.18–2.67; $\chi^2 = 320.7$; $p < 0.001$), labor hardness being higher than permissible levels (RR = 1.39; CI 1.27–1.52; $\chi^2 = 52.2$; $p < 0.001$), biological factors (RR = 1.69; CI 1.42–2.00; $\chi^2 = 37.3$; $p < 0.001$), ionizing radiation (RR = 2.37; CI 1.45–3.88; $\chi^2 = 12.7$; $p < 0.001$), cooling microclimate (RR = 1.31; CI 1.20–1.42; $\chi^2 = 40.1$; $p < 0.001$). Therefore, in 2008–2018 there was both increase and decrease in prevalence of certain adverse occupational factors on enterprises in ChAA and we can't state that working conditions have improved there.

We also performed a complex assessment of working conditions based on data obtained via surveillance over workers distributed into three groups according to sanitary-epidemiologic welfare at their workplaces. It was established that on average in 2008–2018 more than half workers in CAA were employed at industrial objects belonging to the 2nd group (unsatisfactory conditions at workplaces), almost one third were employed at industrial objects form the 3rd group (with extremely unsatisfactory conditions), and only 13.5 % workers were employed at industrial objects from the 1st group (satisfactory conditions). Overall number of workers employed at objects under surveillance in ChAA decreased by more than 5 thousand people or 38.3 % over the examined period of time.

During 11 years (in 2008 against 2018) there was a decrease in absolute number of workers employed at industrial objects belonging to the 1st and 2nd groups, but their shares among all employed workers increased ($p < 0.001$). As for the 3rd group, there was a decrease both in absolute number of workers employed there and their share as well ($p < 0.001$). Therefore, this re-distribution of workers employed at industrial objects under surveillance belonging to three groups indicated that working conditions improved at industrial enterprises in ChAA in 2008–2018 (Table 2).

In 2008–2018 in ChAA occupational pathology was first diagnosed in 171 workers, 170 of them being males (99.4 %) and only one woman (0.6 %). Overall, 216 occupational diseases were diagnosed or 1.26 cases per one worker. Their average age was 55.3 ± 0.5 and their average working experience amounted to 26.9 ± 0.6 years. 110 people (64.3 %) lived in Anadyr district; 44 people (25.7 %), Bilibinskiy district; 10 people (5.8 %), Iul'tinskiy district (Egvekinot municipal district); and 7 people (4.1 %), Chaunskiy district (Pevek municipal district).

Table 1

Number of workers exposed to adverse occupational factors

Adverse occupational factor	Year						Average annual value
	2008	2010	2012	2014	2016	2018	
Noise	2,223	2,427	1,549	2,257	1,282	1,666	1,900.7 (17.4 %)
Cooling microclimate	1,254	1,914	1,167	1,673	887	860	1,292.5 (11.8 %)
Fibrogenic aerosols	1,321	1,386	639	664	479	488	829.5 (7.6 %)
Labor hardness	1,124	611	313	1,503	582	723	809.3 (7.4 %)
Overall vibration	727	1,091	711	916	603	731	796.5 (7.3 %)
Non-ionizing EMF and EMR	835	281	661	874	959	953	760.5 (7.0 %)
Chemical factors	1,359	644	623	943	394	483	741.0 (6.8 %)
Lighting environment	218	346	347	1,389	499	658	576.2 (5.3 %)
Local vibration	198	227	201	604	209	399	306.3 (2.8 %)
Labor intensity	186	26	190	986	157	250	299.2 (2.7 %)
Biological factors	372	466	202	282	204	202	288.0 (2.6 %)
Infrasound	67	71	161	123	64	44	77.2 (0.7 %)
Ionizing radiation	57	27	18	68	39	22	38.5 (0.4 %)
Combined exposure to several factors	1,426	1,718	1,665	2,234	3,109	2965	2,197.3 (20.1 %)
All factors	11,367	11,235	8,447	1,4516	9,467	10,444	10,912.7

Table 2

Number and share (%) of workers employed at objects from three groups with different sanitary-epidemiologic welfare

Surveillance group	Year						Average annual value
	2008	2010	2012	2014	2016	2018	
1st	2,348 (12.0)	2,145 (10.7)	2,401 (14.8)	2,081 (14.1)	1,728 (12.1)	2,048 (14.5)	2,125 (13.5)
2nd	9,333 (47.7)	10,384 (52.0)	8,080 (49.8)	7,479 (50.5)	8,258 (58.0)	7,827 (55.3)	8,560 (54.5)
3rd	7,895 (40.3)	7,446 (37.3)	5,728 (35.3)	5,249 (35.4)	4,258 (29.9)	4,275 (30.2)	5,009 (31.9)
Overall	19,576 (100.0)	17,500 (100.0)	16,209 (100.0)	14,809 (100.0)	14,244 (100.0)	14,150 (100.0)	15,694 (100.0)

Table 3

Reasons for occupational diseases occurrence at enterprises in CAA

Parameter	Occupational diseases (cases)
Factors causing occupational diseases:	
noise	76 (35.2 %)
aerosols with fibrogenic effects	68 (31.5 %)
local vibration	27 (12.5 %)
labor hardness	25 (11.6 %)
overall vibration	16 (7.4 %)
chemical factors	2 (0.9 %)
cooling microclimate	2 (0.9 %)
Circumstances causing occupational diseases occurrence:	
underdeveloped technological processes	139 (64.4 %)
design defects of machinery, mechanisms, equipment, appliances, and tools	53 (24.5 %)
malfunction of machinery, mechanisms, equipment, appliances, and tools	24 (11.1 %)

Occupational pathology occurred in workers employed in three brunches. 176 disease cases (81.5 %) were diagnosed in workers employed in mining including 106 coal miners and 70 mineral ore miners. 38 disease cases (17.6 %) were revealed in workers employed in transportation including 33 cases among air transport workers. 2 occupational diseases (0.9 %) were diagnosed in workers dealing with energy production and distribution.

7 out of 13 adverse occupational factors which workers contacted at their workplaces in ChAA were related to occupational pathology occurrence. In-plant noise and aerosols with fibrogenic effects had the greatest etiological significance. Physical factors (noise, local and overall vibration) prevailed (55.1 %) in the structure of adverse occupational factors that caused occupational diseases.

In most cases occupational pathology occurred due to technological processes being underdeveloped. A much smaller contribution was made by design defects and malfunctions in machinery, mechanisms, equipment, appliances, and tools (Table 3).

Diseases of the ear, respiratory organs, nervous and musculoskeletal system prevailed in the structure of occupational pathology diagnosed in workers employed at industrial enterprises in ChAA. Injuries, poisonings, and some other consequences of external causes were much less frequent. The most widely spread nosologies were such occupational pathologies as noise effects in the internal ear (sensorineural hearing loss), chronic bronchitis, mono- and polyneuropathy. Respiratory diseases (chronic bronchitis, pneumoconiosis) were predominantly diagnosed in coal miners. All occupational disorders were chronic diseases. Occupational pathology was much more frequently diagnosed when workers applied for medical aid themselves in case they felt sick rather than during obligatory medical examinations (Table 4).

Table 4

Clinical features of occupational pathology

Parameter	Occupational diseases (cases)
Nosologic groups including diseases of	
ear and mastoid	76 (35.2 %)
respiratory organs	69 (31.9 %)
nervous system	28 (13.0 %)
musculoskeletal system and connective tissue	26 (12.0 %)
injuries, poisonings, and some other external causes	16 (7.4 %)
malignant neoplasms	1 (0.5 %)
Most widely spread diseases:	
noise effects in the internal ear (sensorineural hearing loss)	76 (35.2 %)
chronic bronchitis	50 (23.1 %)
mono- and polyneuropathy	27 (12.5 %)
pneumoconiosis	19 (8.8 %)
vibration disease	16 (7.4 %)
radiculopathy	15 (6.9 %)
An occupational disease revealed via:	
patients applying for a medical aid on their own initiative	159 (73.6 %)
periodical medical examination	57 (26.4 %)

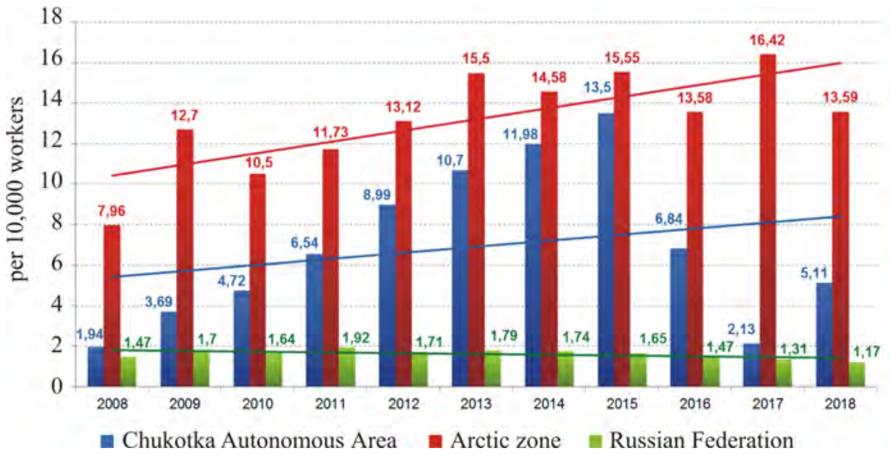

Figure. Occupational morbidity in Chukotka Autonomous Area, Arctic zone in the RF, and the country as a whole (per 10,000 workers)

Annual number of occupational diseases that were diagnosed for the first time varied within a wide range from 6 (2008 and 2017) up to 37 (2015) people. It led to significant changes in occupational morbidity levels among workers employed at industrial enterprises in ChAA. The parameter grew steadily in 2008–2015 and it went down in 2016–2018. As opposed to ChAA, in 2008–2018 overall there was an ascending trend in occupational morbidity in the Arctic zone in the Russian Federation. In Russia as a whole the parameter leveled off in 2008–2013 and then decreased in 2014–2018 (the trend was descending). In 2008–2015 dynamics of occupational morbidity in the Arctic zone as a whole and ChAA in particular was rather similar. There were significant discrepancies in 2016–2018 and it was impossible to detect any relation between drastic fluctuations in a number of first detected occupational pathology cases in ChAA and any objective factors, primarily, changes in working conditions existing at industrial enterprises in the region. Occupational pathology risk in ChAA was higher in 2018 than in 2008: RR = 2.37; CI 1.82–3.09; $\chi^2 = 43.8$; $p < 0.001$ (Figure).

It could be assumed a priori that higher occupational morbidity in ChAA occurred, first of all, due to peculiar economic structure in the region and its natural and climatic specificity. The present work quite logically revealed that more than 80 % occupational pathology cases were detected among miners. Occupational pathologies were similarly distributed as per economic activities in other Arctic regions with developed mining industry such as Murmansk region, polar zones in Krasnoyarsk region, and Komi Republic [5, 14, 15]. It is well-known that it is prohibited to employ women at mining enterprises or mines or their labor is strictly limited at such industrial objects[4]. Very few cases of occupational diseases among women in ChAA can be explained with mining industry prevailing in ChAA as their share is only 0.6 % whereas it amounts to 14.24 %[2] in Russia as a whole and is rather high in such regions as Samara region (29.1 %)[5], Leningrad region (43.2 %)[6], and Buryatia (21.6 %) [16].

Almost all work-related pathology cases (98.2 %) were etiologically related to five adverse occupational factors, namely, in-plant noise that was higher than permissible levels, aerosols with fibrogenic effects, labor hardness, local and overall vibration. Drastic fluctuations in adverse factors prevalence detected over the 11-year observation period were probably cue to methodical defects distorting their assessment. Only 2 (0.9 %) occupational pathology cases were related to cooling microclimate that was typical for extreme climatic conditions in Chukotka. Therefore, local and overall exposure to cold seems underestimated but we should remember that these adverse factors can cause reduction in physical and mental working capacity, coordination disorders, pathologies in the musculoskeletal system, and greater risks of occupational injuries [17–19]. Assumed underestimated impacts exerted by cold on workers' bodies can be due to peculiarities of methodology applied to perform specific assessment of working conditions.

As for positive changes in working conditions, we should mention that in 2008–2018 there was a descending trend in exposure to two most significant adverse factors, namely elevated noise levels and aerosols with fibrogenic effects that accounted for 35.2 % and 31.9 % occupational pathology cases accordingly. There was also a decrease in a share of workers employed at industrial objects belonging to the 3rd hazard group with extremely unfavorable sanitary-epidemiologic situation; and there was a simultaneous increase in number of workers employed at industrial objects form the 1st group (satisfactory working conditions). But at the same time, in spite of all these improvements, a share of workers employed at industrial objects with extremely unfavorable working conditions (31.9 %) in ChAA was significantly higher that on average in the country where the figure was equal to 7.13 %–9.44 % in 2013–2018. And on the contrary, a share of workers employed at industrial objects with satisfactory working conditions was 2 times lower in ChAA than on average in the country (13.5 % against 26.03–27.59 %)[2].

Another alerting fact was a significant change (up to 6 times) in annual number of first diagnosed occupational diseases and it allows assuming that performed medical examinations were not qualitative enough [20, 21]. Other possible evidence here can be an unusually high number of occupational diseases that were diagnosed as a result of workers applying for medical aid themselves (73.6 %). For example, the same parameter amounted to 40.7 % in Krasnoyarsk region [14] and to 12.0 % in Nenets Autonomous Area [22].

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Conclusion. Occupational morbidity in ChAA is steadily higher than on average in the country due to poorer working conditions than in the country in general. Occupational pathology predominantly occurs in workers employed at mining enterprises; noise effects in the internal ear (sensorineural hearing loss) and respiratory diseases prevail in the structure of occupational morbidity. Occupational pathology prevention requires continuous activates aimed at working conditions improvements; first of all, there should be a considerable reduction in exposure to noise and aerosols with fibrogenic effects at mining enterprises in the region.

Funding. The research was not granted any sponsor support.

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

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Received: 24.05.2020
Accepted: 09.11.2020
Published: 30.12.2020

UDC 613.6.02
DOI: 10.21668/health.risk/2020.4.12.eng

Read online

Research article

PECULIARITIES IN ASSESSING OCCUPATIONAL HEALTH RISKS FOR WORKERS WHO ARE IN CONTACT WITH AEROSOLS CONTAINING FINE-DISPERSED DUST PARTICLES

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In Russia there is a system for standardizing and control over aerosols with predominantly fibrogenic effects and dust particles with different structure. But at the same time there are no hygienic standards for fine-dispersed dust contents in working area air and it makes hygienic assessment of working conditions more complicated and impedes use of risk assessment methodology.

Our research goal was to substantiate a concentration of aerosols containing fine-dispersed dust particles (PM_{10} u $PM_{2.5}$) in working are air that were harmless for workers' health. It was done via applying a procedure for determining dust burden and using it when calculating health risks for workers.

We assessed dust content in working area air with focus on fine-dispersed dust particles PM_{10} u $PM_{2.5}$ with a dust measuring device «OMPN-10.0». Chemical structure of dust particles was determined with atomic absorption procedure. Results were estimated according to HS 2.2.5.3532-18. Dust burden was calculated according to State standard GOST R 54578-2011.

We established dependence between duration of working experience under exposure to fine-dispersed dust that was harmless for health and a value of excess in dust contents over the suggested concentration and work shift duration.

To assess health risk for workers caused by exposure to fine-dispersed dust particles taking their chemical structure into account, we determined reference concentrations for working area air; 0.1 mg/m^3 for PM_{10}, and 0.055 mg/m^3 for $PM_{2.5}$. Use of calculated concentrations allowed suggesting models for calculating harmless duration of working experience under exposure to dusts in concentrations higher than recommended ones. The results enable substantiating organizational activities aimed at workers' health preservation.

Key words: *fine-dispersed dusts, working area air, health risk, aerosol with fibrogenic effects, work-related diseases, dust burden, reference concentration, working experience.*

New research techniques aimed at examining occupational factors are being implemented into practice; it leads to changes in concepts regarding working conditions quality and nowadays health risk assessment methodology is required to assess them [1–3]. At present great attention is paid to such physical and chemical factors that pollute working area air as fine-dispersed dust aerosols (PM_{10} and PM $_{2.5}$).

In Russia there is a system for standardizing and control over aerosols with fibrogenic effects and dust particles with various structures. But still, there are no hygienic standards for fine-dispersed dust contents in working area air and it results in certain difficulties in performing hygienic assessment of working area air and makes it difficult to use health risk assessment methodology for well-grounded

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development of activities aimed at working conditions improvement [4–7].

Our research goal was to substantiate fine-dispersed dust particles (PM_{10} and $PM_{2.5}$) concentration in working area air that was harmless for workers' health; it was done basing on a procedure for determining dust burden and its subsequent use in calculating health risks for workers.

Data and methods. To quantitatively assess dust contents in working area air, we took AVA-3-180-001A aspirator and AFA-VP-10 filter. «OMPN-10.0» dust counter was applied to determine PM_{10} and $PM_{2.5}$ concentrations. We determined chemical structure (measured mass fractions of metals compounds) of dust particles with atomic absorption spectroscopy. Results were assessed in accordance with HS 2.2.5.3532-18[1]. Dust burden was calculated according to GOST R 54578-2011[2].

Results and discussion. Aerosols that occur due to technological operations involving use of items made from mineral cotton are poly-dispersed ones. They include ultra-fine dust $PM_{2.5}$ with its Brownian motion being proportionate to gravitational settling: dust particles PM_{10} that settle in still air at a rate determined by their size and density according to Stokes' law; coarse dispersions (with their size exceeding 10 μm) that settle in still air at a growing rate [7].

Our research allowed determining concentrations of dust particles with different dispersity measured at different air humidity in working are air and at a different distance from a dust source when heat insulating operations were performed at a contraction site (tables 1 and 2).

Research results allowed establishing that growing air humidity made for lower dust particles concentrations and it should be noted that coarse dispersions concentrations went down more intensely. When a distance from a dust source was 35 meters, coarse dispersions concentration fell by 7 times; PM_{10}, 1.4 times; and there were practically no changes in $PM_{2.5}$ concentration. It is well in line with previously obtained data on dust contamination dispersity determining dust distribution in the air.

Having examined chemical structure of dust particles in working area air where heat-insulating operations were performed, we detected a wide range of various metals compounds (Tables 3 and 4).

Table 1

PM_{10} and $PM_{2.5}$ concentrations at different working area air humidity at a distance from dust source being equal to 15 meters, mg/m^3, air flow speed being equal to 1.7 ±1.3 m/sec, mg/m^3

Dust particles	Air humidity, %					
	40	50	60	70	80	90
PM_{10}, mg/m^3	1.26	1.17	1.02	1.02	0.96	0.9
$PM_{2.5}$, mg/m^3	0.61	0.58	0.51	0.46	0.43	0.42

Table 2

PM_{10} and $PM_{2.5}$ concentrations on a construction site at different distances from a dust source and air humidity being 42±17%, and air flow speed being equal to 1.5±1.2 m/sec, mg/m^3

Dust particles	Distance forma dust source, m						
	0	10	15	20	25	30	35
PM_{10}, mg/m^3	1.83	1.68	1.59	1.62	1.56	1.35	1.35
$PM_{2.5}$, mg/m^3	0.77	0.65	0.74	0.67	0.62	0.70	0.75

[1] Hygienic standard HS 2.2.5.3532-18. Maximum permissible concentrations (MPC) of adverse substances in working area air. *KODEKS: and electronic fund for legal and reference documentation*. Available at: http://docs.cntd.ru/document/557235236 (03.06.2020) (in Russian).

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Table 3

Chemical structure of dust particles in working area air where heat-insulating operations were performed

Compound	SiO_2	Al_2O_3	Fe_2O_3	MgO	MnO	CaO	TiO_2	P_2O_5	K_2O	Na_2O	others
Share, %	49	16	12	7	<1	10	1	<1	<1	2	<3

Table 4

Metals contents in dust particles structure in working area air where heat-insulating works are performed (mg/kg)

Metal	Cu	Zn	Cd	Ni	Fe	Mn
Contents, мг/кmg/kgг	50	133	15	59	1,780	70

Fine-dispersed dust that occurs when heat-insulating operations are performed is a disintegration aerosol. Our data on quantitative structure of dust particles fit in with data obtained via previous research works [8–12].

Fine-dispersed dust particles are well-known to cause respiratory and cardiovascular diseases and growth in mortality caused by such diseases under long-term intense exposure even in ambient air [13–20]. Consequently, in order to develop and give grounds for activities aimed at making occupational environment more favorable, it is necessary to assess health risks for workers; performing such an assessment may be a complicated task as there is no hygienic standard for fine-dispersed fractions in working area air. Since fine-dispersed dust particles, just as aerosols with fibrogenic effects, have adverse physical and chemical properties and exert negative impacts on a body, we applied a methodology for dust burden calculation[1] for obtaining tentative reference PM_{10} и $PM_{2.5}$ concentrations that could be then applied in assessing health risks for workers. There are rather limited data on effects produced by fine-dispersed dust fractions on a body. But still, there are data that average MPC of mineral cotton dust particles in working area air amounts to 0.5 mg/m^3 over a shift. This concentration is equal to maximum single MPC for particulate matter that are non-differentiated as per their structure (aerosols) in ambient air (0.5 mg/m^3). Therefore, to perform rather tentative calculations, we took data from HS 2.1.6.3492-17 that fixes average daily MPC for PM_{10} at 0.06 mg/m^3 and for $PM_{2.5}$ at 0.035 mg/m^3 as well as average annual MPC, 0.04 mg/m^3 and 0.025 mg/m^3 accordingly.

We applied the following basic formula for our calculations:

$$DB_o = MPC \cdot N \cdot T \cdot Q,$$

where

DB_o is overall dust burden;

MPC is maximum permissible concentration of a specific fine-dispersed dust fraction;

N is a number of workdays per a calendar year;

T is maximum working experience duration, 30 years[3];

Q is lung ventilation volume over a shirt (m^3)[4, 5].

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[3] On Approval of Procedure for conducting a special assessment of working conditions, Classifier of adverse and (or) hazardous production factors, reporting form on a specific assessment of working conditions and instructions how to fill it in: The Order issued by the RF Ministry for labor and Social Protection on January 24, 2014 No. 33n. *KODEKS: and electronic fund for legal and reference documentation*. Available at: http://docs.cntd.ru/document/499072756 (03.06.2020) (in Russian).

[4] The Guide on assessment of occupational risks for workers' health. Organizational and methodical grounds, principles, and assessment criteria issued on June 24, 2003 No. 2.2.1766-03. *KODEKS: and electronic fund for legal and reference documentation*. Available at: http://docs.cntd.ru/document/901902053 (03.06.2020) (in Russian).

[5] R 2.1.10.1920-04. The Guide on assessing population health risks under exposure to chemicals that pollute the environment. *KODEKS: and electronic fund for legal and reference documentation*. Available at: http://docs.cntd.ru/document/499072756 (03.06.2020) (in Russian).

Various regulatory documents contain different data on lung ventilation volume when physical labor is performed. Given that, we took the following parameters for our calculation: lung ventilation volume amounted to 0.63 m^3 per hour for time spent at home (8 hours); 0.88 m^3 per hour for time spent elsewhere (8 hours); and 1.4 m^3 per hour for time spent at a workplace. These parameters are usually applied when health risks are calculated[3]. Number of days per year is 365; number of workdays is 250, and days off, 115.

We took data on average daily MPC and average annual MPC in ambient air; exposure duration was taken as being equal to 24 hours, 7 days a week, and 70 years of life; our calculation allowed establishing average shift PM_{10} concentrations as being equal to 0.1 mg/m^3; $PM_{2.5}$ concentrations, 0.055 mg/m^3, in working area air. These concentrations will not exceed control dust burden (occurring in actual living environment with actual average annual concentrations occurring in ambient air in urban settlements) even when working experience is 30 years and a working shift is 8 hours (40 hours a week). These concentrations can be used for assessing occupational health risks for workers who contact fine-dispersed dusts at their workplaces.

Suggested PM_{10} and $PM_{2.5}$ concentrations obtained via our calculations are in line with reference doses used in determining health risks for population exposed to polluted ambient air. Thus, concentrations recommended for chronic exposure amount to 0.05 mg/m^3 for PM_{10}, and 0.015 mg/m^3 for $PM_{2.5}$. When determining risks caused by acute exposure, it is recommended to use 0.15 mg/m^3 for PM_{10} and 0.065 mg/m^3 for $PM_{2.5}$.

These suggested reference concentrations for fine-dispersed dust particles occurring when items made of mineral fiber are used are truly relevant given essence of impacts exerted by fine-dispersed dust fraction on a body[3] as well as data on a basic dust source at heat-insulating works being items made of mineral cotton (MPC is 2/0.5 mg/m^3) and artificial mineral fiber with silicate glass-like structure (MPC is /4 mg/m^3 for coarse dispersions).

We applied up-to-date methodical approaches to assessing and predicting occupational risks to obtain model parameters of safe working experience duration for workers dealing with heat-insulating given different length of a work shift and different intensity of working area air pollution with fine-dispersed dust particles (Table 5 and Figure). These results are only preliminary and they should be confirmed with actual data on respiratory and cardiovascular diseases prevalence among workers who perform their work tasks under exposure to the examined adverse factors.

Table 5

Models predicting harmless working experience for workers dealing with heat-insulating given different length of contacts with fine-dispersed dusts

Duration of a work shift (hour)	Regression equation
8	$y = -0.0043x^3 + 0.0798x^2 - 1.4478x + 31.225$; $R^2 = 0.9993$
9	$y = -0.0051x^3 + 0.1011x^2 - 1.5982x + 31.195$; $R^2 = 0.9996$
10	$y = -0.0051x^3 + 0.1014x^2 - 1.5927x + 30.886$; $R^2 = 0.9996$
11	$y = -0.0051x^3 + 0.1012x^2 - 1.5779x + 30.399$; $R^2 = 0.9996$
12	$y = -0.005x^3 + 0.1011x^2 - 1.5632x + 29.912$; $R^2 = 0.9995$

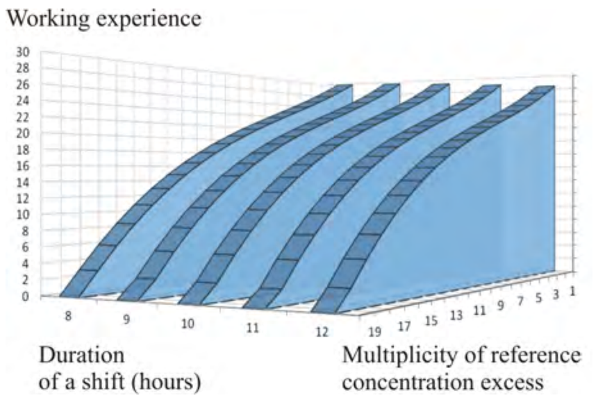

Figure. Duration of harmless working experience depending on multiplicity of reference PM_{10} concentration excess

Conclusion. At present hygienic assessment of working conditions necessarily involves assessing health risks for workers. But still, at present there are no standards for certain occupational factors that outline harmless exposure during the whole working experience (30 years) that has been extended due to an increase in retirement age. We determined tentative reference PM_{10} and $PM_{2.5}$ concentrations in working are air that were equal to 0.1 mg/m^3 and 0,055 mg/m^3 accordingly. These concentrations were determined taking chemical structure of particles into account and basing on control dust burden calculation; therefore, they can be used in assessing health risks for workers dealing with heat-insulating and contacting fine-dispersed dust particles. Exposure to fine-dispersed particles in the given tentative concentrations at a workplace during 30-year working experience and a work shift being 8 hours a day does not increase overall dust burden on a body. These concentrations can be determined without any changes in a procedure for establishing MPC for aerosols with fibrogenic effects and they can be used for preliminary assessment of health risks for workers who are exposed to fine-dispersed dusts at their workplaces. Use of calculated tentative reference concentrations allowed us to suggest models for calculating harmless working experience duration given that the recommended dust parameters (MPC) are violated. Bearing in mind that there are no established MPC for fine-dispersed mineral cotton dust fractions in working area air, we can conclude that our research results allow substantiating organizational activities aimed at workers' health preservation.

Funding. The research was not granted any sponsor support.

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

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Received: 26.06.2020
Accepted: 11.11.2020
Published: 30.12.2020

UDC 502.22: 504.3.054
DOI: 10.21668/health.risk/2020.4.13.eng

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Research article

WORKING OUT A PROCEDURE FOR DETERMINING POTENTIALLY HAZARDOUS VOLATILE ORGANIC COMPOUNDS (TRICHLOROETHYLENE AND TETRACHLOROETHYLENE) IN AMBIENT AIR

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The article dwells on results obtained via experimental research on working out a gas chromatography procedure for determining trichloroethylene and tetrachloroethylene in ambient air. Experiments were performed on substances which had low limits of detection with gas-liquid chromatography with electron capture detection (GLC/ECD) when examined substances were absorbed from ambient air on Tenax TA sorbent. Optimal gas chromatography parameters were established with a hardware-software complex based on «Crystal-5000» gas chromatographer and use of a column from IDBPX-VOL series, 60 m·0.32 mm·1.8 µm, under the following temperatures: column, 50–230 °C; evaporator, 250 °C; detector, 250 °C.

The developed capillary gas chromatography procedure allows determining trichloroethylene in concentrations ranging from 0.000146 to 0.00146 mg/m^3, and tetrachloroethylene, from 0.000081 to 0.00081 mg/m^3 with inaccuracy not exceeding 25.0 %. We performed metrological assessment of the procedure and it allowed determining quality of analysis results for trichloroethylene and tetrachloroethylene; they were as follows: precision, 21.97 % and 14.3 %: repeatability, 4.22 % and 3.38 %; reproducibility, 5.66 % and 4.9 %. Limit of detection (LOD) for trichloroethylene and tetrachloroethylene was C_{min} = 0.0000038 mg/dm^3 and C_{min} = 0.00000083 mg/dm^3 accordingly. Limit of quantitative determination (LOQ) was C_{lim} = 0.000013 mg/m^3 for trichloroethylene, and C_{lim} = 0.0000028 mg/m^3 for tetrachloroethylene.

The developed procedure allowed detecting contents of the examined substances in ambient air near a construction site and a dry-cleaner's, trichloroethylene in a range from 0.00001 mg/m^3 to 0.0009 mg/m^3, tetrachloroethylene, from 0.000011 mg/m^3 to 0.00039 mg/m^3.

This unified high-sensitive and selective procedure is recommended for systemic control over potentially hazardous volatile organic compounds in ambient air as it allows providing objective and reliable hygienic assessment of chemical safety and quality of the environment and health risk assessment.

Key words: *capillary gas chromatography, trichloroethylene, ECD, thermal sorption, LOD, LOQ, tetrachloroethylene, quantitative chemical analysis.*

Issues related to chemical safety became a powerful incentive to create an international strategy on providing protection for human health from impacts exerted by adverse environmental factors. A key component in its implementation is risk assessment, i.e., determining an actual threat that damage can be done to human health and the environment[1].

Health risk assessment methodology is widely used in the Russian Federation as a component in social and hygienic monitoring activities when experts determine priorities in chemical safety of the environment and population. Timely, reliable, and highly precise instrumental laboratory control is a most essential element in correct assessment of the envi-

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[1] On the list of priority substances that occur in the environment and their impacts on population health: The information letter dated August 7, 1997 No. 11/109-111. The RF Public Healthcare Ministry, The Department for state sanitary-epidemiologic surveillance. Available at: http://docs.cntd.ru/document/456018733 (24.09.2020) (in Russian).

ronment and hygienic diagnostics of an existing situation [1, 2].

Growing volumes and wider ranges of hazardous chemicals call for up-to-date instrumental research [3]. Special attention should be paid to developing up-to-date procedures for analytical control over toxic compounds and, when necessary, their hazardous metabolites. The most vital issues being discussed at the moment are related to these procedures having sufficient sensitivity, their selectivity, validity, and reproducibility of analytical results[2] [4, 5].

Halogen-containing compounds such as trichloroethylene and tetrachloroethylene are widely used as solvents and degreasing agents in various industries; they are considered to be hazardous for human health [6]. These organic chlorine compounds persist in the environment for a long time and are considered «highly likely carcinogenic» belonging to A2 category A2 [7–9]. Trichloroethylene is a narcotic; when inhaled, its vapors can cause nausea, dizziness, headache, and overall sickness [10, 11]. As per research data a contact with trichloroethylene results in 6 times higher probability that Parkinson disease might occur [12, 13].

Tetrachloroethylene is toxic when contacted for a long time and produces adverse effects on the central nervous system, liver, and kidneys. Tetrachloroethylene is poorly metabolized in a body as approximately 98 % of it is extracted from the lungs and only 2 % is transformed. Tetrachloroethylene is slowly extracted from a body and is detected 2 weeks after it was inhaled; delay in the lungs is equal to approximately 62 % [14, 15].

Our review of scientific literature has revealed that an issue related to assessing contents of trichloroethylene and tetrachloroethylene in ambient air still remains vital. At present there are no highly sensitive and highly selective procedures for determining contents of these potentially toxic compounds [16]. Procedures for analyzing trichloroethylene and tetrachloroethylene contents in ambient air that are described in methodical documents allow determining these compounds in concentrations ranging from 0.001 up to 0.05 mg/m^3. In order to improve methodical provision for tests, we fixed a task to measure several compounds using only one selected sample.

Data and methods. Our research objects were ambient air, various procedures for taking ambient air samples, sample preparation procedures, quantitative analysis of ambient air contaminants, as well as efficiency achieved in chromatographic separation of determined compounds on different stationary liquid phases and metrological properties of measuring.

We developed a procedure following several stages: trying-out procedures for taking ambient air samples; examining completeness of extraction; trying-out parameters of gas chromatographic determination and selective separation; determining metrological properties.

Optimal gas chromatographic parameters for determining trichloroethylene and tetrachloroethylene in ambient air were established via capillary gas chromatography performed with «Crystal-5000» chromatographer equipped with a IDBPX-VOL- 60 m·0,32 mm·1,8 µm column under the following temperatures: the column, 50–230 °C; vaporizer, 250 °C; detector, 250 °C.

To determine micro-mixtures of toxic volatile organic contaminants (trichloroethylene and tetrachloroethylene) in ambient air, we performed sorption extraction of trichloroethylene and tetrachloroethylene admixtures from ambient air[3] [17]. This procedure was selected as the most efficient as it allowed extracting and concentrating organic compounds that occurred in the air as gas and vapors [18, 19].

[2] On sanitary-epidemiologic situation in the Russian Federation in 2007: The State Report. Moscow, 2008, 397 p. (in Russian).

[3] GOST R ISO 16017-1-2007. Ambient air, working area air, and air inside closed rooms. Taking samples of volatile organic compounds with a sorption tube with the following thermal desorption and gas chromatography analysis on capillary columns. Part 1. Taking samples via pumping. *KODEKS: an electronic fund for legal and reference documentation*. Available at: http://docs.cntd.ru/document/1200057637 (27.09.2020) (in Russian).

Ambient air samples were taken on sorption tubes with the following thermal desorption and analysis performed with «Crystal-5000» chromatographer.

To build a calibrating curve, we prepared several standard solutions with different concentrations. 1 mm^3 of a calibrating solution was introduced on a sorbent in a sorption tube at 10 mm depth and then thermal desorption was performed.

To assess sensitivity and precision of a procedure for determining trichloroethylene and tetrachloroethylene in ambient air, we established limit of detection (LOD) and limit of quantitative determination (LOQ). To do that, we performed an experiment that involved introducing an analytical standard on a sorption tube with Tenax TA in certain quantities equal to limit of detection and it was repeated for five times.

Limit of detection $C_{\min}$ was taken as being equal to triple value of standard deviation in a background signal that was determined for trichloroethylene and tetrachloroethylene concentrations in an ambient air sample with analytical signal / noise ratio being > 3. Limit of detection for trichloroethylene and tetrachloroethylene in an ambient air sample was calculated as per the following formula:

$$C_{\min} = \frac{\text{background signal value} \cdot \text{analyte concentration}}{\text{value of analytical signal given by analyte}} \times 3, \text{ mg/dm}^3 \quad (1)$$

We performed a metrological assessment of the procedure in order to establish its accuracy, repeatability, intra-laboratory precision, and correctness.

Results and discussion. When determining optimal parameters for selecting the examined compounds, we relied on the following controlling factors: a sorbent covered with stationary liquid phase (SLP) and chromatographer temperature mode [19, 20].

We tried out conditions for separating trichloroethylene and tetrachloroethylene from other hydrocarbons with similar physical and chemical properties on capillary columns with different properties of stationary liquid phases: DB-624, HP-FFAP, and HP-VOC. Trichloroethylene and tetrachloroethylene were qualitatively separated on a capillary column IDBPX-VOL-60 m·0.32 mm·1.8 μm which was 60 meters long and stationary phase film was 1.8 μm thick.

Optimal temperature for gas chromatography analysis was determined via picking-up taking into account boiling temperatures, volatility of the examined compounds, and properties of stationary liquid phases on capillary columns. Bearing in mind that temperature rise on a column produces a positive effect on overall separation process and an amount of time necessary for separation is reduced thus making an overall test shorter, we programmed temperatures at columns thermostat in linear mode when determining organic chlorine compounds.

Gas chromatography parameters are given in Table 1.

Modes 2 and 3 didn't allow achieving efficient trichloroethylene and tetrachloroethylene. Qualitative separation was achieved in Mode 1 and it is recommended for future work (Figure 1).

Gas carrier consumption, 20 mL/min, was selected during an experiment.

Table 2 contains gas chromatographic analysis properties for standard trichloroethylene and tetrachloroethylene mixtures.

Table 1

Gas chromatography parameters for determining trichloroethylene and tetrachloroethylene in ambient air

Mode	Temperature, °C		Carrier gas consumption, mL/min
	Column	Heating rate, °C/min	
1	50–230	10	20
2	70–160–180	15	30
3	70–160–200	25	30

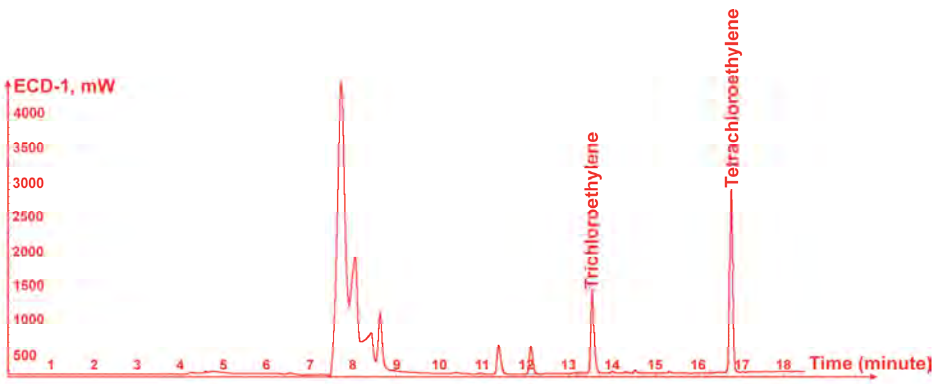

Figure 1. Chromatogram showing a standard trichloroethylene and tetrachloroethylene mixture

Table 2

Gas chromatographic analysis properties for standard trichloroethylene and tetrachloroethylene mixtures

Compound	SLP, carrier, fraction	Column length, м	A sample volume for analysis, мм^3	Detention time, min
Trichloroethylene	ID BPX-VOL	60	1	13.6
Tetrachloroethylene				16.8

Trichloroethylene and tetrachloroethylene were quantitatively determined via absolute calibration as per 6 series of standard solutions in concentrations varying within 0.0000146–0.000146 mg/m^3 for trichloroethylene, and 0.0000081–0.000081 mg/m^3 for tetrachloroethylene. Calibrating property was considered stable provided the following condition was met (2) [15]:

$$S_{\max} - S_{\min} \leq 0{,}01 \cdot r_s \cdot \frac{S_{\max} + S_{\min}}{2}, \quad (2)$$

where $S_{\max}$ is a maximum square of the peak for a corresponding calibration solution, mW;

$S_{\min}$ is a minimum square of the peak for a corresponding calibration solution, mW;

r_s is a limit for repeatability of calibration solution square peak; r_s = 11.68 % for trichloroethylene and r_s = 9.36 % for tetrachloroethylene.

Test results were considered positive provided that the condition (1) was met.

When testing the procedure, we examined how efficient thermal desorption of trichloroethylene and tetrachloroethylene was in case different sorbents were used such as *CSIII*, *TTA/CSIII*, and *Tenax TA*. We determined average thermal desorption values for the examined compounds; the results are given in Table 3.

The performed research allowed us to establish that *Tenax TA* polymer sorbent had optimal properties as the greatest thermal desorption achieved with it amounted to 93 % for trichloroethylene and 95 % for tetrachloroethylene.

To establish validity, we estimated the following parameters: linearity, measurement range, precision (accuracy and reproducibility), and limit of detection[4]. It was established that provided all the necessary conditions were observed and measurements were performed according to the procedure, inaccuracy (and its components) should not exceed values given in Table 4.

Limit of detection LOD for trichloroethylene and tetrachloroethylene amounted to $C_{\min}$ = 0.0000038 mg/dm^3 and $C_{\min}$ = = 0.00000083 mg/dm^3 accordingly.

[4] GOST R ISO 5725-1-2002. Accuracy (correctness and precision) or measuring techniques and results. Part 1. Basic provisions and definitions. *KODEKS: an electronic fund for legal and reference documentation*. Available at: http://docs.cntd.ru/document/1200029975 (27.09.2020) (in Russian).

Table 3

Average thermal desorption values (μg)

Sorbent	Trichloroethylene		Thermal desorption, %	Tetrachloroethylene		Thermal desorption, %
	introduced	detected		introduced	detected	
1. CS III	0.0048	0.00402 ± 0.0007	83.75	0.004	0.0025 ± 0.0004	62.5
2. TTA/CS III		0.00400 ± 0.0002	83.3		0.0025 ± 0.00021	62.5
3. Tenax TA		0.00445 ± 0.003	**93.0**		0.0038 ± 0.00044	**95.0**

Table 4

Measurement range for trichloroethylene and tetrachloroethylene contents in ambient air, measurement accuracy, correctness, and precision

Range, mg/m^3	Accuracy ±δ, %	Repeatability, σ_r, %	Reproducibility, σ_R, %	Correctness ±δ_c, %
Trichloroethylene				
0.0000146–0.000146	22.00	4.21	5.70	19.00
Tetrachloroethylene				
0.0000081–0.000081	14.30	3.40	4.90	10.60

Limit of quantitative determination for trichloroethylene and tetrachloroethylene in ambient air samples was detected as the lowest concentrations in a standard sample with acceptable precision and reliability that gives an analytical signal (a chromatographic peak) with its height being equal to a 10-time basic noise hindrances level.

Chromatograms for trichloroethylene and tetrachloroethylene in concentrations equal to limit of quantitative determination are given in Figure 2.

Limit of quantitative determination for trichloroethylene and tetrachloroethylene in a standard sample was set higher than limit of detection and amounted to C_{lim} = 0.000013 mg/m^3 for trichloroethylene and C_{lim} = 0.0000028 mg/m^3 for tetrachloroethylene.

To test the procedure and assess trichloroethylene and tetrachloroethylene contents in ambient air samples, ambient air samples were taken in an area where a construction site and a dry-cleaner's were located and then analyzed. Analysis results for samples taken near a construction site are given in Table 5.

Trichloroethylene and tetrachloroethylene were detected in 83 % and 100 % ambient air samples accordingly. There were no samples with their contents exceeding the hygienic standards detected during the observation period.

Table 6 contains the results obtained via analyzing ambient air samples taken in an area where a dry-cleaner's was located.

Analysis of the obtained results revealed that 100 % ambient air samples contained

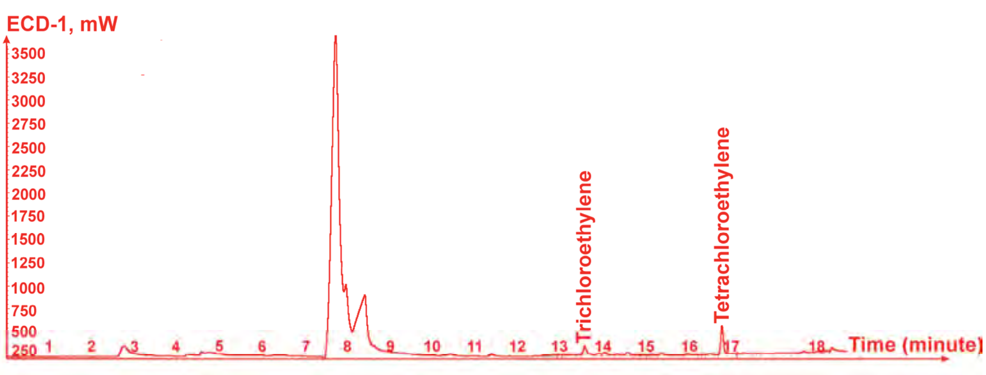

Figure 2. A chromatogram for a standard sample

Table 5

Results obtained via chemical analysis of ambient air samples performed to determine trichloroethylene and tetrachloroethylene contents in ambient air in an area where a construction site is located

Compound to be determined	$MPC_{s.m}$ mg/m^3	mg/m^3					
		13:30		16:00		19:00	
Trichloro-ethylene	4	Lower than LOD	Lower than LOD	Lower than LOD	0.00005± 0.000009	Lower than LOD	Lower than LOD
Tetrachloro-ethylene	0.5	0.0000135± 0.0000014	0.000012± 0.0000013	0.000021± 0.0000022	0.000024± 0.0000025	0.000055± 0.0000058	0.000085± 0.00001

Table 6

Results obtained via chemical analysis of ambient air samples performed to determine trichloroethylene and tetrachloroethylene contents in ambient air in an area where a dry-cleaner's is located

Sample No.	Ambient air	
	Trichloroethylene, Single maximum MPC = 4 mg/m³	Tetrachloroethylene Single maximum MPC = 0.5 mg/m³
1	0.00004 ± 0.00001	0.00007 ± 0.000018
2	0.00002 ± 0.000005	0.00024 ± 0.00006
3	0.00039 ± 0.000098	0.0001 ± 0.000025
4	0.00001 ± 0.0000025	0.00001 ± 0.0000025
5	0.00002 ± 0.000005	0.00004 ± 0.00001
6	0.00003 ± 0.0000075	0.00006 ± 0.000015
7	0.00038 ± 0.000095	0.00018 ± 0.000045
8	0.00013 ± 0.000033	0.00013 ± 0.000033
9	0.00005 ± 0.000013	0.00004 ± 0.00001
10	0.00021 ± 0.000053	0.00013 ± 0.000033

trichloroethylene and tetrachloroethylene. Tetrachloroethylene concentrations detected in a period when screening observation were performed were up to 3 times higher than the lower concentrations range.

Conclusions. We have developed an up-to-date gas chromatographic procedure for quantitative chemical analysis of potentially hazardous chemical compounds (trichloroethylene and tetrachloroethylene) in ambient air. Sample preparation for instrumental measuring is aimed at extracting and concentrating organic chlorine compounds out of ambient air on *Tenax TA* sorbent combined with thermal desorption.

Sensitivity of the procedure varies from 0.000146 to 0.00146 mg/m^3 for trichloroethylene and from 0.000081 to 0.00081 mg/m^3 for tetrachloroethylene.

The developed procedure has been properly tested and it allowed determining the examined compounds in ambient air near a construction site and a dry-cleaner's, in a range from 0.00001 mg/m^3 to 0.0009 mg/m^3 for tetrachloroethylene and from 0.000011 mg/m^3 to 0.00039 mg/m^3 for trichloroethylene.

This unified highly sensitive and selective procedure is recommended for systemic control over potentially hazardous volatile organic compounds (trichloroethylene and tetrachloroethylene) in ambient air; such control is necessary for providing objective and reliable hygienic assessment of environmental chemical safety and health risk assessment.

Funding. The research was not granted any sponsor support.

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

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Received: 09.09.2020
Accepted: 10.12.2020
Published: 30.12.2020

HEALTH RISK ANALYSIS IN EPIDEMIOLOGY

UDC 616.98:579.842.23
DOI: 10.21668/health.risk/2020.4.14.eng

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Research article

IMMUNOLOGIC MONITORING OVER PEOPLE VACCINATED AGAINST PLAGUE IN CASPIAN SAND NATURAL FOCUS IN ORDER TO ASSESS AND MANAGE HEALTH RISKS

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To provide better opportunities for managing both risks caused by vaccination and risks of epidemiological complications, immunologic monitoring over people vaccinated with live dried plague vaccine (LPV) due to epidemiologic indications was performed.

Our research goal was to assess whether immunologic monitoring over people vaccinated against plague yielded informative results; it was done to substantiate activities aimed at improving procedures for LPV application. Immunologic monitoring was performed from 2016 to 2019 in the Caspian sand natural plague focus according to conventional procedures for assessing humoral and cellular components in immunity.

We determined immunologic parameters in 217 volunteers vaccinated with LPV and 130 healthy donors (the reference group) prior to and 1 and 12 months after vaccination. We suggested a methodical approach based on aggregated analysis of the summated immune response predictors chosen for estimation in volunteers vaccinated with LPV and giving score values to them; it allows revealing people who react to plague microbe antigens predominantly as per cellular, humoral, or mixed type.

Immunologic monitoring results proved that it was safe to apply LPV; they allowed characterizing trends occurring in immunological restructuring in vaccinated volunteers, determining limits of fluctuation in individual parameters of an immune response to the vaccine, and revealing people with both normal and changed (reduced or increased) immunologic reactivity to LPV. If monitoring data are taken into account, it provides an opportunity to predict vaccination results as per epidemiological parameters, to reveal groups with normal, high, or low immune reactivity to plague microbe antigens in order to determine people in them who need an individual approach when it comes down to anti-plague vaccination.

Key words: *plague prevention, live plague vaccine (LPV), immunologic monitoring, cellular and humoral immunity, plague microbe antigens, immune reactivity, epidemiologic complications, health risk management.*

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Fleas and rodents that are common for the Caspian natural sand plague focus often get infected with plague and such epidemics are wide-scale and appear with certain periodicity [1]. As a rule, in the past when an epizootic situation deteriorated drastically in the Caspian sand natural plague focus, the process was accompanied with epidemiological complications [2]. In 2014 it was only timely reacting that allowed preserving epidemiologically favorable situation when there was another wave of epizooties on the territory; this reacting involved timely activities aimed at specific and non-specific plague prevention [2, 3]. Breaking a chain of epidemic complications occurring in the Mountain Altai natural plague focus in 2014–2016 is a good example of successfully implemented activities aimed at specific plague prevention [4, 5].

Anti-plague vaccination is a component in the set of activities aimed at providing prevention from this infection in its natural foci. And a scope of specific anti-plague prevention can be different in each specific natural focus. It depends on intensity of epizootic activity in a natural focus, epidemic peculiarities, overall population density in a focus, types of economic activities performed on an enzootic territory as they determine how frequently people can enter a contact with infected objects, natural and climatic conditions, and socioeconomic development of a region that determines availability of laboratory and medical support.

In Russia specific plague prevention involves using live dried plague vaccine (LPV) which is a dried live culture of a vaccine strain belonging to a plague microbe

Yersinia pestis EV developed by the Scientific Research Institute for Epidemiology and Hygiene and produced by Rospotrebnadzor's Stavropol Scientific Research Anti-plague Institute. A single cutaneous vaccination with LPV results in high-level immunity occurrence that persists up to a year and it means that people living on risk territories are to be revaccinated annually in case there is epizootic activity among plague agents.

Specific plague prevention strategy is determined by the National Calendar for Preventive Vaccinations as per epidemic indications[1] and involves vaccinating people who live on a territory that is enzootic as per plague and personnel working at specialized institutions who deal with live plague agent cultures. In case there are complications in an epizootic situation (plague epizooty among rodents) and/or epidemic one (farm animals or people get infected or there is a risk that plague will be transferred onto a territory), tactic anti-plague activities aimed at specific prevention among people who temporarily or permanently live in a natural plague focus involve vaccination of all people on a limited territory, starting from 2-year old children; or only selected occupational groups who run the highest risks are to be vaccinated (cattle-breeders, agronomists, farmers, geologists, hunters, or suppliers). To provide vaccination for all the people living a region can be rather costly, and, bearing in mind negative attitudes most people usually have towards vaccinations, it implies a necessity to implement wide-scale sanitary-educational activities. Given that, a probable solution could be providing people with convincing motivation for vaccination necessity confirmed with explicit data on assessing immune reactions to plague microbe in each vaccinated person.

Providing vaccination with maximum possible excess of benefit (efficiency) over risks is a basic goal in risk management in vaccine studies [6, 7].

Immunologic monitoring over people who got vaccinated with LPV as per epidemic indications provides better opportunities for managing risks caused by vaccination itself and risks related to possible complications of an epidemiologic situation. When vaccination is performed without taking into account hetero-

[1] On Approval of the National Calendar for Preventive Vaccinations and Vaccinations required as per epidemiologic indications: The Order by the RF Public Healthcare Ministry No. 125n dated March 21, 2014. *KODEKS: an electronic fund for legal and reference documentation*. Available at: http://docs.cntd.ru/document/499086215 (10.02.2020) (in Russian).

geneity of vaccinated population groups (immunization scheme and doze are the same), it doesn't allow applying a methodology for managing potential risks related to vaccination prevention; therefore, an epidemic process is not managed efficiently [8]. Hence, a key moment in optimizing specific plague prevention is to create a methodical approach to a complex assessment of results obtained via immunologic, epizootologic, and epidemiologic monitoring in a natural plague focus; such an approach should be aimed at determining a risk territory and a risk period as well as at substantiating targets and scopes of prevention activities regarding risk groups among population.

Our research goal was to assess information value of results obtained via immunologic monitoring over people who got vaccinated against plague in order to substantiate implementation of activities aimed at improving tactics in LPV application.

Data and methods. We performed monitoring over 347 volunteers in the Caspian sand natural plague focus in 2016–2019. Our participants were people living in Chernozemelskiy district, Kalmyk Republic, and experts employed at 2 anti-plague institutions 9 in Elista and Astrakhan). The research was performed in accordance with the research program and procedure approved by the Biological Ethical Committee of V.I. Razumovskiy's Saratov State Medical University. All the volunteers gave their written informed consent to take part in the research.

All the volunteers (217 people) got cutaneous vaccination with LPV (LSR-005759/08) produced by Rospotrebnadzor's Stavropol Scientific Research Anti-plague Institute (Russia). We applied the following preparation series in our research: 1–15; 2–16; 3–15; 5–14.

We assessed immunologic efficiency and safety of LPV applied for vaccinating different research groups prior to vaccination as well as 1 and 12 months after it. Our research groups included Group 1 (volunteers who got vaccinated for the 1st time); Group 2 (people who got vaccinated for the 2nd and the 3rd time); Group 3 (experts from anti-plague institutions located in the Caspian sand natural plague focus who were vaccinated multiple times); and the Reference group (130 healthy donors who permanently resided in Kalmyk Republic). Overall characteristics of people who participated in the research are given in Table 1.

To characterize risks that adverse effects related to vaccination might occur among volunteers, we analyzed primary medical documents (Form No. 025/u) and questionnaires that were offered to volunteers during their second visit (1 month after vaccination). LPV safety was assessed as per results obtained via analyzing indirect immunologic tests aimed at determining the following:

– contents of circulating immune complexes (CIC) in blood serum of vaccinated people via PEG-precipitation;

– E immunoglobulin (IgE) concentration according to the instructions provided with a reagents set for ELISA determination of total E immunoglobulin in blood serum, total IgE, IFA-BEST test as per TU (technical conditions) 9398-048-23548172-2006;

– CD95+ (APO-1) apoptosis marker, Fas ligand cellular receptor, via flow cytometry according to the instructions provided by a manufacturer (Beckman Coulter Inc., the USA) [9].

Table 1

Research participants: overall characteristics

Parameter		Group 1 (n = 20)	Group 2 (n = 94)	Group 3 (n = 103)	Reference group (n = 130)
Age (years) Me (Q25%–Q75%)		38 (30–44)	39 (32–48)	43 (38–53.5)	33 (31–36)
Sex (Abs./%)	Males	11 (55 %)	32 (34 %)	54 (52 %)	44 (33.8 %)
	Females	9 (45 %)	62 (66 %)	49 (48 %)	86 (66.2 %)

Table 2

Parameters of LPV safety, Me (Q25%–Q75%)

Monitoring period	Group 1 (n = 20)	Group 2 (n = 62)	Group 3 (n = 59)	Group reference (n = 30)	P<0.05*	P<0.05**
IgE (conditionally healthy donor: 20–100 IU/ml)						
Prior to vaccination	5.2 (1.4–65.4)	35.6 (16.7–123.1)	18.3 (3.8–75.8)	14.7 (5.6–32.9)	1; 2	1; 2
1 month after	11.0 (6.1–27.1)	49.0 (14.8–143.7)	12.8 (2.9–58.4)		2	1; 2 2; 3
CD95 (conditionally healthy donor: 0–7 %)						
Prior to vaccination	3.6 (3.05–3.85)	3.2 (2.95–3.35)	6.0 (4.98–6.4)	4.4 (3.99–4.55)	3	1; 3 2; 3
1 month after	3.7 (2.95–3.75)	4.0 (3.89–4.32)	6.0 (5.48–6.21)		3	1; 3
CIC (conditionally healthy donor: 90–95 %)						
Prior to vaccination	71.2 (68.4; 93.9)	84.5 (42.8; 92.1)	90.4 (65.4; 87.4)	76.9 (54.2; 82.1)	–	–
1 month after	81.2 (45.8; 91.7)	86.9 (56.4; 90.5)	89.7 (49.8; 97.2)		–	–
IRI						
Prior to vaccination	1.7 (1.4–2.2)	1.6 (1.2–1.9)	1.4 (1.2–1.9)	1.7 (1.4–2.2)	–	–
1 month after	2.7 (2.3–3.2)***	1.2 (1.0–1.5)	1.6 (1.3–2.2)		1; 2	1; 2 1; 3

Note:
* means validity of discrepancy against reference group;
** means validity of discrepancy between groups 1; 2; 3;
*** means validity of discrepancy against «prior to vaccination» period.

These parameters were estimated prior to vaccination and 1 month after it. We assessed changes in immune regulatory index (IRI) that was determined as a ratio of a number of cells with CD4 phenotype to a number of cells with CD8 phenotype (CD4/CD8) prior to vaccination with LPV and 12 months after it.

We performed ELISA tests with ELISA commercial sets (Vector-Best, Cytokine, Russia) and «ELISA-AT-F1 YERSINIA PESTIS» test system («Microbe», Rospotrebnadzor's Russian Scientific Research Anti-plague Institute) and assessed immunologic efficiency of vaccination with LPV in accordance with manufacturers' instructions as per changes in parameters of Th-1 (IFN-γ, TNF-α) and Th-2 (IL4) associated cytokines production induced by Concanavalin A (Sigma), and in the level of specific antibodies to capsule plague microbe antigen (F1). We analyzed parameters obtained prior to vaccination as well as 1 and 12 months after it.

Research results were processed with non-parametric statistic procedures using STATISTICA 10 RU and MS Office Excel 2007 software packages. Mathematic analysis procedures applied to analyzed results obtained via immunologic monitoring over the volunteers involved assessing authenticity of all obtained laboratory parameters via calculating inter-group associations with Mann-Whitney U-test; to make comparisons within a group, we applied Wilcoxon's T-test [10]. Discrepancies were considered to be significant at $p < 0.05$. To analyze correlations between basic parameters of cellular and humoral immunity and to determine significance of their key parameters, we performed multidimensional trial analysis with StatSoft-Statistica.ru software package. We determined parameters that predicted immunologic restructuring efficiency of anti-plague vaccination [11].

Results and discussion. When analyzing records on prevention vaccination of volunteers who got vaccinated with LPV and questionnaires, we didn't detect any cases when somebody applied for medical aid due to overall or local reactions to vaccination. There were no complaints about any changes in health, and questionnaires allowed revealing that skin reddening on a spot where vaccine was introduced into a body developed in only 5–7% volunteers.

Table 2 contains the results obtained via assessing indirect immunologic parameters of LPV safety.

Overall analysis of all these parameters didn't reveal any significant CIC accumulation and statistically authentic increase in a share of cells that had CD95+, early apoptosis activation marker. Values of all these parameters were within ranges fixed for conditionally healthy donors and didn't differ authentically from data obtained for the reference group that was made up of volunteers who hadn't previously been vaccinated with LPV.

A detected increase in IgE contents in blood of some volunteers was still within reference values for conditionally healthy donors and didn't correlate with increased IL-4 contents. Increased IgE contents in people who were going to get vaccinated or just after vaccination were also revealed in similar research performed in the Mountain Altai natural plague focus and they were also within reference ranges fixed for conditionally healthy donors [12].

There was evidence that LPV was quite safe; namely, absence of people with a decrease in IRI 12 months after vaccination against the initial level of this parameter in volunteers prior to vaccination.

Immunologic monitoring also involves characterizing immunologic restricting in vaccinated volunteers during 12-month monitoring period; we determined ranges of fluctuations in individual immune responses to LPV depending on sex, age, number of previous vaccinations and HLA haplotype of vaccinated people [13].

We characterized induced production of Th1 (INF-γ, TNF-α) and Th2 (IL-4) associated cytokines in dynamics and established that there was significant Th1-cells activation aimed at producing cytokines associated with them during the whole monitoring period [13]. As an inductor, Concavalin A, a standard commercial T-cell mitogen and TLR2 ligand, was applied [14]. High IFN-γ and TNF-α concentration was detected in all volunteers who got vaccinated with LPV and it was authentically ($p < 0.05$) higher than the same parameter in people from the reference group. In most cases the trend persisted, especially for IFN-γ, up to the 12th month of monitoring. We estimated stimulation index (SI) that was determined as a ratio of induced cytokine production to spontaneous one for IFN-γ and TNF-α and revealed an ascending trend for the parameter as a response to vaccination with LPV. It is interesting to note that SI value in volunteers from Group 2 didn't just go down but grew significantly 12 months after vaccination. There was a descending trend in IL-4 concentration up to the 12th month of monitoring but there was a certain increase in IL-4 concentration among people from Group 3 1 month after vaccination. At the same time, SI for IL-4 grew in all groups but this growth persisted up to the 12th months in Group 3 only. It should be noted that similar trends in IFN-γ, TNF-α and IL-4 responses were registered in volunteers who got vaccinated for the 1st time in the Mountain Altai and Tuva Mountain natural plague foci [12, 15].

We assessed specific antibody response regarding capsule plague microbe antigen (F1); the assessment revealed gradual growth in specific antibodies titer in all vaccinated volunteers. A number of people with specific antibodies titer at a diagnostic level (1:80) in Group 1 reached 60 % only by the 12th month after vaccination with LPV, but as for Groups 2 and 3, specific antibodies at a diagnostic titer level and higher were registered in 57.5 % and 78% cases accordingly already 1 month after vaccination. We preformed statistical analysis (χ^2 or Pearson's test) of specific antibodies to plague microbe and revealed that a number of previous vaccinations exerted its influence on detected antibodies level ($\chi^2_{1,2}$=16.79; $p < 0.05$ and $\chi^2_{1,3}$=45.97; $p < 0.001$ and $\chi^2_{2,3}$=10.92; $p < 0.05$), but these discrepancies between Groups 1 and 2 leveled off ($\chi^2_{1,2}$=5.25; $p > 0.05$) 12 months after vaccinations and remained only against Group 3 ($\chi^2_{1,3}$=14.5; $p < 0.05$ and $\chi^2_{2,3}$=7.04; $p < 0.05$ 6 months after; $\chi^2_{1,3}$=9.54; $p < 0.05$ and $\chi^2_{2,3}$=3.13; $p > 0.05$ 12 months after). However, a share of people with positive seroconversion didn't reach 100 % among those vaccinated against plague and as per literature data specific antibodies occurrence doesn't always correlate with a body being protected from plague infection [16]. A leading role in anti-plague immunity formation belongs to cellular factor; therefore, serologic assessment of immunologic efficiency doesn't properly describe actual immune-biological restricting in a body as a response to LPV introduction [17]. The most adequate way to describe it is to assess cytokines in cultures of whole blood cells in vivo as it allows obtaining data in functional activity of different immune-competent cells and ratios between activation of T-helpers, Type 1 and 2 [18].

Experiments performed on bubonic and pneumonic plague models allowed proving that high titers of antibodies to *Y. pestis* antigens combined with low activity of IFN-γ, TNF-α, IL-17 cytokines synthesis didn't protect biological model animals (inbred mice, anthropoid and non-anthropoid apes) from death due to plague infection [19].

We assessed cellular immunity activation using results obtained via analyzing data given in Table 3.

Table 3

Characteristics of induced cytokines production in volunteers vaccinated with LPV, Me (Q25%–Q75%)

Monitoring period	Group				$P<0.05$*	$P<0.05$**
	1 (n = 20)	2 (n = 62)	3 (n = 59)	reference (n = 30)		
IFN-γ (conditionally healthy donor: 165–7,450 pg/ml)						
Prior to vaccination	85.5 (12.8; 214.2)	7.4 (3.3; 11.8)	121.7 (58.1; 169.5)	112.0 (101.4; 122.2)	2	1; 2 2; 3
1 month after	159.2 (14.6; 457.6)	10.4 (4.5; 17.1)	313.6 (143.0; 467.3)***		2;3	1; 2 2; 3
12 months after.	245.9 (194.6; 281.7)***	235.7 (135.6; 325.7)***	250.0 (137.2; 329.5)***		1; 2; 3	–
TNF-α (conditionally healthy donor: 391–2,700 pg/ml)						
Prior to vaccination	26.5 (21.7; 41.7)	18.9 (14.6; 22.0)	29.0 (26.6; 39.4)	63.7 (60.8; 104.1)	1; 2; 3	–
1 month after	67.3 (5.7; 102.2)	3.1 (1.8; 5.0)	69.5 (35.4; 147.4)		2	1; 2 2; 3
12 months after.	32.9 (20.4; 49.7)	64.9 (33.5; 109.9)	33.5 (19.5; 58.9)		1;3	1; 2 2; 3
IL-4 (conditionally healthy donor: 0–24 pg/ml)						
Prior to vaccination	2.1 (1.3; 3.8)	6.0 (4.4; 8.1)	3.6 (0.6; 2.7)	1.8 (1.2; 2.2)	2	1; 2
1 month after	3.0 (2.3; 6.8)	2.9 (0.9; 8.8)	5.3 (0.5; 4.3)		1; 2; 3	–
12 months after.	0.4 (0.2; 0.8)	0.8 (0.4; 1.4)***	0.6 (0.3; 1.3)***		1	–

Note:
* means validity of discrepancy against reference group;
** means validity of discrepancy between groups 1; 2; 3;
*** means validity of discrepancy against «prior to vaccination» period.

When assessing efficiency of anti-plague vaccination, there is an issue that remains unresolved, namely, what instruments are to be used for monitoring over population immunity and it is still unclear what level of specific antibodies can provide proper protection from the disease. Therefore, when it is necessary to determine scopes of specific plague prevention for the next epidemiologic season, we suggest assessing LPV immunologic efficiency as per data obtained during the previous season but taking into account predicted and current epizootic situation in a natural focus and/or risks that epidemiologic complications might occur. Further planning of activities on specific plague prevention in a specific natural focus should be based on these data taking into account individual immune reactivity of people who are going to get vaccinated.

This stage in our research was performed with the use of a created database entitled «Parameters of immunologic monitoring over people vaccinated against plague» (RU 2019620831).

We have developed a methodical approach according to which a reaction to vaccination with LPV in a volunteer should be given with scores (from 1 to 4); 1 score means an immune response to vaccination has not occurred; 2 scores mean that predominantly humoral response has occurred and there are specific antibodies to capsule plague microbe antigen F1 (1:80 and higher for those vaccinated for the 1st time, and 1:160 and higher for revaccinated people) and there are no reaction from cellular response predictors (induced production of Th1-associated cytokines is at the same level as prior to vaccination/revaccination); 3 scores mean that there is a mixed response when there is a growth in specific antibodies to F1 titer (higher than a diagnostic level of an applied test-system) and a positive trend in cellular immunity activation (level of induced Th1-associated cytokines production is not less than 2 times higher 12 months after vaccination than prior to it); 4 scores mean that immune response is predominantly cellular (marker cytokines content is 5 or more times higher 12 months after vaccination/revaccination than prior to it regardless of specific antibodies to F1 occurrence). It is possible to determine predominant type of immune response to LPV for each person who is going to get vaccinated against plague before a next vaccination campaign starts basing on assessment of immunologic monitoring results obtained during a previous season; consequently, we can predict efficiency of anti-plague protection and assess necessity (scope) of prevention activities and optimal time when next vaccination against this infection should be performed.

Basing on score estimates of immune reactivity obtained for volunteers vaccinated with LPV, we determined groups of people who reacted to plague microbe antigens predominantly as per cellular, humoral, or mixed type (Table 4).

Table 4

Number of people with reaction to LPV (Abs./%)

Score estimate	Immune response type	Group 1 (*n* = 20)	Group 2 (*n* = 76)	Group 3 (*n* = 100)
1	No response	6 (30 %)	7 (9 %)	6 (6 %)
2	Humoral	6 (30 %)	14 (18 %)	10 (10 %)
3	Mixed	5 (25 %)	30 (40 %)	51 (51 %)
4	Cellular	3 (15%)	25 (33 %)	33 (33 %)

According to the obtained data, a share of people with predominantly cellular or mixed response was authentically higher in Group 3, and, bearing in mind that it is cellular immunity that plays a leading role in protection from plague, we can conclude that specific prevention was more efficient in this group [17, 20].

Population immunity characteristic is a basic risks related to anticipatory effect produced by mass anti-plague vaccination. But we should remember that endogenous risks related to population immunity formation are to a great extent determined by peculiar immune reactivity of each vaccinated person [6].

Our assessment allowed revealing people with both normal and changed (increased or decreased) immunologic reactivity to LPV among volunteers who got vaccinated with the preparation. Parameters obtained for volunteers with changed reactivity were beyond the suggested score range. In case a respondent had normal immune reactivity to plague microbe, it was optimal and economically justified to apply LPV according to a standard procedure as per epidemiologic indications, namely 1 month prior to future activities in a natural plague focus given a predicted growth in epizootic activity. In case a person has lower immune reactivity, it is necessary to work out certain activities aimed at raising immunologic competence and creating individual vaccination schedules in such a way so that not less than 1 month and not longer than 6 months passed after vaccination by the moment epizootic activity in natural plague focus reached its peak. «Vaccine protection» program was implemented for getting population protected from certain vaccine-manageable infections as a part of the National Prevention Vaccination Calendar and it provided an opportunity to raise population immunity efficiency due to various schemes of specific response immune modulation [21]. At the same time, in case a person has elevated immune reactivity, it is permissible to pursue individual approach to revaccination taking into account existing risks and actual probability that epidemiologic situation might deteriorate.

Therefore, basing on immunologic monitoring results, we proved it was safe to apply LPV and it was possible to predict results of vaccination as per epidemic indications taking into account detected groups of people with normal, high, and low immune reactivity to plague microbe antigens. The latter was done in order to determine people who needed an individual approach to anti-plague vaccination; therefore, we managed to minimize risks related to excessive of insufficient scopes of activities aimed at specific plague prevention in natural foci.

Funding. The research was not granted any financial support.

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

Acknowledgement. We express our gratitude to supervisors and personnel of Rospotrebnadzor Regional office in Kalmyk Republic, Center for Hygiene and Epidemiology in Kalmykia, Rospotrebnadzor’s Elista Anti-Plague Station and Astrakhan Anti-Plague Station for their assistance rendered in organizing clinical materials collection.

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Received: 11.08.2020
Accepted: 11.11.2020
Published: 30.12.2020

UDC 614.8.026.1
DOI: 10.21668/health.risk/2020.4.15.eng

Read online

Research article

FACTORS THAT CAUSE CONTAGION AND SPREAD OF HIV AMONG PEOPLE FROM SOCIAL RISK GROUPS

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Despite all significant efforts being made by the public healthcare, state authorities, and public organizations, HIV-infection has been a topical issue over the last 30 years. Commercial sex workers (CSW) are a basic risk group when it comes down to this infection.

Our research goal was to determine HIV prevalence among commercial sex workers and risk factors that cause their contagion with it.

We performed an epidemiologic analytical ecologic examination to study HIV prevalence risk factors that cause spread of this infection among CSW. 154 CSW were questioned with a sociological procedure applied to do it; they lived in three cities in Perm region, and morbidity with HIV was higher than on average in the region in two of them, B. and K. The city P. was taken as a reference territory due to a relatively favorable situation with HIV infection spread there. Risk factors that caused HIV infection were determined via an observational analytical case-control study; the «case» group was made up of 46 CSW who were infected with HIV and the control group included 108 CSW who didn't have this infection. All the obtained data were statistically processed with SPSS Statistics 17.0 and Statistica 6.0 software packages.

HIV prevalence among commercial sex workers was rather different on the examined territories. It amounted to 42.6 % and 35.0 % in cities B. and K. and it was 2.3 and 1.9 times higher accordingly than in city P. It was detected that there were several factors making for HIV infection spread among CSW; they were high morbidity with HIV on a given territory; an early start of sexual life; disregard of contraception; drug abuse; medical services and prevention programs being hardly available to CSW. A high probability that CSW would get infected with HIV was determined for people who didn't use condoms, took drugs intravenously, and were not epidemiologically alerted to HIV infection.

Key words: *HIV-infection, prevalence, contagion, susceptible groups, commercial sex-workers, ecological epidemiological study, case-control study.*

Prevention from HIV-infection/AIDS is a priority issue for pubic healthcare due to pandemic HIV spread, gravest socioeconomic consequences of the pandemic and absence of any specific prevention tools at the moment. The most susceptible population groups include people who take drugs via injections, men who have homosexual contacts, and commercial sex workers (CSW)[1] as well.

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HIV-infection burden among CSW was analyzed in 50 countries with low and middle income; the analysis revealed that overall HIV-infection prevalence amounted to 11.8 % in these population groups and it was significantly (13.5 times) higher than among overall female population in those countries [1, 2]. The parameter was different in different regions, varying from 0.2–1.8 % in the Middle East and North Africa up to 36.9 % in African countries located to the south from Sahara [3–7]. In Southern Asia countries and in Latin America HIV-infection prevalence among CSW doesn't differ authentically from the same parameter among overall population and amounts to 5.1 % and 4.4 % accordingly. HIV-infection prevalence is higher in Eastern Europe, 10.9 %, and the USA, 15.0 %; the parameter is 1.8 % in high-income European countries [5, 8].

In Russia HIV-infection prevalence among CSW remains unknown due to this target population group being almost unavailable for any systemic research. There are results obtained via some sporadic studies; according to them, HIV-infection prevalence among CSW varies from 2.3 % to 20.3 % and is 2–12 times higher than among overall country population [9–15].

Given all the above stated, **our research goal** was to examine HIV-infection prevalence among CSW and to determine risk factors that caused their contagion with the infection.

Data and methods. HIV-infection prevalence among CSW and risk factors that make for the infection spread in this population group were examined via an epidemiologic analytical and ecological study; 154 CSW from three urban settlements located in Perm region took part in it. Two settlements, B. (*n* = 54) and K. (*n* = 40) were characterized with high morbidity with HIV-infection that was 1.9 times and 1.5 times higher accordingly than in the region in general. The 3rd settlement, P. (*n* = 60) was included as a reference territory since situation there regarding HIV-infection was relatively well. All the examined groups were similar in terms of sex and age; average respondents' age amounted to 32.7, 32.9 and 30.8 in settlements B., K., and P. accordingly ($p = 0.000$).

Risk factors that made for CSW getting infected with HIV were examined via «case – control» epidemiologic observation analytical study. «Case» group included 46 CSW who were infected with HIV; reference group was made up of 108 CSW who were not infected with it.

Sociological questioning was performed via formalized interviews. They were performed anonymously with a questionnaire specifically designed by the «Open Health Institute» (a structured questionnaire). It was created taking into account recommendations by the World Health Organization and Russian regulatory-methodical documents on performing biological-behavioral studies among population groups who ran elevated risks of getting infected with HIV. The questionnaire included the following sections: record data (sex, age, and education); sexual contacts history (age at which the 1st sexual contact took place, number of sexual partners, and use of condoms); psychoactive drugs intake; access to public healthcare services and HIV-infection preventive programs.

All the obtained data were statistically processed with SPSS Statistics 17.0 and Statistica 6.0 software packages. We applied Kolmogorov-Smirnov test to assess whether parameters were distributed normally. In case quantitative parameters distribution was normal, data were processed with Student's t-test (t) for two independent samplings and results were given as a simple mean (M) ± standard error (m); in case quantitative parameters distribution was not normal, data were processed with Mann-Whitney test for two independent variables and results were given as median with lower and upper quartiles (Me [LQ; UQ]). To determine statistical significance of discrepancies between results obtained for quantitative parameters, we applied Fischer's angular transformation test (φ). Critical significance was taken as 0.05 ($p \leq 0.05$) in this research.

Results and discussion. We assessed HIV-infection prevalence among CSW; the assessment revealed that 42.6 ± 6.7 % respondents from B. were HIV-infected; 35.0 ± 7.5 %, from K. (p = 0.15). HIV-infection prevalence amounted to 18.3 ± 3.6 % in P. and it was 2.3 and 1.9 times lower than in B. and K. ($p = 0.000$ and $p = 0.000$ accordingly). HIV-infection prevalence among CSW correlated with HIV-infection epidemic intensity on the examined territories ($r = 0.78$). Thus, average long-term (2015–2019) morbidity with HIV-infection in P. where HIV-infection prevalence among CSW was the lowest amounted to 126.1 ± 3.5 cases per 100 thousand people against 193.2 ± 11.8 and 185.9 ± 18.9 in B. and K. accordingly.

Comparative assessment of results obtained via questioning performed among CSW living on the examined territories and aimed at determining their sexual behavior traits revealed certain discrepancies (Table 1).

Thus, there were no authentic discrepancies in the age at which respondents in the settlements B. and K. had their first sexual contact as it was 15.6 and 15.7 accordingly. CSW from the settlement P. started their sexual life significantly later, at 16.3 ($p = 0.044$ and $p = 0.05$). The lowest sexual activity was detected in B. where CSW had up to 65 [40; 120] sexual partners annually; this number was 5 times higher for CSW from K. and P., 325 [100; 662.5] and 400 [106; 685] accordingly. And only 64.8 ± 6.5 % CSW from B. and 62.5 ± 7.7 % CSW from K. used condoms whereas all the CSW from P. did it ($p = 0.000$). Each second respondent in B. (50.5 ± 6.8 %) stated there were people infected with HIV among her sexual partners over the last year; the parameter was lower in K. and P. and amounted to 25 ± 6.8 % and 16.7 ± 4.8 % accordingly ($p = 0.000$). We should note that 56 ± 6.8 % CSW from B. who had sexual contacts with HIV-infected people didn't use condoms. We established that more than half CSW from B. took drugs via injections (50.7 ± 6.8 %); only 27.5 ± 7.1 % respondents from K. admitted intravenous drug intake, and as for CSW from P., they took drugs via injections much less frequently ($p = 0.000$ and $p = 0.05$ accordingly).

We assessed whether CSW had easy access to medical aid and prevention programs; our assessment revealed that 9 out of 10 CSW from B., K., and P. had had HIV-infection tests (95.0 ± 2.9 %; 90 ± 4.7 %, and 93.3 ± 3.2 %

Table 1

Risk factors of HIV spread among commercial sex workers on unfavorable territories (settlements B. and K.) and a favorable (settlement P.) one regarding HIV-infection in Perm region (%)

No.	Risk factors	Settlement		
		B.	K.	P.
1.	Average age at which the 1st sexual contact took place	15.6	15.7	16.3*
2.	Number of sexual partners per year	65 [40; 120]	400 [106; 685]	325 [100; 662.5]
3.	Use of condoms	64.8 ± 6.5 %	62.5 ± 7.7 %	100 %*
4.	HIV-infected people among sexual partners	50.5 ± 6.8 %*	25 ± 6.8 %	16.7 ± 4.8 %
5.	Intravenous drugs intake	50.7 ± 6.8 %	27.5 ± 7.1	16.9 ± 4.8 %*
6.	HIV-testing during the last year	45.3 ± 6.8 %	52.6 ± 7.9 %	80.4 ± 5.1 %*
7.	Pre-testing consultation	28.3 ± 6.1 %	39.5 ± 7.7 %	55.4 ± 6.4 %*
8.	Consultations after testing	32.1 ± 6.4 %	34.2 ± 7.5 %	50.0 ± 6.5 %*
9.	Participation in programs aimed at complex HIV prevention	7.4 ± 3.5%	30.9 ± 7.3 %	73.3 ± 5.7 %*

Note: * means validity at $p \leq 0.05$.

accordingly). Approximately half CSW from B. and K. had got their HIV tests over the last year (45.3 ± 6.8 % and 52.6 ± 7.9 % accordingly); the parameter was authentically higher in P. and amounted to 80.4 ± 5.1 % ($p = 0.004$ and $p = 0.000$ accordingly). But still, pre- and after-tests consulting was provided for rather few people from this social group. Thus, in B. and K. only one third of respondents got any consultation before testing (28.3 ± 6.1 % and 39.5 ± 7.7 % accordingly) and after testing (32.1 ± 6.4 % and 34.2 ± 7.5 % accordingly); the parameter was 1.2–2.0 times higher in P. and amounted to 55.4 ± 6.4 % ($p = 0.004$; $p = 0.05$ accordingly) and 50.0 ± 6.5 % ($p = 0.05$; $p = 0.05$) accordingly. Pre- and after-tests consultations are obviously a significant prophylactic activity that allows preventing HIV-infection spread; in spite of this fact each second tested respondent was not provided with necessary information on the infection burden and basic ways to prevent it.

Only 4 CSW from B. were aware that there was a complex HIV-infection prevention program for them (7.4 ± 3.5 %) and even they had never participated in it. Only each third respondent from K. knew about the existing prevention programs (30.9 ± 7.3 %) ($p = 0.000$) and took part in them. More than half CSW from P. (73.3 ± 5.7 %) were not only well aware of such programs but also took active part in them.

Our research results indicate that there are several risk factors that make for HIV-infection spread among CSW. They are early age at which the 1st sexual contact took place; negligent attitude towards using condoms; intravenous drugs intake; HIV-testing being rather rare, rarer than once a year; rather few CSW provided with pre- and after-tests consulting and participating in the existing complex programs aimed at HIV-infection prevention.

Risk factors that can cause HIV-infection spread among CSR were estimated via «case – control» study; the estimation revealed that each sixth HIV-infected CSW took drugs via injections (60.9 ± 7.2 %) against 13.9 ± 3.3 % in «control» group (Table 2). CSW who took drugs intravenously ran 9.6 times higher risks to get infected with HIV than CSW who didn't take drugs (OR 9.6; [95 % CI: 4.3–21.6]). Intravenous drug intake is obviously a significant factor that makes for CSW getting infected with HIV.

Meth cathinones, or synthetic drugs (usually called «bath salts»), are at present the most widely used drugs in Perm region. They belong to psychoactive drugs and can change a person's sexual behavior due to specific effects produced on human mind; it results in growing number of promiscuous and unsafe sexual contacts and such contacts, in their turn, lead to HIV-infection spread via sex becoming more significant among CSW [10, 16].

We established that use of condoms by CSW was a protection factor that led to lower risks of getting infected with HIV (OR 0.14; [95 % CI: 0.06–0.31]). These results are well

Table 2

Frequency of behavioral risk factors among HIV-infected («case») and not infected («control») commercial sex workers

No.	Risk factor	«case» ($n = 46$)		«control» ($n = 108$)		p
		abs.	%	abs.	%	
1.	Intravenous drug intake	28	60.9	15	13.9	$p = 0.000$
2.	Use of condoms	24	52.2	96	88.9	$p = 0.000$
3.	Awareness about basic ways and factors that make for HIV-infection spread	37	80.4	39	36.1	$p = 0.000$
4	HIV-infection testing over the last year	37	80.4	54	50	$p = 0.000$
5.	Pre- and after-tests consultations	26	56.5	35	32.4	$p = 0.005$

in line with data obtained via foreign research works according to which use of condoms results in at least 80 % lower risk of getting infected with HIV [17–20].

We assessed awareness among CSW about how they could get infected with HIV and revealed that HIV-infected CSW were quite well aware about ways and factors that made for HIV-spread; CSW who were not infected were not so well aware (2.2 times lower number, $p = 0.000$). Obviously, CSW become interested in the infections and ways to get infected with it only after the contagion. Low awareness among CSW who are not infected and absence of any stimuli to have safe sexual contacts indicate that this population group still runs rather high risks of getting infected with HIV.

Our sociological questioning revealed that CSW with HIV-infection got pre-and after-tests consultations 1.6-1.7 times more frequently that CSW who were not infected ($p = 0.000$); it indicates that CSW who are not infected are also not alerted regarding the infection and pre-and after-tests consulting has rather low preventive influence on them.

Given all the above stated, we can conclude that probability of getting infected with HIV is higher among those CSW who do not use condoms, take drugs intravenously, and are not properly alerted regarding HIV-infection.

Conclusions.

1. Factors that make for HIV-infection spread among CSW are high morbidity with HIB-infection on a given territory; early age at which the 1st sexual contact took place; negligent attitude towards using condoms; intravenous drugs intake; CSW having limited access to medical aid and prevention programs.

2. Unsafe sex, intravenous drugs intake, low awareness about risks of infection result in significant increase in probability that CSW may get infected with HIV; commercial sex workers themselves are a real threat for their customers when it comes down on HIV-infection.

Funding. The research was not granted any sponsor support.

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

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Received: 18.08.2020
Accepted: 05.11.2020
Published: 30.12.2020

MEDICAL AND BIOLOGICAL ASPECTS RELATED TO ASSESSMENT OF IMPACTS EXERTED BY RISK FACTORS

UDC 616.153.478.6-008.61-02-07 (470.53)
DOI: 10.21668/health.risk/2020.4.16.eng

Read online

Research article

POLYMORPHISM OF FOLATE CYCLE GENES AS A RISK FACTOR OF HYPERHOMOCYSTEINEMIA

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Hyperhomocysteinemia (HHc) is a new factor being considered at the moment that can cause damage to vessel walls. Its occurrence depends on genetic peculiarities of a body.

Our research goal was to estimate frequency of genetic polymorphisms (SNP) in folate cycle genes among people living in Perm region and its influence on homocysteine (Hc) concentration in blood serum.

We examined 189 women (32.2 ± 5.25). Hc concentration in blood serum was determined with immune chemiluminescent procedure. We examined frequency of SNP in folate cycle genes with pyrosequencing.

Homozygote state as per minor alleles in methylene tetrahydrofolate reductase (MTHFR) gene (rs 1801133 u rs 1801131) and MTR gene (rs 1805087) was registered 7.5, 5.4, and 13.75 times less frequently than homozygote state as per neutral alleles. Heterozygote state prevailed for genes of methionine synthase reductase and folate transport protein among examined SNP. Homozygotes as per minor allele SNP in MTHFR gene (Ala222Val; rs 1801133) had higher Hc concentration in blood serum that amounted to 8.476 ± 3.193 mmol/L and was 1.276 times higher than the same parameter in homozygotes as per neutral allele (p=0.0036). We didn't establish any influence on Hc contents in blood serum for the remaining 4 SNP in folate cycle genes (p> 0.1).

Examined SNP in MTHFR and MTR genes tended to have neutral alleles more frequently than minor ones. SNP in genes of other examined proteins belonging to folate cycle didn't have any differences in frequency of examined alleles. We didn't detect a combination of homozygote state as per two SNP in MTHFR gene or homozygote state as per one SNP and heterozygote state as per another one in a genome. Only SNP in MTHFR gene (Ala222Val, rs 1801133) authentically causes increase in homocysteine concentration out of all the examined SNP in genes of folate cycle enzymes and proteins.

Key words: *homocysteine, hyperhomocysteinemia, single-nucleotide polymorphisms, folate cycle genes, methylene tetrahydrofolate reductase, methionine synthase, methionine synthase reductase, folate transport protein.*

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Homocysteine (Hc) is a proteinogenic amino acid that is not used to synthesize proteins but instead is formed in intermediate metabolism of amino acids and their derivatives [1, 2]. Healthy people usually have rather low Hc concentration in their blood serum [3–5]. Its elevated concentration in blood serum (hyperhomocysteinemia or HHc) is a risk factor that can cause damage to vessels endothelium and endothelial dysfunction thus resulting in higher risks of thrombosis leading to disrupted blood supply to various organs and systems [4–7]. At present HHc is seen as a factor that participates in pathogenesis of multiple diseases [8–10]. HHc role in implantation defects and defects in fertilized ovum development has also been proven; it can result in infertility, miscarriage, and fetus development pathologies [11, 12]. Several researchers have drawn attention to a correlation between HHc and atherosclerotic damage to arteries, disrupted blood supply to the brain, and neurodegenerative diseases occurrence [13–17]. Besides, it has been proven that there is a correlation between elevated Hc contents in blood serum and diseases of other organs [18–20].

HHc occurs due to diseases of the liver when there are disorders in intermediate amino acids metabolism, or there is vitamin deficiency (vitamin B_6, vitamin B_c or folic acid, and vitamin B_{12}). The highest homocysteine contents in blood serum are detected in case a person suffers from hereditary hyperhomocysteinemia, a disease that is caused by congenital defects in the process of synthesizing enzymes that participate in Hc metabolism [21].

Nowadays hyperhomocysteinemia is considered to be a disorder with hereditary predisposition that can develop into an actual disease due to many other factors. It should be interesting to study influence exerted by single nucleotides replacements or so called *single nucleotide polymorphism or SNP* in folate cycle genes and their effects produced on homocysteine metabolism [22, 23]. Folate cycle is a complex cascade process controlled by enzymes that use folic acid derivatives as coenzymes. In some cases gene polymorphism that occurs due to SNP results in one amino acid being replaced with another. As a result, there are slight changes in the structure of a protein that is produced by a mutant gene. In some cases these changes can be adverse under certain conditions or they can bring about certain advantages for a person who carries such a gene in other circumstances. It is these mutations that provide basis for natural selection since mutations that are adverse under certain conditions can provide competitive advantages in other circumstances given changes in the environment an organism has to live in.

Interest a lot of researchers pay to genetic versions of genes that code folate cycle enzymes is mostly due to multiple publications dwelling on a correlation between various SNP and frequency of multiple different diseases. Thus, there are publications on a correlation between SNP in folate cycle genes and risks of vascular diseases, oncologic diseases, obstetric pathology, and infertility [16, 17, 24–31].

In relation to that it seems only natural to have interest in examining SNP in folate cycle genes among different population groups and its correlation with hyperhomocysteinemia occurrence. Over the last years there have been publications in the Russian Federation focusing on examining SNP in folate cycle genes among people living in Penza region and Altai region [32, 33]. However, we haven't been able to find any research on frequency of SNP in folate cycle genes in people living in Perm region; therefore, results obtained via such research are truly vital and they can be of significant interest for experts in the sphere.

Our research goal was to assess frequency of SNP in folate cycle genes in people living in Perm region; to analyze influence exerted by SNP in folate cycle genes as risk factors causing elevated Hc concentration in blood serum.

Data and methods. The study was accomplished in conformity with ethical principles for medical examinations with people participating in them fixed in the WHO's Helsinki Declaration. The study was also approved upon by the Ethical Committee of E.A. Vagner's Perm State Medical University of the RF Public Healthcare Ministry.

189 women who were in their fertile age took part in our research (32.2 ± 5.25; median 31 and interquartile range 28–36); they all were employed at enterprises located in Perm city.

Participants were included according to the following criteria:

– females;

– pregnancies in case history;

– all the examined women belonged to at least the 2nd generation living in Perm region.

Participants were excluded according to the following criteria:

– a woman was pregnant at the moment the study took place;

– pathology in the liver determined as per results obtained via examining activity of enzymes in blood serum (alanine aminotransferase; aspartate aminotransferase; gamma glutamyl transferase; alkaline phosphatase) and bilirubin concentration;

– a woman was taking sulfanamides, polyvitamins, or folic acid at the moment the study was accomplished;

– pancreatic diabetes, arterial hypertension, smoking, alcoholism.

Blood samples were taken in the morning on an empty stomach 12 hours after the last meal. We determined Hc concentration in blood serum with immune-chemical luminescent procedure performed with «Immulite-2000» immune-chemical analyzer (Siemens, Germany) and using original reagents kits. Genetic polymorphism in folate cycle genes was examined via pyrosequencing with the use of «AmpliSens® Pyroscreen» «FOLATE – screen» system for genetic analysis (The Central Scientific Research Institute for Epidemiology).

We examined frequency of the following SNP:

– mutation of methylenetetrahydrofolate reductase gene (MTHFR) (Ala222ValC>T, rs 1801133);

– mutation of methylenetetrahydrofolate reductase gene (MTHFR) (Glu429AlaA>C, rs 1801131);

– mutation of methionine-synthase gene (MTR) (Asp919Gly, A>G, rs 1805087);

– mutation of methionine-synthase reductase gene (MTRR) (Ile22Met, A>G, rs 1801394);

– mutation of folate transporter gene (SLC19A1) (His27Arg, A>G, rs 1051266).

Alleles frequency was calculated as per Hardy-Weinburg equation [34].

All the results were statistically processed with STATISTIC Av. 7 software package (StatSoft Inc., the USA). We calculated descriptive statistic parameters for each data array such as simple mean (M), standard deviation (SD), median (Me), and interquartile range (LQ; UQ), as well as minimum (min) and maximum (max) value. All the obtained results were estimated with Shapiro-Wilk test and it allowed us to reject a zero hypothesis that all the obtained results were distributed normally. Given that, we used Kruskal – Wallis non-parametric test H to make comparisons.

Maximum permissible probability of type I error (p) was taken at statistical significance level equal to or lower than 0.05.

Results and discussion. We analyzed genotypes of SNP in various folate cycle proteins and enzymes in the examined group and detected significant discrepancies. Results are given in Table 1 and shown in Figure (Table 1, Figure).

Most examined SNP in MTHFR gene (rs 1801133 и rs 1801131) and MTR gene (rs 1805087) were characterized with homozygous state as per variants of allele that prevailed among the examined population. Homozygous state as per minor alleles was registered 7.5, 5.4 and 13.75 times less frequently that homozygous state as per neutral alleles (Table 1).

Methionine-synthase reductase enzyme and folate transporter protein predominantly had heterozygous state for the examined SNP and a number of homozygous state genotype cases, both for traditional alleles and minor ones, was almost the same (Figure). Homozygous state frequency as per minor and neutral (wild type) allele was practically the same for folate transporter; as for methionine-synthase reductase, homozygous state here occurred 1.44 times more frequently as per minor allele than as per neutral (wild type) one.

Table 1

Distribution of relative frequency (%) of examined genetic polymorphisms in folate cycle genes in women living in Perm region (n = 189)

No	SNP in folate cycle genes	Alleles combinations		
		Homozygous as per neutral allele	Heterozygous	Homozygous as per minor allele
1	Methylenetetrahydrofolate reductase (MTHFR) (Ala222ValC>T, rs 1801133)	105 (55.6%)	70 (37%)	14 (7.4%)
2	Methylenetetrahydrofolate reductase (MTHFR) (Glu429AlaA>C, rs 1801131)	81 (42.9%)	93 (49.3%)	15 (8 %)
3	Methionine-synthase (MTR) (Asp919GlyA>G, rs 1805087)	110 (58.2%)	71 (37.6%)	8 (4.2%)
4	Methionine-synthase reductase (MTRR) (Ile22Met, A>G, rs 1801394)	43 (22.8%)	84 (44.4%)	62 (32.8%)
5	Folate transporter (SLC19A1) (His27Arg, A>G, rs 1051266)	46 (24.3%)	97 (51.4%)	46 (24.3%)

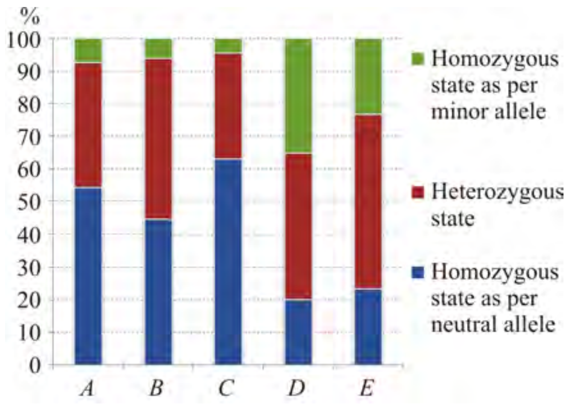

Figure. Folate cycle proteins genes: frequency (%) of genotypes (A – Methylenetetrahydrofolate reductase; B – Methylenetetrahydrofolate reductase; C – Methionine-synthase; D – Methionine-synthase reductase; E – folate transporter)

Table 2 contains results obtained via calculating neutral and minor alleles frequency; the calculations were performed according to Hardy-Weinburg formula (Table 2).

Frequency of various allele variants was significantly different in the examined population for SNP in MTHFR gene (rs 1801133 и rs 1801131) and MTR gene (rs 1805087) (Table 3). The said SNP were characterized with neutral allele being much more frequent than minor one. Thus, the discrepancy amounted to 2.86 times for SNP in MTHFR gene (rs 1801133) and 2.07 times for SNP in MTHFR gene (rs 1801131). The greatest discrepancies were detected for SNP in MTR gene (rs 1805087) where minor allele occurred 3.34 times less frequently than a variant that was prevailing in the examined population.

Table 2

Relative frequency (%) of neutral and minor alleles in folate cycle genes in women living in Perm region (n = 189)

No	A type of SNP in folate cycle gene	Alleles frequency	
		neutral	minor
1	Methylenetetrahydrofolate reductase (MTHFR) (Ala222ValC>T, rs 1801133)	0.7408	0.2592
2	Methylenetetrahydrofolate reductase (MTHFR) (Glu429AlaA>C, rs 1801131)	0.6746	0.3254
3	Methionine-synthase (MTR) (Asp919GlyA>G, rs 1805087)	0.7698	0.2302
4	Methionine-synthase reductase (MTRR) (Ile22Met, A>G, rs 1801394)	0.4497	0.5503
5	Folate transporter (SLC19A1) (His27Arg, A>G, rs 1051266)	0.5	0.5

Table 3

Frequency of SNP in MTHFR gene among all the examined women

Parameter		SNP MTHFR (Glu429Ala A>C, rs 1801131) Homozygotes as per neutral allele	Heterozygotes	Homozygotes as per minor allele
SNP MTHFR (Ala222Val C>T, rs 1801133)	Homozygotes as per neutral allele	17.07 %	30.84 %	6.29 %
	Heterozygotes	20.06 %	18.26 %	–
	Homozygotes as per minor allele	7.48 %	–	–

Table 4

Homocysteine concentration (μmol/L) in blood serum of healthy women (n = 189) with different variants of SNP in folate cycle genes

Single nucleotide polymorphism (SNP) types	Genotype as per single nucleotide polymorphism (SNP): Homozygous as per neutral allele	Heterozygous	Homozygous as per minor allele	p
Methylenetetrahydrofolate reductase (MTHFR) (Ala222ValC>T, rs 1801133)	6.642 ± 2.242 / 6.21 (5.09–7.54) 2.57–16.8	7.656 ± 2.885 / 6.915 (6.05–8.47) 3.6–21.2	8.476 ± 3.193 / 7.095 (6.74–9.46) 5.03–15.5	0.0036 (H = 11.27)
Methylenetetrahydrofolate reductase (MTHFR) (Glu429AlaA>C, rs 1801131)	7.271 ± 2.576 / 6.85 (5.57–8.2) 2.57 – 16.8	6.998 ± 2.745 / 6.33 (5.24–7.63) 3.84 – 21.2	7.479 ± 2.245 / 6.86 (5.61–9.24) 4.43 – 11.6	0.27 (H = 2.64)
Methionine-synthase (MTR) (Asp919GlyA>G, rs 1805087)	7.275 ± 3.009 / 6.435 (5.37–8.03) 2.57 – 21.2	6.916 ± 1.901 / 6.79 (5.45–7.76) 3.6 – 12.9	7.59 ± 2.745 / 6.985 (5.745–8.745) 4.67 – 13.1	0.85 (H = 0.32)
Methionine-synthase reductase (MTRR) (Ile22Met, A>G, rs 1801394)	7.019 ± 2.395 / 6.38 (5.1–8.24) 4.14 – 14.7	6.802 ± 2.281 / 6.585 (5.325–7.595) 2.57 – 16.7	7.723 ± 3.125 / 7.14 (5.61–8.77) 3.6 – 21.2	0.16 (H = 3.72)
Folate transporter (SLC19A1) (His27Arg, A>G, rs 1051266)	7.009 ± 1.996 / 6.825 (5.37–7.83) 3.84–12.4	7.171 ± 2.989 / 6.37 (5.43–7.6) 2.57–21.2	7.261 ± 2.41 / 6.905 (5.61–9.15) 3.6–13.1	0.66 (H = 0.84)

Note:
Numerator is $M \pm SD$, denominator is Me (LQ – UQ), minimum and maximum values are given under each fraction; p is determined as per H values of Kruskal – Wallis criterion.

Discrepancies in allele variants frequency detected for folate transporter protein (SLC19A1) and MTRR enzymes were not so drastic as opposed to significantly asymmetric distribution of alleles frequency detected for SNP in MTHFR and MTR enzymes (Table 2). Thus, neutral and minor allele frequency was practically the same for folate transporter protein, and as for methionine-synthase reductase, minor allele here was 1.22 times more frequent that neutral one.

We examined 189 women and analyzed the results; there was not one case when an examined woman has a combination of homozygous state as per SNP for two minor alleles in MTHFR gene (Table 3).

Table 4 contains the results obtained via examining Hc concentration in blood serum depending on a type of genetic polymorphism in the examined genes.

We analyzed dependence between Hc concentration in blood serum and SNP in folate cycle and revealed statistically significant discrepancies only for SNP in methylene-tetrahydrofolate reductase gene (MTHFR) (Ala222ValC>T, rs 1801133). Hc concentration in blood serum of homozygotes as per minor allele was 1.276 times higher than in that of homozygotes as per neutral allele ($H = 11.27$; $p = 0.0036$); average Hc concentration in blood serum of heterozygous women was somewhere in between values obtained for women with homozygous state (as per traditional and minor allele) of the examined genetic polymorphism.

As for the rest examined single nucleotide polymorphisms in folate cycle genes, we didn't establish any statistically significant effects produced by them on Hc concentration in blood serum ($p > 0.1$).

Regularities which we detected in frequency of alleles in folate cycle genes are typical for population living on the examined territory. We analyzed relative frequency of the examined alleles and established that their distribution was quite typical for people living in the European part of Russia.

Discrepancies in frequency of alleles in genes caused by SNP probably determine their influence on adaptability (advantages) their carriers have. Thus, more frequent neutral alleles probably determine certain advantages that their carriers have in specific conditions in comparison with minor allele carriers. At the same time practically the same frequency of alleles indicates that their carriers don't have any advantages. This conclusion is the most probable for the examined SNP in folate transporter protein gene and SNP in methionine-synthase reductase gene.

It is especially interesting to note that there was no homozygous combination of two SNP in the genome of the same protein. Having examined 189 women, we didn't detect any case in which an examined woman had homozygous state as per SNP for two minor alleles in MTHFR gene. Replacement of one nucleotide in the genome is probably accompanied with replacement of one amino acid and it has insignificant influence on functions performed by a coded protein. Combination of two SNP, each producing insignificant effects on functional activity of a protein molecule, probably results in synthesis of a defect protein with gravely distorted properties. In homozygous state such a combination may lead to disorders in body vital capacity. We also didn't detect any states of genotypes in MTHFR genes in which there would be a combination of homozygous SNP state as per one SNP with heterozygous state as per another SNP.

Hc concentration in blood serum depends on multiple factors that could be rather conditionally divided into non-modifiable and modifiable ones depending on impacts exerted on damage to vessel walls.

Modifiable factors that make for hyperhomocysteinemia are factors that can be adjusted, for example, deficiency of group B vitamins (B_6, B_c and B_{12}), metabolic disorders caused by liver and kidneys diseases, nutrition habits, or hormonal background.

Sex, age, and genotype peculiarities are non-modifiable risk factors that can cause hyperhomocysteinemia.

Reference range for Hc concentration in blood serum is 5–15 µmol/L. Hc concentration in blood serum equal to 15–30 µmol/L is considered moderate increase in homocysteine contents; values within 30–100 µmol/L are seen as average hyperhomocysteinemia. Hc concentration in blood serum being higher than 100 µmol/L means there is grave hyperhomocysteinemia.

Our analysis of SNP in folate cycle genes allowed revealing that some of them were associated with elevated homocysteine concentration and risks of hyperhomocysteinemia occurrence. In particular, homozygous state of single nucleotide replacement in methylenetetrahydrofolate reductase gene (MTHFR) (Ala222ValC>T, rs 1801133) should be treated as an independent risk factor that might cause HHc occurrence.

Despite there is slight increase in Hc concentration in blood serum (by 26.7% against values obtained for women with homozygous state as per neutral allele), this effect can result in clinical manifestations of various diseases and can be considered an independent risk factor that might cause hyperhomocysteinemia occurrence. Over recent years there have been publications where it is stated that Hc concentration in blood serum within 12–15 µmol/L, or the upper limit of the reference range, should be considered mild HHc for people older than 50 and not a physiologically normal state [35].

Elderly people didn't take part in the present research; despite that, all the obtained data allow assuming that statistically significant HHc occurs in patients with homozygous state as per single nucleotide replacement in methylenetetrahydrofolate reductase gene (MTHFR) (Ala222ValC>T, rs 1801133).

Other examined polymorphisms in folate cycle genes do not have any associations with statistically significant increase in homocysteine concentration in blood serum and can't be considered risk factors that might cause hyperhomocysteinemia occurrence.

Bearing in mind that genetic shapers are non-modifiable risk factors for patients with homozygous state of minor allele in methylenetetrahydrofolate reductase gene (MTHFR) (Ala222ValC>T, rs 1801133), it is necessary to pay great attention to control over modifiable risk factors that can cause hyperhomocysteinemia.

Folate cycle is a complex metabolic process that is aimed at turning sulfur-containing acid, or homocysteine, into methionine catalyzed by enzymes with their co-enzymes being vitamin B_c (folic acid) derivatives. A key role in folate cycle belongs to such an enzyme as 5,10-methylenetetrahydrofolate reductase (MTHFR) [36]. Mutation in a gene that codes MTHFR is the most frequent enzyme defect that is related to elevated homocysteine contents. At present there are several known mutations in MTHFR gene located in the locus 1p36.3. The most frequent one is replacement of C677T nucleotides (alanine being replaced with valine in MTHFR protein) that becomes apparent via their thermal lability and a 60% decrease in MTHFR enzyme activity [35, 36]. Another possible polymorphism in MTHFR gene is adenine being replaced with cytosine in position 1298. It results in glutamine acid residue being replaced with alanine residue in the regulatory domain of the enzyme and it is usually accompanied with a slight decrease in enzyme activity. People who are homozygous as per A1298C mutation tend to have 35 % lower activity of their MTHFR gene than the physiological standard. This decrease can probably result in elevated homocysteine contents but there have been no significant changes in Hc concentration detected in practice.

Conclusions. Women living in Perm region tend to have different frequency of SNP alleles in folate cycle genes. SNP in MTHFR and MTR genes usually have prevailing neutral allele against minor one. We haven't been able to detect any significant discrepancies in the examined alleles frequency for SNP in methionine-synthase reductase gene and folate transporter gene.

We haven't either detected a combination of homozygous states as per two SNP in MTHFR gene or homozygous state as per one SNP and heterozygous state as per another.

Our analysis of the examined SNP in genes of folate cycle enzymes and proteins allowed establishing that only SNP in MTHFR gene resulted in authentic decrease in homocysteine concentration; when this SNP occurs, it can be considered an independent risk factor causing hyperhomocysteinemia. People who are homozygous as per SNP in MTHFR (Ala222ValC>T, rs 1801133) tend to have elevated average homocysteine concentration that is by 27.6 % higher than in people who are homozygous as per neutral allele. Other examined polymorphisms were not accompanied with elevated homocysteine concentration in blood serum and they can't be considered risk factors that might cause an increase in homocysteine concentration in blood serum.

Funding. The research was not granted any sponsor support.

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

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Received: 06.07.2020
Accepted: 05.11.2020
Published: 30.12.2020

UDC 613.9: 378.172
DOI: 10.21668/health.risk/2020.4.17.eng

Read online

Research article

STRESS BEFORE EXAMS AS A RISK FACTOR CAUSING FUNCTIONAL DISORDERS IN THE CARDIOVASCULAR SYSTEM IN STUDENTS WITH DIFFERENT METABOLIC STATUS

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Students who attend a medical HEE often face strain in their adaptation mechanisms when preparing for exams; it can create substantial preconditions for functional deregulation in body systems. The articles outlines some results obtained via examining heart rate variability (HRV) in students of the 2nd and the 3rd year attending the North Ossetia State Medical Academy who had different metabolic status in a period prior to exams.

Our research goal was to assess the state of the vegetative nervous system and regulatory systems in students with different metabolic status (BMI < 25; BMI=25–29.99; BMI=30–34.99.) who had to face excess stress during preparation to exams. Heart rate intervals were registered during five minutes in an examined person being at rest. HRV parameters were analyzed in time and frequency domains.

We revealed that medical students had elevated activity of the sympathetic section in their vegetative nervous system (VNS) during a period prior to exams; in particular, it was apparent for the regulation system of the vasomotor center (PLF = 48.4 %). Students' bodies had apparent strain in their regulatory systems (SI=177.5 a.u.). Total activity of the regulatory system was significantly elevated (TP=2,293 msec^2) due to central regulation levels. As students' BMI grew, there was a decrease in activity of the parasympathetic component in vegetative regulation and heart rate management became more centralized (IC=3.2–4.5 a.u.). Students with Class 3 obesity had the maximum spectrum power of the superlow component in heart rate variability (PVLF=29.3 %). HRV parameters analysis allows estimating whether adaptation processes in students' bodies are adequate during preparation to exams; it can be done in screening mode and provides an opportunity to perform timely prevention activities.

Key words: *stress, adaptation, risk factor, vegetative nervous system, heart rate variability, metabolic status, autonomous regulatory contour, central regulatory contour.*

Studying in a HEE involves permanent psychoemotional strain, hypokinesia, improper labor, nutrition, and leisure regime; all this allows assigning HEE students into a specific social group with elevated health risks. Necessity to master new materials and fulfill learning tasks in rather short time, a wish to get high ratings, and exam-related stresses are risk factors for most students that cause deregulatory disorders in functional activity of body systems [1]. Homeostatic systems are permanently strained, especially when a student is getting prepared for his or her exams, and it creates certain preconditions for diseases occurrence and hidden pathologies becoming apparent. Outer stressor impacts result in specific and non-specific reactions being mobilized in a body which are primarily regulated by the vegetative nervous system (VNS). A lot depends on its functional state including adaptation reserves capacity, efficiency and choice on adaptation strategy, working abilities and success in studies [1]. Anxiety that usually occurs in students during pre-exams time naturally makes for adaptation processes mobilization; however, in case

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it is too intense and long-term, adaptation mechanisms fail and it leads to growing strain in regulatory systems and a decrease in functional reserves ultimately resulting in dysregulation [2]. A lot of authors mention that depressions are widely spread among medical students [3–7]. It is becoming a serious problem for medical educational establishments in many countries [8, 9].

A concept on the cardiovascular system being a significant indicator of body adaptation reactions was formulated more than half a century ago. Heart rate variability (HRV) analysis is a procedure for assessing overall activity of regulatory mechanisms that support cardiovascular homeostasis, nuerohumoral heart regulation, and balance between sympathetic and parasympathetic sections in the VNS. HRV parameters allow estimating body adaptation abilities as well as using them for diagnosing and predicting various states: normal, pre-nosology, or pathology. Adaptation mechanisms overstrain and vegetative nervous system dysfunction underlie pre-nosology state of multiple somatic pathologies [10]. Heart is a very sensitive indicator showing all events and processes that occur in a body. Heart rate that is regulated via sympathetic and parasympathetic sections in the vegetative nervous system keenly reacts to any stress factors. Students' adaptation to studies in HEE is a serious medical and social problem. Irrational nutrition, hypodynamia, and great stresses are basic predictors of a life style typical for medical students; it leads to metabolic disorders and failures in regulatory systems functioning and creates significant risks of cardiovascular pathology occurrence. Educational process is an extreme factor for many students as it changes dynamic stereotype of physiological processes in regulatory systems; it can be a predecessor of hemodynamic, metabolic, and energetic health disorders and requires detecting at a pre-nosology stage.

Our research goal was to assess the vegetative nervous system and regulatory systems in students with different metabolic states during a pre-exam period.

Data and methods. We conducted a single cross-study of heart rate variability in 217 medical students attending the North Ossetia State Medical Academy (NOSMA) with different metabolic status in spring and summer 2019. Our examined group was made up of 166 female students (average age was 20.3 ± 0.1) and 51 male students (average age was 20.8 ± 0.2). HRV was recorded during 5 minutes (short-term recordings) with «Varikard 2.51» hardware-software complex. RR-intervals sequence was automatically analyzed in order to detect artifacts and arrhythmia with their subsequent exclusion from the analysis. According to the standards fixed by the European Society of Cardiology and the North American Society of Pacing and Electrophysiology we examined two groups of HRV parameters, namely those from Time Domain and Frequency Domain[1]. We analyzed the following basic time domain HRV parameters: heart rate (strokes per minute); the root mean square of successive differences between normal heartbeats (RMSSD, msec); the standard deviation of NN intervals (SDNN, msec); % of heart intervals pairs that differed from each other by more than 50 ms from overall number in the total measured data (pNN50, %); coefficient of variation (CV, %). All differences to a certain extent reflect activity of the parasympathetic section in the vegetative nervous system and belong to autonomous regulatory contour. We also analyzed stress index (SI) that showed intensity of strain in regulatory systems and prevalence of central regulation mechanisms over autonomous ones. As for frequency parameters, we analyzed total power of HRV range (TP, msec^2); power of high frequency (0.15–0.4 Hz) component in the range (HF,

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msec^2); power of low frequency (0.04–0.15 Hz) component in the range (LF, msec^2); power of superlow frequency (≤0.04 Hz) component in the range (VLF, msec^2); LF/HF and VL/HF ratios that characterized ratio between central and autonomous regulation activity; time of high frequency (THF, sec) and low frequency (TLF, sec) component in the range; index of centralization (IC) that allowed estimating to what extent heart rate was regulated with centralized mechanisms; power of high frequency (PHF, %), low frequency (PLF, %), and superlow frequency (PVLF, %) components in heart rate variability given in % from the total power of HRV range and characterizing activity of different sections in regulation. To perform integral quantitative assessment of body functional state, we analyzed regulatory systems activity index (RSAI) calculated according to a specialized algorithm developed by R.M. Baevskiy; this parameter characterizes functional reserves with relation to adaptability to the environment [11]. HRV parameters obtained in our research were compared with parameters formulated with «Out-Wind» software program and given in a table with their standard ranges for typicality assessment being created automatically depending on a patient's age. Since our study was a single and a cross one, and all the examined students were practically of the same age, standard ranges for assessing parameters typicality were applicable for the whole sampling.

We determined body mass index (BMI) for each student bearing in mind his or her age, height, and body mass. Average body mass amounted to 58.8 ± 0.93 kg (BMI = 21.5 ± 0.30) among girls; 77.47 ± 2.96 kg (BMI = = 24.4 ± 0.85) among boys. To analyze dynamics of HRV parameters in medical students with different body mass, we ranked all the data as per BMI gradations take as follows: «lower than 25» was normal body mass (183 students); «25–29.99», overweight (28 students); «30–34.99», obesity I degree (6 students).

All the data were statistically processed with Statistica 6.1 software package. We analyzed dynamic series of heart rate intervals and revealed that HR, SI, and PLF parameters were distributed normally. Accordingly, to describe these parameters, we applied average sample values and their errors; median, upper and lower quartiles were applied to analyze the remaining parameters. Statistical analysis included descriptive procedures, comparison between two independent samplings as per Mann-Whitney, comparison between several samplings with dispersion rank and factor analysis.

Results and discussion. We analyzed basic parameters of heart rate intervals obtained for medical students; the analysis revealed prevailing sympathetic VNS impacts during a pre-exam period. When examining Time Domain parameters, we established that heart rate (HR) was significantly higher in medical students (85.9 ± 12.0 strokes per minute) that physiological standards (55–80 strokes per minute) (Table 1).

When students are studying for their exams, their regulatory systems are strained and the central regulation mechanisms prevail as it is indicated by group stress index (SI) value being 177.5 ± 158.9 arbitrary units and it is higher than upper boundary of standard typicality assessment (150 arbitrary units).

Having analyzed basic HRV parameters in Frequency Domain, we revealed that the total power (TP) of heart rate variability range, a parameter that characterized total activity of regulatory systems, was significantly higher than physiological standard, 2,293.7 (1,424.0; 3,413.3) msec^2 against 1,500 msec^2. Regulatory systems activity depends on functional state of a body. Regulatory systems in students were obviously under stress and moved from «control» stage that was typical for ordinary living conditions to «regulation» and «centralization» stages that were activated due to necessity to spend more energy under stress and overloads during a pre-exam period.

We established that the main contribution into elevated total power of the range was made by power of low frequency (PLF) component in heart rate variability which reflected elevated activity of the sympathetic section;

Table 1

Descriptive statistics of basic HRV parameters in medical students

HRV parameters	Average	-95 % CI	+95 % CI	Median	Lower quartile	Upper quartile	Dispersion	Standard deviation (SD)	Standard error of the mean (m)
HR, str/min	85.9	84.3	87.5	86.3	78.0	93.9	143.2	12.0	0.8
Mean, msec	713.4	698.6	728.3	695.1	638.8	768.9	12,195.7	110.4	7.5
RMSSD, msec	41.0	37.4	44.7	34.0	24.3	49.7	729.8	27.0	1.8
pNN50, %	14.9	12.9	17.0	9.6	4.2	21.7	235.2	15.3	1.0
SDNN, msec	56.1	53.1	59.1	52.6	41.1	65.8	490.5	22.1	1.5
CV, %	7.8	7.4	8.1	7.5	6.1	8.9	6.0	2.5	0.2
SI	177.5	156.1	198.9	131.9	75.0	223.4	25,268.3	158.9	10.9
TP, $msec^2$	2,882.9	2,534.4	3,231.4	2,293.7	1,424.0	3,413.3	6,690,135.6	2,586.5	176.8
HF, $msec^2$	1,012.5	789.6	1,235.5	522.2	282.0	1,068.1	2,738,052.5	1,654.7	113.1
LF, $msec^2$	1,107.6	1,008.5	1,206.7	960.2	582.8	1,437.0	540,696.4	735.3	50.3
VLF, $msec^2$	446.2	390.1	502.3	332.8	180.8	541.0	173,294.7	416.3	28.5
ULF, $msec^2$	316.5	264.6	368.5	210.8	108.3	413.5	148,677.7	385.6	26.4
PHF, %	32.6	30.4	34.7	28.2	20.6	41.4	247.6	15.7	1.1
PLF, %	48.4	46.6	50.2	49.2	40.0	58.7	175.1	13.2	0.9
PVLF, %	19.1	17.9	20.2	17.7	13.0	24.3	74.3	8.6	0.6
LF/HF	2.1	1.9	2.3	1.8	1.0	2.7	2.2	1.5	0.1
VLF/HF	0.8	0.7	0.9	0.6	0.3	1.1	0.5	0.7	0.0
IC	2.9	2.6	3.2	2.5	1.4	3.9	4.1	2.0	0.1
ПАРС	4.8	4.6	5.1	5.0	4.0	6.0	3.0	1.7	0.1

Table 2

Results obtained via rank dispersion analysis of HRV parameters

HRV parameters	Kruskal-Wallis test	*p*	Median test (common median)	χ^2	*p*
HR, str/min	59.98	0.0000	86.31	50.46	0.0000
Mean, ms	59.98	0.0000	695.1	50.5	0.0000
RMSSD	55.76	0.0000	30.02	48.11	0.0000
pNN50 %	68.6	0.0000	9.63	60.95	0.0000
SDNN	31.87	0.0000	52.62	23.51	0.0000
CV, %	18.24	0.0004	7.50	14.12	0.0027
SI	44.79	0.0000	131.98	37.12	0.0000
TP, ms^2	28.61	0.0000	2,293.6	28.24	0.0000
HF, ms^2	54.68	0.0000	522.19	43.57	0.0000
LF,ms^2	12.62	0.0055	960.16	10.11	0.0179
VLF, ms^2	23.12	0.0000	332.75	17.60	0.0005
ULF, ms^2	11.84	0.0079	210.79	11.89	0.0078
IC	46.65	0.0000	2.54	31.46	0.0000

the parameter was equal to 48.4 ± 13.2 %. This result indicates there is growing activity of sympathetic section in the VNS, in particular, vasomotor center regulation system.

Complex HRV assessment allowed establishing that medical students had apparently activated regulatory systems in a body since group median of regulatory systems activity index (RSAI) was equal to 5 (4; 6) scores with physiological standard being 1–3 scores; it corresponds to apparent strain in regulatory systems, including elevated activity of the sympathicoadrenal system and hypophysis-adrenals system. It can be caused by a stress occurring due to increased mental and emotional loads and chronic lack of proper sleep during a pre-exam period [12]. As it was shown by S.Y. Dong, M. Lee et al., when examined people were tested with mental arithmetic, it resulted in growing low frequency components R-R and SBP, that is, sympathetic activity markers, and in declining high-frequency component in R-R interval changeability, a parasympathetic activity marker [13].

In order to determine HRV parameters that were most closely related to intensity of regulatory systems strain, we analyzed the whole data array with rank dispersion analysis; as a result, we managed to establish HRV parameters that were the most informative and had significant discrepancies depending on RSAI value (Table 2).

As an example, we made a figure that illustrated dynamics of heart rate (HR) depending on RSAI value (Figure 1).

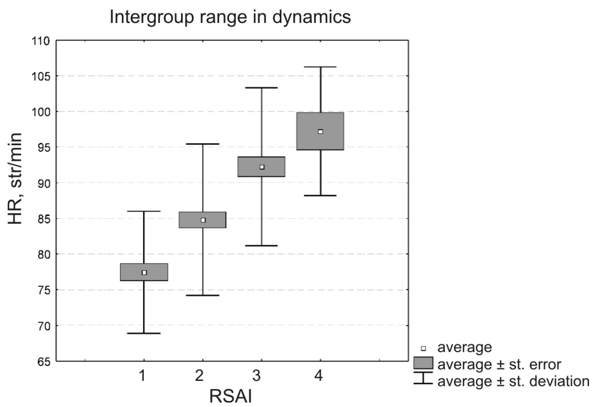

Figure 1. Correlation between heart rate (HR) and RSAI (1 is physiological standard; 2 is pre-nosology; 3 is pre-morbid state; 4 is adaptation failure)

We analyzed HRV parameters in medical students with different body mass; the analysis revealed that there were discrepancies in HRV parameters depending on BMI gradation (Figure 2).

Rank dispersion analysis of HRV parameters and students' ranked BMI values allowed establishing that as body mass grew, there was a decline in activity of parasympathetic section in vegetative regulation, as it was indicated by RMSSD drop from 34.7 msec (25.8; 50.3) among students with normal BMI to 20.7 (17.5; 27.8) among those with obesity I degree; drop in power of high frequency component (PHF) from 28.2 (26.5; 41.4) to 18.2 (12.7; 27.4); and an increase in time of high frequency component (THF) from 4.9 (3.4; 5.7) to 6,2 (5.8; 6.6). Index of centralization (IC) is another important parameter that reflects an extent to which non-respiratory components in sinus arrhythmia prevail over respiratory ones. The index is calculated basing on power of high- and low frequency components in HRV and allows making quantitative assessment of ratio between central and autonomous heart rate regulatory contours. Autonomous regulatory contour is related to respiratory component in sinus arrhythmia and parasympathetic regulation; however, the more actively centralized regulatory contour participates in heart rate management, the greater is a decrease in respiratory waves range, and vegetative homeostasis is shifted towards sympathetic regulation prevalence. In our research students tended to have a growth in centralized heart rate regulation as their BMI grew since index of centralization (IC) increased from 2.5 (1.4; 3.8) among students with normal BMI to 4.5 (2.9; 6.8) among those with obesity I degree. PostHoc analysis revealed that RMSSD, PHF, THF, and IC were authentically different among students with normal BMI and obesity I degree ($p \leq 0.05$). We revealed that VLF/HF ratio also grew as BMI increased (Figure 3) and amounted to 0.54 (0.32; 1.01) among students with normal BMI; 0.87 (0.53; 1.56), among students with overweight; 1.87 (1.00; 3,02), among students with obesity I degree.

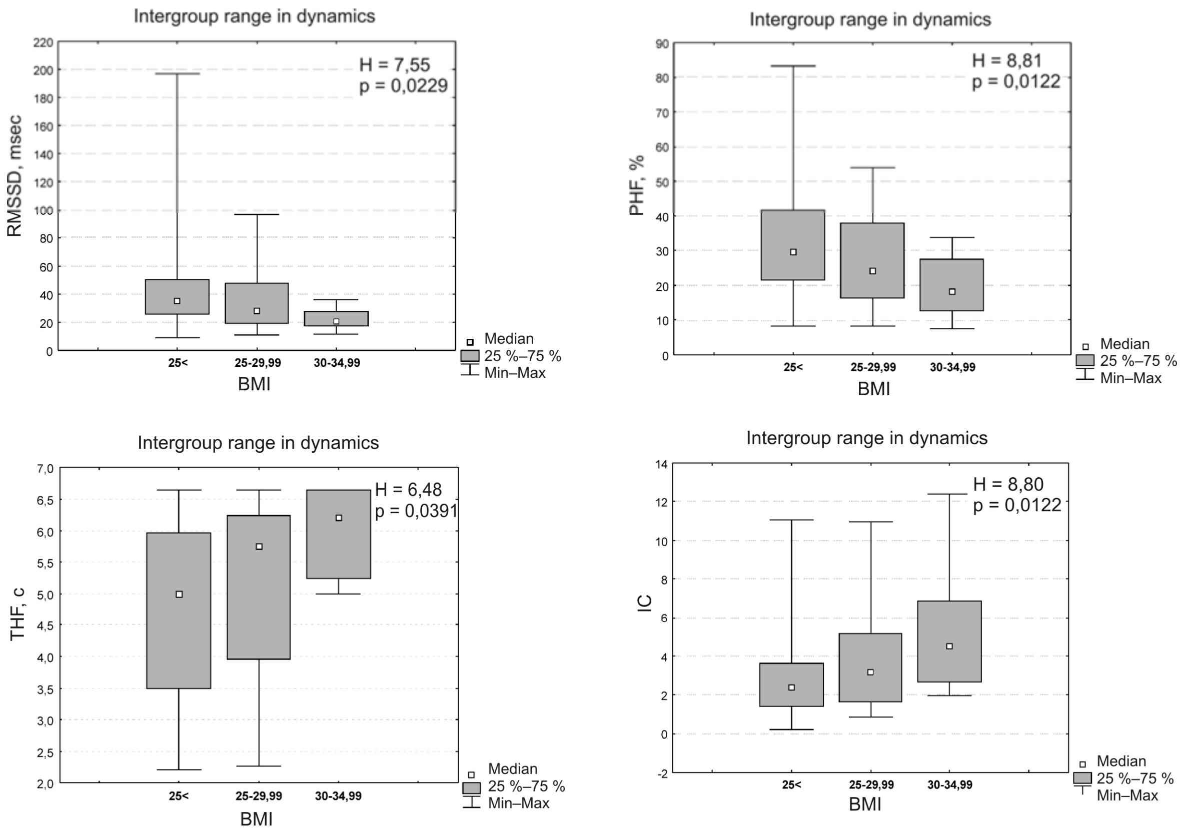

Figure 2. Heart rate variability parameters (RMSSD, PHF, THF, IC) taken in dynamics depending on BMI

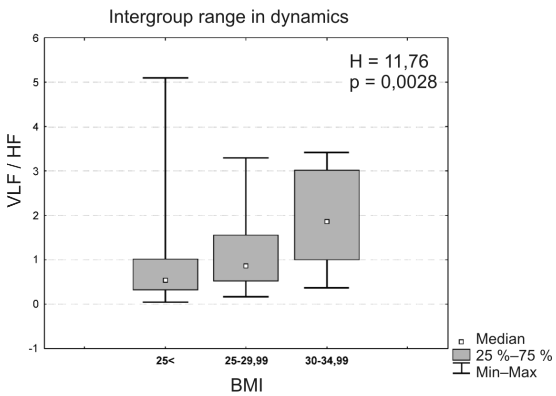

Figure 3. VLF/HF dynamics depending on BMI

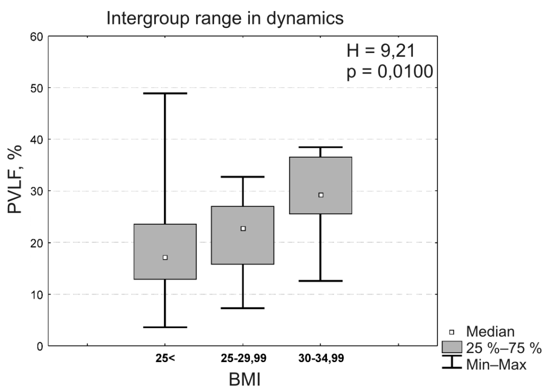

Figure 4. Power of superlow frequency component in heart rate variability (PVLF, %) taken in dynamics depending on BMI

This VLF/HF dynamics indicates that central heart rate regulatory contour is becoming more active against autonomous one. Since autonomous regulatory contour is actually a parasympathetic one, growing centralization in regulation means that vegetative homeostasis is shifted towards sympathetic regulation prevalence.

We revealed that students with BMI that corresponded to obesity I degree had maximum power of superlow frequency component in heart rate variability (PVLF, %) that was equal to 29.3 % (25.6; 36.5) against 22.7 % (15.8; 27.04) among students with overweight and 17.2 % (12.9; 23.5) among students with normal body mass (Figure 4). PVLF characterizes relative activity of sympathetic section in regulation and thermal regulation processes, but apart from that it can be also used as a marker showing intensity of relation between autonomous (segmental) circulation regulation with above-segmental one including hypophysis-hypothalamus and cortical regulation. Moreover, it is a good indicator reflecting regulation over metabolic processes [14–16].

Obesity is known to be a significant risk factor causing diseases occurrence and development. A correlation between high BMI values and overall mortality is confirmed with results obtained via meta-analyses that describe a J-like functional correlation between this factor and mortality and stratify its low risks at BMI varying from 20.0 kg/m^2 to 25 kg/m^2 [17, 18]. And here cardiovascular pathology takes the first rank place among nosologies associated with overweight and obesity since more than two thirds of deaths related to high BMI all over the world are deaths due to cardiovascular diseases [19]. Dependence between HRV parameters that characterize vegetative regulation and metabolic disorders has been described by V.A. Nevzorova and E.A. Abramov, given that there were no discrepancies in the structure of carbohydrate metabolism disorders between the examined groups [20]. Vegetative dysfunction detected in patients with metabolic syndrome is thought to be related to obesity degree and it is also predicted that further metabolic disorders development will result in diabetic vegetative neuropathy occurrence. It should be noted that a concept of metabolic syndrome (MS) as a cluster of risk factors causing type 2 diabetes and cardiovascular diseases (CVD) has undergone certain evolutionary changes over recent years. In particular, S.I. Kseneva, E.V. Borodulina et al. revealed that frequency of cardiac vegetative neuropathy reached 37.5 % due to MS [21]. It was also noted that vegetative nervous system dysfunction (just as resistance to insulin) was a primary reason for MS development. Integration of vegetative dysfunction in MS pathogenesis provides an opportunity to include certain nosologies into MS cluster [22]. Despite there are multiple scores for assessing CVD risks occurrence (the Framingham Risk Score, PROCAM, SCORE, UKPDS, ULSAM, and others), none of them allows precise prediction of CVD risks for young people aged 18–35 without any clinical signs of atherosclerosis; however, there have been multiple attempts to adapt some of predictive models for assessing risks of CVD occurrence among young people [23]. Given that there is usually low probability that cardiovascular events might occur in the nearest future and less apparent risk factors, it is more difficult to assess absolute CVD risks for young people. Young males in general are more susceptible to risks of CVD occurrence than young females since stresses result in changes in lipid blood structure in them towards atherogenicity and increased blood pressure [24, 25]. Apart from this, obesity among young males is a predictor that determines occurrence of atherosclerosis in coronary arteries in 15 % cases [26].

An existing problem related to proper CVD risks stratification among young people makes it necessary to develop a predictive model that should include new criteria and be able to detect young people who run high CVD risks with significant precision. It is vital for further examinations and timely preventive activities and it will allow preventing CVD-related morbidity and mortality at an older age. Given that, it is necessary to further examine HRV parameters as biomarkers in predicting CVD risks occurrence among students involving greater numbers of participants.

Conclusions. We performed a complex assessment of HRV in medical students during a period prior to exams; the assessment revealed that there was apparent strain in their regulatory systems due to elevated activity of the sympathico-adrenal system and hypophysis-adrenals system. Integral regulatory systems activity was significantly increased due to a drastic growth in central regulation activity.

Growing body mass was accompanied with the parasympathetic section in vegetative regulation being less active as it was indicated by a decrease in RMSSD, power of high frequency component, and growing time of high frequency component. And there was also a growth in centralization of heart rate regulation, and accordingly index of centralization and VLF/HF ratio also increased. Non-respiratory component in sinus arrhythmia prevailed over respiratory ones in cardiointervals array, and as respiratory waves range decreased, vegetative homeostasis was shifted towards sympathetic regulation prevalence. As metabolic disorders became more intense, there was a growth in power of superlow frequency component in heart rate variability, and it allowed using this parameter as an indicator of metabolic disorders that resulted in elevated risks of cardiovascular events.

Analysis of HRV parameters in students allows assessing adaptation processes adequacy as a response to stressors, such as mental and emotional loads in educational processes, obtaining data on VNS state, and using these data as a basis for preventive and recovery activities. It is necessary to further investigate HRV parameters as biomarkers predicting CVD risks for students involving greater numbers of participants and to implement these biomarkers in practical activities.

Funding. The research was not granted any sponsor support.

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

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Received: 20.02.2020
Accepted: 11.11.2020
Published: 30.12.2020

ANALYTICAL REVIEWS

UDC 616-097
DOI: 10.21668/health.risk/2020.4.18.eng

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Review

VANADIUM IN THE ENVIRONMENT AS A RISK FACTOR CAUSING NEGATIVE MODIFICATION OF CELL DEATH (SCIENTIFIC REVIEW)

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The review dwells on results obtained via examinations that focused on effects produced by vanadium and its compounds contaminating the environment on health disorders related to cell death deregulation.

Research works that have been performed over the last decades and focused on revealing the essence of apoptosis mechanism under exposure to technogenic chemicals are truly vital due to this phenomenon having great biological significance within a system of a body trying to adapt to influences exerted by environmental factors.

The present work focuses on apoptosis peculiarities under exposure to excess technogenic concentrations of vanadium compounds. Published research works have been analyzed, analysis results are outlined, and a scientific hypothesis has been formulated within the subject matter. We have described an immune-modulating effect produced by vanadium compounds that is able to modify apoptosis events due to changes in cell death modes (apoptosis activation/inhibition) and it provides body adaptation to changing environmental conditions.

A range in vanadium concentrations between essential and toxic ones predetermines multi-directional changes in apoptosis induction and completion. Thus, induced apoptosis activation makes for development of autoimmune and immune-proliferative processes; at the same time, cell death inhibition can result in immune deficiency, inflammatory reactions, and neurodegenerative diseases. It was shown that vanadium compounds produced modifying effects on mitochondrial functions regulation, changes in phosphorilation/dephosphorilation ratio in protein products, and imbalance in free radical processes; all this ultimately disrupts a balance between pro- and anti-apoptotic signals in a cell. Monitoring over apoptosis parameters that characterize cell death under exposure to vanadium and its compounds will allow timely detecting risks of prenosology state occurrence and prevent damage to health.

Key words: *risk, vanadium, environment, cell death, apoptosis mechanism, mitochondrial activity modification, free radical oxidation, damage to health.*

A risk that damage to health will occur under exposure to technogenic chemicals in the environment is realized with the immune system directly participating in the processes at early stages in a disease. The immune system is a most significant regulatory one that provides adequate adaptation of a body to impacts exerted by environmental factors including various chemicals. Cell death plays a key role in immune regulation. Cell death is a process that involves irreversible changes in vital cellular functions (primarily, adenosine

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triphosphate synthesis and redox homeostasis preservation); it results in cell integrity loss (disorders in plasmatic membrane permeability or cell fragmentation) [1]. Cell death can be regulated and genetically programmed (regulated cell death, RCD) or accidental (accidental cell death, ACD). Regulated cell death occurs due to activation of one or several signal cascades and is modulated (regulated) via pharmacological or genetic interferences. RCD includes apoptosis, autophagy, anoikis, pyroptosis, partanosis, and necroptosis [2].

Apoptosis is an evolutionary conservative process which is necessary for maintaining cellular homeostasis in a body. Apoptosis regulates balance between proliferation, differentiation, and elimination of cells that are no longer necessary. Accidental cell death (ACD) is instant and uncontrollable cell death when plasmatic membrane is destroyed completely due to extreme physical, chemical, or mechanic factors. Necrosis is traditionally seen as an accidental and non-regulated cell event.

Chemicals with different essence cause persistent hazards for human health in contemporary social, economic, and ecological conditions. Vanadium is among most significant environmental contaminants; being a hapten, it exerts adverse impacts on the cardiovascular, respiratory, and reproductive systems and produces neurotoxic and immune-toxic effects [3]. But at the same time, the latest achievements in medicine such as creation of vanadium-containing orthodontic / orthopedic implants and development of anti-parasitic, antiviral, anti-bacterial, anti-thrombotic, anti-hypertensive, hypolipidemic, spermicidal, anti-tuberculosis, anti-tumor, and anti-diabetic medications make it necessary to resolve disputable issues related to influence exerted by vanadium on the immune system [4–9]. Adverse consequences caused by effects produced by chemical environmental factors on human health can become apparent not only via immune-dependent diseases occurrence but also failure in body adaptation mechanisms. Disorders in regulated cell death are a reason for deadaptation that occurs under exposure to chemicals. It has been established that different metals and organic compounds can modify cell death mechanisms [10–12]. But at the same time as we generalized and analyzed literature data, we revealed certain contradictions regarding influence exerted by different chemical factors on cell death.

Despite there are multiple published works that focus on how lethal programs in cells are realized, there is no scientifically substantiated concept about modifying effects produced by vanadium on apoptosis. The present work concentrates on peculiarities of apoptosis under exposure to vanadium.

Vanadium (hapten) is a biologically significant element that participates in many physiological processes [13–16]. Vanadium is n ultra-microelement and it occurs in trace quantities in all organs and tissues in a human body [9, 17]. Overall, according to generalized data, vanadium contents in a body amount to lower than 10 ng/g of body weight [7]. Vanadium is detected in the heart, kidneys, liver, brain, muscles, bones, fat tissue, testicles, thyroid gland, colostrums, breast milk, and hair [3, 7, 9, 18, 19].

Vanadium enters a body from the environment predominantly via the gastrointestinal tract or bronchopulmonary system. In occupational environment vanadium and its compounds can also enter a body via skin and eye mucosa [20]. It has been shown that vanadium that enters a human body with food is poorly absorbed in the gastrointestinal tract (from 0.2 to 1.0 %). Most vanadium that was consumed orally turns into poorly soluble vanadium dioxide (IV) $VO(OH)_2$ and is extracted with feces; due to it, it doesn't cause any potential hazard for human health [21]. However, a decrease in overall fat, carbohydrates, and proteins consumption can influence vanadium absorption [7].

Primarily vanadium enters a body via respiratory tracts. Respiratory organs are basic target ones when it comes to inhalation exposure to vanadium. It was shown that already after a 2-day chronic exposure to vanadium in doses equal to 0.28 mg/m^3 mice and rats had changes in their lung tissue that involved inflammation, fibrosis, and cell hyperplasia in bronchiolar and alveolar epithelium [22]. Health disorders among children and adults occur due to impacts exerted on them by high vanadium concentrations in ambient air as well as in working area air [4, 8]. Size of vanadium-containing particles and vanadium compounds solubility are significant factors determining a rate at which vanadium is absorbed in respiratory tracts.

Previous research revealed that vanadium that entered a human body caused changes in immune reactivity and increased genetic variability in population. Workers employed at a metallurgic enterprise where a full cycle for vanadium iron production was used had by up to 37 % greater quantity of apoptotic cells and lymphocytes expressing CD25$^+$-receptor in their bodies in case vanadium was identified in their blood at a level close to an upper boundary of a reference value [13]. Pro-apoptotic cytokines hyper-production and hyper-expression of early activation CD25 marker as well as growth in Annexin V-positive lymphocytes quantity were detected in examined children who lived under chronic aerogenic exposure to V_2O_5 that was introduced into ambient air as a component in industrial emissions from metallurgic productions. Studies on gene polymorphism under exposure to vanadium allowed revealed polymorphic changes as per heterozygote type in genes of P450 (*CYP2D6rs38*) cytochrome, corpoporhyrine genase (*CPOXrs1131857*), methylentetrahydrofolate reductase (*MTHFRrs1801133*), and peroxisome proliferation (*PPARG rs4253778*) that were responsible for the 1st and 2nd stage in metals detoxification. For example, frequency of mutant gene *CYP2D6rs38* was 4.3 times higher among adults who were exposed to vanadium than among non-exposed ones. Children exposed to vanadium had polymorphic changes that involved heterozygote polymorphism of genes responsible for detoxification and oxygenation (*CPOX*, sulf transminase – *SULT1rs9282861*, glutathione transferase – *GSTA4rs3756980*). It was established that children exposed to vanadium had mutant allele 4 times more frequently than non-exposed ones.

Vanadium is to a greater extent absorbed in a body as vanadate anion than as vanadyl-cation. In certain physiological states vanadium occurs in a body as vanadates (oxidation rate^{5+}), meta-vanadate (VO^{3-}), and probably ortovanadate (VO_4^{3-}). Vanadium is able to change its oxidation rate when it travels from one medium to another and it results in vanadyl spontaneously transferring into vanadate and back again. A rate at which vanadium compounds transform in a body and types into which they transform have considerable influence on a share of absorbed vanadium. Vanadium has another significant property and it is its ability to create new types; this ability depends on biologic or synthetic chelators or biogenic ligands being present in a body [23].

When vanadium enters the systemic blood flow, it gets bonded to plasma proteins, in particular, to transferrin and albumin and low-molecular ligands such as citrate, oxalate, lactate, phosphate, glycine, hystidine, as well as with hemoglobin; if a concentration is high, it can also create a bond with immunoglobulin G [6, 8, 24, 25]. Vanadium contents in blood fall by approximately 30 % during the first 24 hours after it has entered a body [26]. But at the same time vanadates are able to replace phosphates in bone tissue and it leads to vanadium accumulation and long-term persistence in bones, longer than 1 month [27].

Vanadium penetrates into a cell due to transport structures in cell membranes (transporters, phosphates or sulfate-ion channels) or receptor-mediated endocytosis [3]. As vanadium has a strong ability to change oxidation or exchange ligands (H_2O, CO, H^+, OH^-, Cl^-, PO_4^{3-} etc.) depending on the micro-environment, molecules that are close to it can exert significant influence on vanadium transportation through cell membranes. Vanadium distribution inside cells depends on what vanadium compound has penetrated a body. In a cell vanadium interacts with glutathione, ascorbic acid, or nicotinamide adenine dinucleotide (NADH) and it results in its recovery from V^{5+} to V^{4+} [8, 9, 28]. And here vanadyl (four-valent state) prevails inside a cell. Intracellular oxidizers such as NAD^+, O_2 и O_2^{2-} can oxidize vanadyl back into vanadate [3]. Mutual transformation between different vanadium types in a cell (basically V^{+4}/V^{+5} and to a lesser extent V^{+3}) occurs constantly. Different compartments in a cell have different pH and due to it they have different ability to absorb and accumulate vanadium [7]. Inside a cell vanadium compounds can either exert direct influence on various organelles thus changing their functional activity or they can interact with a wide range of protein molecules and modify intracellular signal cascades.

Mice that had been aerogenically exposed to vanadium (V) had inflammatory processes in their lungs 6 hours after the exposure; after 72 hours there was a significant increase in apoptotic cells quantity. Absorbed vanadium stimulated NADH-oxidase activity of mitochondria responsible for apoptosis realization [28]. Experimental models *in vitro* and *in vivo* allowed establishing dose-dependent effects produced by sodium ortovanadate (Na_3VO_4) on anaplastic carcinoma in the thyroid gland; the effect involved the cellular cycle stop at G2/M phase and a decrease in mitochondria membrane potential (Ψ) [29]. It was proven that decavanadate changed antioxidant enzymes activity when accumulating in mitochondria and also induced mitochondrial membranes de-polarization [30]. Human cholangiocarcinoma (PC-1) cells were used in an experiment and it allowed establishing that V^{5+} inhibited an electrons transfer chain and apoptosis induction an also led to mitochondrial potential collapse ($\Delta\Psi$) [4]. Isolated mitochondria from rat liver were treated with five-valent vanadium (concentrations ranging from 25 to 200 μM) and it resulted in cytochrome *c* release from mitochondria [31]. Mitochondria membrane potential went down by 50 % when human hepatocellular carcinoma (HepG2) cells were incubated for 72 hours with VO (250 μg/mL) [32]. Besides, vanadium can have direct influence on internal mitochondria membrane and it can later disrupt electrons transfer between respiratory complexes thus resulting in excessive reactive oxygen species (ROS) occurrence in mitochondria [33]. Considerable ROS production also results from p53 activation. We should note that some molecules of p53 itself can transfer into mitochondria and the process is accompanied with cytochrome *c* leaving mitochondria (bcl-2 prevented such effects) [34]. Interaction between p53 and MAPK-cascade that took place during cell cycle regulation was also described. It was established that p53 played certain role in necrosis initiation under direct interaction with cyclophilin D (CYPD), a mitochondrial matrix protein and a component in mitochondrial pore [1]. Vanadium is able to release Ca^{2+} from intracellular depots and its concentrations contribute significantly into regulation of mitochondrial pore opening [7]. Mitochondria and endoplasmatic reticulum are considered capacitive calcium depots. A change in calcium contents in a cell results in various cellular mechanisms being activated or inhibited including cell death mechanism. Vanadium (V) oxide V_2O_5 accumulated in mitochondrial lysosomes and stimulated autophagy in breast cancer (MCF-7) cells [14]. It was revealed via experiments that, depending on exposure duration, vanadium oxide both caused pro-oxidant effects and stimulated anti-oxidant properties in MCF-7 cells culture. Mitochondria play a key role in control over cellular calcium homeostasis and ROS generation and it means that mitochondria participate in regulation of various cell death types. It is in mitochondria that a cell «makes a choice» on a lethal program it is going to follow (apoptosis or necrosis). Apoptosis is initiated in case there is moderate damage done to mitochondria membranes whereas considerable damage results in a cell dying via necrosis.

Vanadium is an element that can be in different oxidation states and that participates in reactions resulting in free radicals occurrence. Free radicals, regardless of their origin and reasons that caused their generation, can interact with nucleic acids, proteins, lipids, and carbohydrates. Cellular dysfunction caused by oxidative stress is often linked to damage to DNA and it can cause cell death. The International Agency on Cancer Research (IARC) experts consider that vanadium pentoxide belongs to 2B category or «is probably carcinogenic for people». It was shown in *in vivo* system that vanadium tore apart certain DNA threads, caused chromosome aberrations (structural and numerical) and nitrogen bases oxidation [35]. In a normal state genetically defective cells are to be eliminated via apoptosis. There is a hypothesis that insufficient apoptosis results in malignant transformation of damaged cells and tumor dissemination. There was an experiment performed on human hepatocellular carcinoma cells; it revealed that vanadium caused damage to nuclear and mitochondrial DNA and reduced cell vital capacity [36]. Mediated negative effects produced by vanadium on DNA as a result of reactive oxygen species generation involved desoxyribose oxidation, nitrogen bases modification, chains sewing together and tearing up. However, other researchers didn't believe vanadium had any carcinogenic properties [22, 37]. Depending on a suggested experimental model, vanadium concentrations and other vanadium-containing chemical compounds can have either anti-tumor or carcinogenic properties [21, 38]. Obviously, a key role in carcinogenesis occurrence belongs to cells being insusceptible to apoptosis or this process being inhibited.

Vanadium and its compounds inhibit activity of H^+,K^+-ATPase, Na^+,K^+-ATPase, and Ca^{2+},Mg^{2+}-ATPase. Depending on ATPase type, there can be a wide range of their affinity with vanadate [39]. It was shown that decavanadate $[V_{10}O_{28}]^6$ was the most powerful Ca^{2+}-ATPase inhibitor in comparison with other vanadates [40]. ATPhases are most significant regulators of multiple cell functions including cell death [41]. In particular, non-apoptotic cell death (autosis) critically depends on Na^+,K^+-ATPase activity [1]. ATPhases were proven to have a signal function. For example, a direct interaction between sodium-potassium ATPhase (Na^+,K^+-ATPhase) and Src-family kinase initiate phosphorilation of certain signal cascades that control cell death. It was established that metavanadate and ortovanadate inhibited Na^+,K^+-ATPhase in neuronal cells obtained from rat hippocampus [38].

The fact that vanadate is able to replace phosphate indicates that these two substances are similar to each other. Many benign or adverse effects produced by vanadate are at least partially due to similarities between these two anions. Vanadate and phosphate are groups with tetrahedral morphology and a charge almost spherically distributed in the outer sphere. Therefore, vanadate can easily replace phosphate in such enzymes as phosphatases and kinases [8]. However, an overall ionic charge of basic particles that occur at pH 7 is different as it is equal to 2 in phosphate and 1 in vanadate; it can result in different interactions with elecrophilic groups. Lower *d* orbital and a coordination number exceeding 4, usually 5 and 6, leads to one-electron vanadate recovery. As a result there is a growth in fixation of vanadates with side chains consisting of amino acid protein remnants [42]. There is a peculiarity vanadate has in physiologically significant concentrations and it makes it different from phosphate; this peculiarity is protonation state: at pH7 vanadate almost exclusively occurs in its diprotonated form whereas phosphate occurs as a mixture of mono- and dihydrophosphate [8]. Therefore, vanadate can easily replace phosphate in such enzymes as phosphates and kinases. In case vanadium occurs in a body in excess quantities, a change in enzyme cascades activity in a cell results in a change in apoptotic signal conductivity.

Protein kinases (phosphotrasferases and kinases) and phosphatases are enzymes that accordingly catalyze phosphorilation (phosphate group addition) and de-phosphorilation (phosphate group removal) of a substrate. Under exposure to vanadium enzymes that participate in phosphate group transfer are inhibited or activated as a result of «vanadate – phosphate antagonism». Vanadate, due to its stronger bonding with phosphate-containing enzymes, is able to induces changes in activity of phosphorilation / de-phosphorilation enzymes. Kinases and phosphatases are responsible for activity of signal pathways that activate physiological effects cascade; due to this ability these enzymes are responsible for cell responses regulation. Imbalance between phosphorilation and de-phosphorilation can have negative influence on processes that are vital for cells functioning including cell survival or death. Experiments allowed establishing that vanadate inhibited phosphatases activity [43]. But at the same time vanadate is not a specific inhibitor for all phosphatases as it is still unclear how vanadium-containing chemical complexes inhibit many enzymes that catalyze substrate phosphorilation [7]. It was shown that oxovanadium (IV) complex (Na2[VO(Glu)2 (CH3OH)] (Glu=glutamate)) in concentration ranging from 0.21 to 0.37 μM inactivates protein tyrosine phosphatase 1B (PTP1B) [44]. PTP1B, as a negative regulator of insulin signal pathway, interacts directly with insulin receptor and de-phosphorilates tyrosine remnants [3]. Super-expression of this enzyme was detected in case of HER2-positive cancer. Protein tyrosine phosphatase 1B indirectly potentiates Src activity (cytosolic tyrosine kinase that is not bound to receptor). Certain vanadium compounds, pervanadates in particular, have oxidative properties in low concentrations and therefore they can directly activate Src [45]. Src-kinases are able to inhibit caspase-8 protease activity [46]. In case caspases are inactivated, FASL can initiate cell death as per necrosis type. As vanadium changes Na^{+},K^{+}-ATPhase activity, it exerts indirect influence on Src. Src-kinase in an active component in activation of transcription factors such as AP-1 and NF-kB as well as mitogen-activated protein kinases (MARK-kinases) and membrane-bound proteins (Ras) that participate in transferring Ras/MAPK-signal cascade signals. Signal is transferred from cellular membrane to nucleus via Ras/MAP-kinase pathway activation thus influencing expression of a wide range of genes. Such activation of protein kinase signal pathways results in changes in protein products synthesis, mitochondria functional activity etc. [47]. Ras is also a component in multi-protein complex that regulates opening of mitochondrial membrane pores. When this complex is being formed, Ras molecules come from cytoplasm whereas proteins belonging to BCL-2family come from inside. Vanadium changes balance between pro- and anti-apoptotic members of BCL-2 family, disrupts functional activity of MAP-kinase cascades and transcription factors, and also increases generation of reactive oxygen species; in other words, it modifies cell death mechanisms and therefore plays a significant role in cell life cycle regulation.

Vanadium and its compounds cause imbalance in «oxidation – anti-oxidation» system via ROS formation. Reactive oxygen species are a key segment in initiating intracellular signal transduction and signal transfer in separate molecules thus making significant changes into MAP-kinase cascades activity. When MEK, ERK1/2, PI3K, p38, or JNK phosphorilation is modified (activated or inhibited) by vanadium, it modifies apoptosis start-up and development [35]. It was proven that intracellular protein p53 influenced activation or inactivation of MEK, ERK1/2, PI3K, p38, JNK, TNF-alpha, and NF-κB [48]. Molecular restructuring in PI3K and MAPK cascades under exposure to vanadium causes changes in cells survivability. Due to inhibited signal transfer through PI3K/Akt/mTOR cascade FAS-mediated apoptosis is induced [49]. Phosphatidylinositol-3-kinase (PI3K) activity directly correlated with calcium ions concentration. CD95 doesn't have any enzyme activity; however, it can activate various signal pathways due to its ability to create inter-protein (protein-protein) interactions [50]. FAS-induced signal cascades lead to NF-κB and MARK activation, apoptosis or necrosis initiation [51]. An immune-modulating effect produced by ERK1/2 which is phosphorilated close to cellular membrane involves B-lymphocytes and T-lymphocytes activation [52]. CD25-receptor is early T-lymphocytes activation marker; CD95-receptor, their late activation.

Research works that involved use of MEK1/2 kinases pharmacological inhibitors allowed proving that ERK1/2 participated in modifying functions performed by mitochondria that participated in apoptotic cascade amplification and regulation. Activation of protein kinases that belong to ERK family is most frequently associated with cells survival and proliferation stimulation. ERK protein kinases make for cellular cycle advancing as they inactivate protein kinase MYTI, one of its inhibitors. ERK signal pathways can be activated as a response to signals coming from receptors bound to G-protein via receptor tyrosine kinase, T-cellular receptor, N-methyl-D-aspartate receptor and C-type lectins receptors [52]. A set of signal cascades creates a network where ERK signal pathway communicates with various signal pathways via multiple branchings and collaterals, and it is regulated as per feedback principle and kinase-substrate ratio [52].

Some researchers described anti-apoptotic effects produced by ERK1/2 whereas others mentioned pro-apoptotic ones [7, 53]. As experiment performed on cells with melanoma origin (A375) showed that certain vanadium compounds (non-organic anion vanadate (V) and oxovanadium (IV) complex [VO (1.2-dimethyl-3-hydroxy-4(1)H)-pyridine nonate)$_2$]) in different concentrations (4.7 and 2.6 μM accordingly) induced cell apoptosis and cellular cycle stop. A375 line cells were treated with these vanadium-containing compounds (four- and five-valent vanadium) and it inhibited ERL phosphorilation by approximately 80 % together with inducing MAPK-cascade kinases inactivation [54]. Anti-tumor effects produced by vanadium on melanoma cells are determined by its ability to induce apoptosis via ROS generation. Experiments allowed establishing that when vanadium (V^{5+}) was added into cellular culture in quantity equal to 100 μmol/L^{-1}, it reduced vital capacity of epithelial oviduct cells. Meanwhile, treatment of cultivated SB203580 cells (p38 MAPK inhibitor) and U0126 cells (ERK1/2 inhibitor) eliminated apoptosis-inducing effects produced by vanadium [48]. Incubation of epithelial oviduct cells with MAPK inhibitors increased catalase and glutathione peroxidase activity (up to 89 %) as well as prevented increase in malonic dialdehyde concentration. It was shown that oxidative stress in epithelium oviduct cells caused by vanadium was partially due to p38 MAPK and JNK/Nrf2 activation that reduced expression of the 2nd phase detoxification enzymes. MEK/ERK signal cascade regulates expression of bcl-2 that prevents occurrence of transmembrane pores in mitochondria [55]. ROS, acting indirectly via ERK1/2, can activate caspase-3 and increase bak and bax expression. When activated, ERK1/2 and JNK kinases are able to participate in coordinating Keap1/Nrf2/ARE redox-sensitive signal system functioning. It was shown that p38 MAK and JNK stimulation exerted anti-apoptotic impacts in most cases. It was established that JNK was activated with FAS in many cell types [56]. But at the same time only long-term JNK activation provides an opportunity for apoptosis initiation and occurrence. An experiment revealed that p38 MAPK signal cascade was involved in regulation of p53, NF-κB, Stat1 transcription factors as well as bcl-2, Cdc25A apoptosis mediators [56]. It was proven that p38 MAPK and JNK participated in regulating FAS/FASL-system activity. p38 MAPK plays a significant role in regulating early expression of FASL and FAS-mediated caspases activation. Activated caspases stimulate JNK for further growth in FASL expression [57].

Analytical review of Russian and foreign scientific works has revealed that at present significant data have been accumulated on modifying effects produced by vanadium on apoptosis programs activation. Meanwhile multiple issues related to probable new ways for vanadium inducing or changing cell death processes remain disputable. Some researchers showed that vanadium had apoptosis-inducing properties and was able to initiate necrosis [54, 58–60]. However, other experts proved that vanadium was able to inhibit apoptosis [61]. But at the same time nowadays most experts in medical and biological sciences adhere to an opinion that apoptosis is the primary cell death way under exposure to vanadium [35]. But here we should clarify that most research works that focused on examining modifying effects produced by vanadium on apoptosis mechanisms were performed on tumor cells lines.

Oxovanadium in concentrations from 0.1 to 5.0 mg/kg reduced FAS-dependent apoptosis in *in vivo* system [61]. SOV (sodium ortovanadate) which inhibits tyrosine phosphoproetin phosphatases inhibited apoptosis of oral squamous cell carcinoma (Cal27) cells and inhibition was dose-dependent [60]. When natural killers (NK-92MI) were exposed to V_2O_5, it resulted in FAS, FASL, and CD25 hyper-expression. Vanadium-initiated lipid peroxidation in membrane makes for a change in membrane receptors expression. An increase in FAS-ligand quantity was registered under vanadium pentoxide concentration equal to 50 mM; maximum CD95-anmtigen expression was detected at its concentration being 100 mM; CD25-antigen, 400 mM [49]. It was shown that exposure to complex vanadium (IV) compounds resulted in inhibiting FAS-mediated apoptosis caused by protein kinase B (PKB) phosphorilation [48]. There was imbalance between anti-apoptotic and pro-apoptotic members of BCL-2 protein family, c-fos oncoprotein activation, poly (ADP-ribose) polymerase-1 disintegration and dose-dependent apoptosis activation when human epidermal keratinocytes were exposed to vanadyl sulfate (HaCaT) [62]. Vanadium ability to initiate receptor-dependent and p53-regulated apoptotic signal in a cell was shown in experiments performed on cellular lines. Greater initiating caspases-8 activity in mice fibrosarcoma (L929) cells and greater p53 expression in human hepatocellular carcinoma (HepG2) resulted from vanadium (IV) being added to the cell cultures [59]. Vanadium stimulated reactive oxygen species occurrence and thus induced autophagy, necroptosis, and mitotic disaster in a cell line of metastatic pancreatic adenocarcinoma (AsPC-1) [63]. Vanadium in an exposure dose equal to 0.0005 $\mu g/cm^3$ caused cell death as per necrosis type in *in vitro* system (leukocytes suspension obtained from peripheral blood of practically healthy children exposed to vanadium). Vanadium pentoxide nanoparticles (30–60 nm) inhibited proliferation of melanoma cells (B16F10), lung carcinoma cells (A549), and pancreatic carcinoma cells (PANC1). V_2O_5, internalization generated ROS inside cells, activated p53 protein and inhibited survivin in cancer cells thus inducing apoptosis. However there were no apparent cytotoxic effects produced by vanadium on normal cells (fibroblastic kidney cells NRK-49F, cells obtained from human embryo cells HEK 293, cell culture obtained from Chinese hamster ovaries CHO-K1) [64]. Obviously, modifying effects produced by vanadium on cell death depend on many components such as vanadium oxidation rate, exposure dose, exposure duration, cells species and cells belonging to a specific organ, differentiation stage, maturity stage, and cell functional state; it requires relevant interpretation of obtained results [13, 21, 27, 36, 44, 54, 58, 60].

In order to get a complete insight into modifying effects produced by vanadium on apoptosis, it is necessary to accomplish further profound research on cell death mechanisms taking into account fundamental regularities in the process as well as apoptosis peculiarities determined by the hapten influence. In order to extrapolate impacts exerted by vanadium on a healthy body, in future it will be necessary to experimentally model apoptosis not only on tumor cells but also to more widely involve cells or cell lines taken from a healthy body to be used in *in vitro* systems. Probably, a small range of vanadium concentrations between its essentiality and toxicity predetermines multi-directional changes in apoptosis induction and completion [16, 38]. Moreover, peculiarities of an object (body) exposed to vanadium are also to be taken into account (age, sex, genetic peculiarities if xenobitoics metabolism, etc.) [3, 4, 7, 8, 31–33, 37, 48, 62, 63]. A hypothetic cell death mechanism modified by technogenic vanadium compounds is given in the Figure.

Control over cells population in a multicellular organism is a vital biological process that provides an opportunity for a body to get rid of potentially hazardous cells. Apoptosis activation makes for auto-immune and immune-proliferative processes development; cell death inhibition can result in immune deficiency, inflammatory reactions, and neurodegenerative diseases. Disorders in cell death become more probable under exposure to chemicals that pollute the environment. Environmental contamination with vanadium and its compounds due to technogenic activities create hazards for exposed adults' and children's health and this fact is truly alerting. Hazards caused by vanadium are predetermined by its ability to modify apoptosis mechanisms. Thus, vanadium-induced lipid peroxidation that has chain character results in changes in biophysical properties of membranes (greater permeability and changes in their fluidity), free radicals accumulation, and changes in membrane reception. Inside cells, vanadium and its compounds can also stimulate free oxygen species occurrence when metabolic reactions are developing in various cellular compartments. ROS produce their effects on separate protein molecules acting as inhibitors or activators and influence biochemical and physiological mechanisms of intracellular signalization. Immune-modifying effects produced by vanadium are related to blocking / activating enzymes via creating complexes with their substrates and via competing with phosphate in phosphate-binding

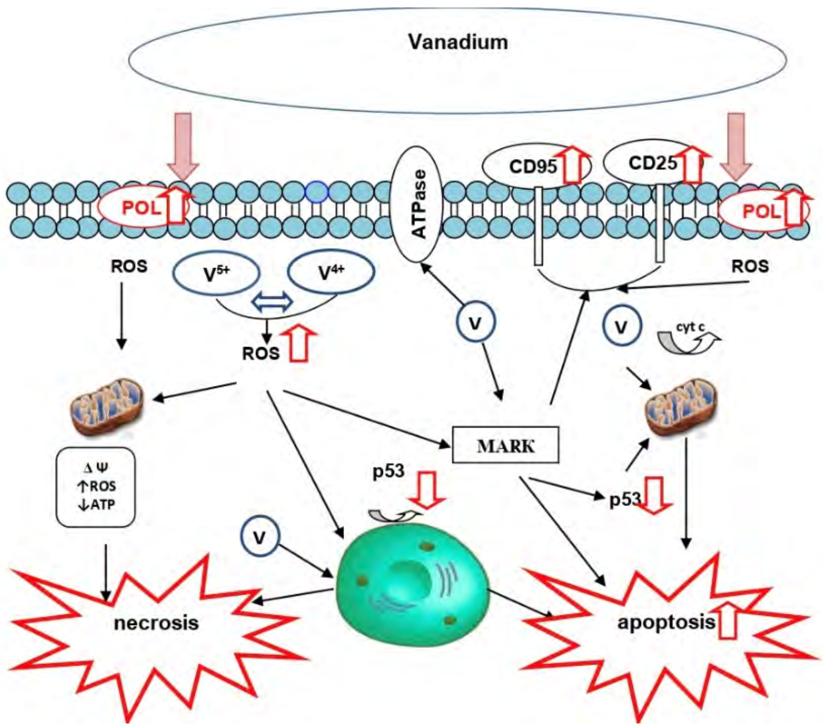

Figure. A hypothetic cell death mechanism modified by technogenic vanadium compounds; POL is lipid peroxidation, MARK are mitogen-activated protein kinase cascades; ROS are reactive oxygen species; *cyt c* is cytochrome *c*; ΔΨ is mitochondrial potential collapse enzymes; ultimately, it induces changes in sections of intracellular transmission cascades [9]. Obviously, vanadium has significant immune-therapeutic potential since it is able to modify processes that result in cell life or death; it predetermines significance of further examination and analysis of molecular mechanisms and signal cascades under exposure to a hapten (vanadium). Monitoring over biological parameters that determine cell death under exposure to vanadium and its compounds provides an opportunity to timely identify risks of disease occurrence and prevent damage to health. The performed analysis of scientific works allowed revealing peculiarities and determining probable cell death scenarios under exposure to technogenic vanadium and its compounds.

Funding. The research was not granted any sponsor support.

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

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Received: 17.08.2020
Accepted: 23.11.2020
Published: 30.12.2020

UDC 614.40: 615.7
DOI: 10.21668/health.risk/2020.4.19.eng
Review

Read online

COVID-19: WELL-KNOWN DRUGS, NEW OPPORTUNITIES

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Up to now, coronavirus infection that causes an acute respiratory syndrome has been detected almost in all countries worldwide. Global spread of SARS-CoV-2 virus has become a world pandemic and there is no efficient and commonly accepted conventional therapy against COVID-19. Due to the existing emergency most drugs that can potentially be used to treat COVID-19 are allowed to be applied only basing on certain data probing their safety and efficiency against SARS-CoV. At present only Lopinavir/Ritonavir and Remdesivir are the only anti-virus drugs that are included into well-recognized management procedures for COVID-19 treatment; an acceptable alternative could probably be combined therapy that includes Hydroxychloroquine and Azithromycin. Given the existing situation, a lot of drugs that are usually used to treat other diseases are now being suggested as probable ways to treat COVID-19 taking into account all the available knowledge on pathophysiology of the infection.

In this review, basing on available data on how SARA-CoV-2 virus enters a cell and pathophysiological aspects of cytokine storm development, we have strived to highlight certain prospects related to applying anti-viral medications, anti-inflammatory and immune-suppressing drugs, vitamins and microelements that are widely used to treat and prevent various diseases. Most tested drugs as well as zinc preparations, and vitamins C and D_3 turned out to have not only immune-modulating but also anti-inflammatory properties; or either they were able to block ways for the virus to enter a cell or disrupt SARS-CoV-2 intracellular replication.

Having leant from previous experience in fighting against SARS and MERS, doctors have applied some existing drugs to treat COVID-19 infections in their clinical practices; clinical tests aimed at confirming their safety and efficiency in treating COVID-19 are still being performed at the moment. Although a lot of various treatment procedures have been suggested, it is necessary to perform specifically planned randomized clinical trials based on evidence-based medicine principles, if we want to determine the most suitable ones.

Key words: *coronavirus, SARS-CoV-2, COVID-19, anti-viral medications, immune-modulating drugs, anti-inflammatory drugs, medications, clinical tests.*

Starting from severe acute respiratory syndrome (SARS-CoV) in 2002 and Middle-East respiratory syndrome (MERS-CoV) in 2012 caused by coronaviruses, SARS-CoV-2 occurrence has become the third event when highly pathogenic and wide-scale coronavirus epidemic has spread throughout human population in the 21st century. On January 30, 2020 the World Health Organization (WHO) officially declared COVID-19 epidemic to be an internationally significant emergency in public healthcare [1, 2].

The epidemic outbreak was established to have been caused by a new virus that was different either from Middle-East respiratory syndrome coronavirus (MERS-CoV) or severe acute respiratory syndrome virus (SARS-CoV) [3, 4]. This virus belongs to RNA viruses' family called Coronaviridiae, is probably recombinant and is carried by

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bats [5]. Recombination occurred in glycoprotein area on virus surface thorns where receptor of cell surface endocytosis was recognized, namely angiotensin-converting enzyme 2 (ACE2) [6, 7].

Accumulated data indicate that SARS-CoV-2 infection can cause acute respiratory syndrome that is greatly similar to a clinical picture usually occurring in case of pneumonia developed in people suffering from autoimmune diseases (that is, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis, and eosinophilic granulomatosis with poly-vasculitis), and auto-inflammatory diseases (for example, systemic idiopathic arthritis etc.) [8–10].

COVID-19 disease occurrence was related to full-blown anti-inflammatory status which was very similar to cytokine storm and involved producing and maintaining high contents of various cytokines including interleukins (IL)-1β, IL-1Rα, IL-2, IL-10, fibroblast growth factor (FGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP10), monocytes chemoattractant protein 1 (MCP1), macrophage anti-inflammatory protein 1 alpha (MIP1A), platelet-derived growth factor (PDGF), tumor necrosis factor alpha (TNFα), and vascular endothelium growth factor (VEGF) [11, 12]. Patients who are in critical state suffer from a drastic increase in contents of these factors, and IL-6 concentrations correlate with an increased in mortality [13, 14].

At present there are no standard procedures for treating COVID-19. Bearing in mind that the virus has a unique structure and the disease has different pathogenesis, it is necessary to develop COVID-19-specific treatment procedures, especially vaccines and antiviral medications. However, new vaccines development according to international standards will require not less than 18 months. As for new antiviral medications, it is still impossible to predict when they will be created and tested despite all promising possibilities available in the field. Given that, it is quite obvious that when the epidemic is at its peak, it is necessary to look for other solutions. Therefore, there has been an opinion that certain research works that could really make for finding these solutions should be aimed at developing and suggesting medications with their therapeutic properties being well-known from previous examinations, both traditional and non-traditional ones, that focused on studying other diseases with similar pathogenetic mechanisms. Bearing in mind that the epidemic is spreading rapidly and complications caused by it are rather severe, at present doctors who are treating infected patients need as much available therapeutic alternatives as it is only possible. This emergency the scientific society has to face when searching for ways to overcome COVID-19 pandemic calls for necessity to use medications that have not been properly approved as their usability for treating COVID-19 infections has only preliminary scientific justification.

When it comes to antiviral medications, experts have chosen to turn to previous experience gained in overcoming SARS and MERS; there are clinical tests being performed at the moment with their focus on estimating efficiency and safety of these existing medications when they are applied to treat COVID-19 [15]. In particular, bearing in mind that there are certain similarities between SARS-CoV-2 and other beta-coronavirus associated with such past epidemics as SARS-CoV and MERS-CoV experts took the same medications that had been used to treat them and yielded contradictory results (interferon, ribavirin, and lopinavir/ritonavir) and considered them as tool for treating COVID-19 [16, 17]. But it turned out that antiviral medications and systemic therapy with corticosteroids that was earlier applied in clinical practices, including neuraminidase inhibitors (oseltamivir, peramivir, zanamivir, etc.) as well as ganciclovir, acyclovir, and ribavirin used to eliminate flu virus, were not efficient for treating COVID-19 and were not recommended [18, 19].

Such protease inhibitors as lopinavir and ritonavir that were used for treating human immunodeficiency virus (HIV), MERS-CoV, and SARS-CoV turned out to be quite efficient in treating COVID-19 in South Korea [20, 21].

Besides, remdesivir which is now being developed as an adenosine analogue for treating Ebola infection has recently been accepted as a promising antiviral medication against a wide range of RNA viruses; it has yielded positive preliminary results in treating SARS-CoV-2 infection [22]. Remdesivir has been shown to produce effects on virus RNA-dependent RNA polymerase (rdRp); it is able to efficiently avoid correction by virus exoribonuclease and prevents RNA virus transcription from completion [23]. Since its efficiency in treating patients with SARS-CoV-2 infection was estimated in March 2020, the medication has been recommended to be applied in a single oral dose equal to 200 mg on the 1st day with the subsequent maintaining doses equal to 100 mg taken once a day for 3–5 days [24].

Another nucleotide analogue used to destroy RdRp-dependent virus replication is called favipiravir; it has been approved on by research experts in several countries and has been proven to be able to make outcomes better for patients with COVID-19 [25]. As per preliminary results, favipiravir turned out to be more efficient in 80 cases than lopinavir/ritonavir and patients who took it didn't suffer from any significant adverse reactions [26].

Arbidol and arbidol mesylate have also been shown to produce significant inhibiting effects on SARS-CoV reproduction [27]. Basing on that, clinical experts combined western and Chinese treatment procedures, accordingly including lopinavir/ritonabir (Kaletra®), arbidol, and Shufeng Jiedu Capsule (SFJDC, traditional Chinese medicine); it allowed them to achieve significant improvement of symptoms related to COVID-19 pneumonia in Shanghai Clinical Center of China Public Healthcare [28]. At present, a wide range of antiviral medications are being tested as possible tools to overcome COVID-19 infection including nitazoxanide, nafamostat, darunavir, cobicistat, emtricitabine/tenofovir, etc. [29, 30].

Apart from using certain antiviral medications, experts have also suggested a lot of other medications usually applied to treat various diseases as probable tools to treat COVID-19; these suggestions result from considerable data being accumulated on the infection pathophysiology.

Glucocorticoids play a significant role in rheumatologic clinical practices and are widely used to treat such diseases as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), vasculitis, etc. due to their immune-depressing properties [31, 32]. However, high corticosteroid doses are closely connected with such adverse effects as secondary infections and virus resistance occurrence. In accordance with the Chinese clinical guidance for COVID-19 pneumonia diagnosis and treatment (the 7th edition)[1], in China only low and moderate corticosteroid doses can be potentially useful in therapy applied to treat seriously ill patients with COVID-19 pneumonia. The preliminary guide on clinical practices for treating COVID-19 published by the WHO does not recommend using corticosteroids excluding such clinical reasons as chronic lung disease exacerbation or septic shock [33].

Chloroquine and its derivative, hydroxychloroquine, are aminoquinoline com-

[1] Chinese clinical guidance for COVID-19 pneumonia diagnosis and treatment (7th edition). Beijing: National Health and Family Planning Commission of China (NHPFC), 2020. Available at: http://kjfy.meetingchina.org/msite/news/show/cn/3337.html (13.05.2020).

plexes that are registered as medications for treating and preventing malaria and many other auto-immune diseases [34]. Chloroquine use as an anti-malaria medication is significantly limited nowadays to widely spread resistant malaria plasmodium, but hydroxychloroquine is now considered a vital component in primary treatment of RA and SLE due to its apparent immune-modulating effects [35].

Chloroquine can inhibit pH-dependent stages in replication of certain viruses including significant effects produced on SARS-CoV infectious agents. Besides, it has immune-modulating effects as it inhibits TNF-α and IL-6 production /release and it also acts as a new autophagy inhibitor that can prevent viruses from reproducing themselves [36]. Several research works revealed that chloroquine was able to block glycosilation of angiotensin-converting enzyme 2 (ACE-2) with an ability to inhibit SARS CoV-2 virus ability to enter cells. Preliminary results confirm that the medication can suppress COVID-19 pneumonia development thus improving a lung x-ray picture and reducing duration of the disease. Basing on this evidence, chloroquine and hydroxychloroquine were included into certain treatment procedures in China and Italy as well as in most other countries worldwide [37, 38].

However, experience gained via applying these medications in an actual epidemiologic situation has also revealed risks related to probable adverse effects [39, 40]. In rheumatology chloroquine and hydroxychloroquine are most widely prescribed and they are proven to have potential adverse effects such as retinopathy, cardiotoxicity, and myelotoxicity; these effects are a real threat for patients with rheumatoid arthritis and collagenosis in case the medications are taken for a long time [41]. In case there is acute COVID-19 infection, these medications can only be used for a very short period of time (5–20 days according to a recommended treatment procedure) with probably an insignificant risk of adverse effects [37, 38]. Nevertheless, we should remember that such acute side effects as hyper-sensitivity and gastrointestinal intolerance require special attention, especially when it comes to patients with COVID-19 who are in critical condition.

Soon we expect to get access to results obtained via clinical tests with use of the 1st hydroxychloroquine dose equal to 400 mg taken in the 1st day and subsequent maintaining doses equal to 200 mg taken for the following 4 days; it will allow clarifying whether a theoretically strong effect can be produced by the medication on survival and recovery of patients with COVID-19 [42]. Until then, the medications remain basic ones in the current treatment procedures due to their impeccable safety profiles and huge experience on their use in clinical practices.

According to a recent research work, when azithromycin was added to a treatment strategy applied to treat a patient with severe COVID-19 (500 mg the 1st single dose, then 250 mg once a day for 2–5 days), it resulted in significant growth in hydoxychloroquine efficiency (200 mg thrice a day for 10 days) [43]. And at present several randomized clinical examinations are performed that involve use of such a combination to treat COVID-19 with different severity (NCT04321278, NCT04322396, NCT04322123, NCT04324463).

Non-steroid anti-inflammatory medications (NAFM) are easily available and are usually prescribed to treat pains, fever, and inflammations in case of many diseases, especially in rheumatology. Several years ago it was shown that a protein part in SARS-CoV thorn activated cyclooxigenase-2 expression, and naproxen turned out to have a counteracting effect; besides, it was detected that ibuprofen had inhibiting effects on ACE2 [44, 45]. It has been decided to examine naproxen efficiency when the medication is included into a standard treatment procedure for patients with COVID-19 who are in critical conditions; clinical tests are now at their 3rd stage [46]. But at the same tine regular symptomatic use of NAFM is still not recommended as the primary variant in basic COVID-19 treatment due to such patients running higher risks of hospitalization, critical condition, and mortality which correlates with age and concomitant diseases, especially hypertension [47].

There has been a report recently on efficiency of tocilizumab, interleukin-6 inhibitor (humanized monoclonal antibody against IL-6 receptor which is used in rheumatoid arthritis treatment) for treating patients with severe COVID-19 pneumonia [48]. A randomized clinical examination aimed at estimating tocilizumab safety and efficiency in treating COVID-19 is still going on (ChiCTR2000029765). In China it was recommended to use tocilizumab as it provided an opportunity to treat patients with extensive and bilateral pneumonia or seriously ill patients with high IL-6 contents [48].

Another interesting anti-inflammatory medication is baricitinib, cytokine production inhibitor. It inhibits JAKkinase and is licensed to treat rheumatoid arthritis; reported efficiency and safety are quite satisfactory. Use of baricitinib in treating COVID-19 can bring good results as the medication acts against a wide range of cytokines. And finally, a minimal interaction between baricitinib and relevant CYP P-450 enzymes that metabolize it makes the medication a possible option to be included into treatment procedures in a combination with anti-viral medications such as lopinavir/ritonavir and remdesivir [49].

It is known that SARS-CoV-2 enters target cells via ACE2 receptor and transmembrane protease, Serin 2 (TMPRSS2). And here TMPRSS2 inhibitors can prevent the virus from entering a cell due to blocking SARS-CoV-2 thorn protein [50]. Such effects are produced by camostat, a protease inhibitor used to treat chronic pancreatitis [51]. At present there is a randomized placebo-control examination focusing on use of this medication to treat COVID-19 (NCT04321096).

A vital task when it comes to treating COVID-19 is to block cytokine storm; very promising results were detected for dapson, a sulfone medication with anti-inflammatory effects; doxycycline, an antibiotic from tetracycline group; and promazien, a neuroleptic drug used in psychiatric practices [52–54]. There are randomized clinical examinations with participating out-patients with COVID-19 that involve use of these medications (NCT04322682) together with colchicine, anti-tumor and anti-inflammatory medication that inhibit cellular microchannel polymerization [53]. And finally, basing on data regarding produced effects, there is a clinical examination going on at the moment that focuses on efficiency of treatment with losartan for out-patients (NCT04311177) and hospitalized patients (NCT04312009) with COVID-19.

Vitamin D is known to control inborn and adaptive immunity and its deficiency is related to auto-immune reactions growth and increased susceptibility to infections; it can well play a significant role in decreasing COVID-19 risks [55, 56]. Since vitamin D deficiency is widely spread, especially among elderly people [57, 58] and it tends to grow in case sunshine is also in deficiency, it was probably not accidental that the 1st SARS-Cov-2 outbreak occurred in winter season and involved high mortality among elderly people [59, 60]. In order to slow down virus replication and prevent anti-inflammatory cytokine production, there are several clinical examinations being performed on patients with COVD-19 at the moment; they involve use of vitamin D3 in a dose equal to 10.0 units per day during several weeks (NCT04334005, NCT04344041) [61].

Besides, basing on clinical results obtained in COVID-19 infection focus in China, experts made an assumption that taste and smell loss could be caused by zinc deficiency as such symptoms are quite typical for this state [62, 63]. Since preliminary research has revealed that zinc produces inhibiting effects on coronavirus replication, it is assumed that if a person consumes zinc in a dose equal to 50 grams a day, it can provide certain protection against COVID-19 due to a body more efficiently resisting against the viral infection. The 1st clinical examination that involves intravenous zinc introduction into patients with COVID-19 is going on in Australia (ACTRN12620000454976). Besides, there are several clinical examinations being performed at the moment that involve use of zinc combined with other medications (that is, hydroxychloroquine, vitamin D, vitamin C) to treat COVID-19 (NCT04326725, NCT04351490, NCT04342728).

Conclusions. Therefore, we can conclude that the world is facing a new dangerous virus with higher pathogenicity than all the known infections. Over a few short months SARS-CoV-2 has spread throughout the world with menacing speed and is now threatening global and individual health and economic prosperity. At present there are no registered vaccines or standardized treatment procedures specifying certain medications and schemes for their use that are efficient against SARS-CoV-2. As it is a real emergency, most medications that can potentially treat COVID-19 are allowed to be used basing only on data on their safety and efficiency against SARS-CoV-2. At the moment only lopinavir/ritonavir and remdesivir are anti-viral medications that are included into serious treatment procedures for COVID-19 treatment; an acceptable alternative might be combined therapy with hydroxychloroquine and azithromycine. Given the existing situation and taking into account available data on the infection pathophysiology, experts have started to suggest many medications that are usually used to treat various diseases as possible treatment methods against COVID-19. We hope that clinical examinations involving use of these medications will allow obtaining high quality data; these data can be used to objectively estimate a probable therapy aimed at both treating and preventing this disease that causes a global emergency worldwide. Enhanced international cooperation and clinical examinations performed on a global level with a great number of patients participating in them should become a way for achieving valid and ultimate results.

Funding. The research was not granted any sponsor support.

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

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Received: 30.08.2020
Accepted: 11.11.2020
Published: 30.12.2020

UDC 616.24-002
DOI: 10.21668/health.risk/2020.4.20.eng

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Review

CONTEMPORARY RISK FACTORS THAT CAUSE DISSEMINATED LUNG DISEASES

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As per data provided by Rosstat, in 2018 primary morbidity with respiratory diseases amounted to 35 982 per 100 thousand people; respiratory diseases account for more than 25 % in the structure of overall population morbidity and they to a great extent depend on risk factors occurrence. Disseminated lung diseases are combined into one specific group among respiratory diseases as per x-ray evidence.

Our research goal was to review contemporary risk factors that cause disseminated lung diseases in order to apply them in diagnostics. We searched for scientific works that were relevant for our research in such databases as RSCI, Cyber-Leninka, Scopus, Web of Science, MedLine, and PubMed.

There are a lot of classifications for disseminated lung diseases based on morphologic substrate peculiarities, etiology and other signs; it proves the issue is truly complicated. Patients with disseminated damage to lungs have similar x-ray picture of the disease and results obtained via general clinical tests also have no pathognomonic peculiarities. Clinical experts usually divide disseminations into those with infectious genesis (tuberculosis, HIV-associated disseminations, and fungus diseases) and those with non-infectious genesis (tumor disseminations, interstitial lung diseases, lysosomal storage disorders, etc.). The review outlines factors that influence both occurrence and development of lung diseases accompanied with dissemination syndrome. The greatest attention is paid to socially significant diseases as risk factors that cause them can be detected by a doctor in a patient's case history and applied for differential diagnostics. It is necessary to develop relevant prevention activities aimed at reducing risks of disseminated lung diseases as they will allow preventing morbidity and mortality among patients suffering from lung disseminations caused by correctable risk factors.

Key words: *lung dissemination syndrome, risk factors, interstitial lung diseases, tuberculosis, pneumonia, HIV-infection, bronchiole-alveolar cancer, amyloidosis, pneumoconiosis.*

In the 21st century respiratory diseases occupy leading rank places in morbidity structure among the RF population; mortality and disability caused by them also remain high. According to Federal State Statistic Service data in 2018 primary morbidity with respiratory diseases amounted to 35,982 cases per 100 thousand people, and respiratory diseases accounted for 25.1% in the structure of overall population morbidity[1]. High morbidity with respiratory diseases to a great extent depends on risk factors including lifestyle, smoking, bacterial and viral infections, concomitant diseases, exposure to adverse occupational factors, environmental factors, and ecology [1].

Disseminated lung diseases account for a great share in the structure of morbidity with respiratory diseases; they are assigned into a separate group as per their specific x-ray picture but still differ significantly as per their etiology and treatment procedures [2, 3]. A classification suggested by M.M. Il'kovich and A.N. Kokosov is widely used in clinical practice; it is based on peculiarities of morphologic substrate which is typical for different lung disseminations. There are also etiology-based classifications. For everyday practice, we can conditionally divide diseases that involve lung dissemination syndrome into communicable (tuberculosis, HIV-associated disseminations, and fungus diseases) and non-

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[1] Public healthcare in Russia. 2019: statistical data collection. Moscow, Federal State Statistic Service Publ., 2019, pp. 29–31 (in Russian).

communicable ones (tumor disseminations, interstitial lung diseases, storage disorders, etc.) [2, 3].

Since «the list of diseases» is rather extensive and their x-ray signs are rather common, it is vital to develop procedures that would allow reducing time required for differentiated diagnostics of disseminated lung diseases. There are various approaches to differential diagnostics optimization described in literature; they include, for example, mathematical procedures. Here we can mention that A.E. Yankovskaya, I.V. Gorbunov, and G.E. Chernogoryuk (2017) suggested developing an applied hybrid intellectual system for differential diagnostics of disseminated lung diseases that was based on fuzzy logic principles [4].

Our research goal was to review contemporary risk factors that could cause disseminated lung diseases in order to apply them in diagnostics.

The present work dwells on revising literature on the issue related to detecting risk factors causing disseminated lung diseases. When accomplishing our work, we searched for relevant literature sources published over the last 10 years in such databases as RSCI, CyberLeninka, Scopus, Web of Science, MedLine, and PubMed.

When a primary health care specialist detects dissemination in a patient, he or she should first of all exclude disseminated tuberculosis as a probable diagnosis. Initial data collection here should concentrate on estimating risks of the disease in a patient's case history, primarily, probable contacts with people who already have tuberculosis. Disseminated tuberculosis holds the second rank place as per prevalence following infiltrative one that is on the first place. At present disseminated tuberculosis accounts for 20–30 % in overall morbidity with all tuberculosis types.

HIV-infection is a factor that causes growth in number of people suffering from disseminated tuberculosis, especially when it has already transformed into AIDS [5, 6]. As per data obtained via meta-analysis performed by M. Straetemans, A. Bierrenbach, and N. Nagelkerke, patients with HIV run 20 times higher risks of tuberculosis than immune-competent people in countries with HIV prevalence exceeding 1 % [6]. Diagnostics reveals HIV and tuberculosis comorbidity more and more frequently as these two diseases naturally accompany each other due to their prevalence predominantly among the same population groups [7].

Disseminated tuberculosis is the most common type that occurs in HIV-infected people; it develops more frequently in case CD4-lymphocytes content in blood goes down to 200 cells/μL and lower [8].

Disseminated tuberculosis can develop many years after spontaneous or medication-induced recovery from primary tuberculosis (delayed generalization) among HIV-infected people; a key component in its pathogenesis is hematogenic, lymphogenic, or lymphohematogenic spread of tuberculosis mycobacteria [9].

CT-scan allows detecting three types of acute tuberculosis dissemination at later HIV-infection stages that involve immune suppression: they are miliary, mixed (foci with different sizes, from small to large ones), and bronchial lobular caseous pneumonia. Patients with miliary (lymphohematogenic) dissemination usually have small foci (2–4 mm diameter) with low and middle intensity, and CD4-lymphocytes contents in blood vary within 98–40 cells/μL range. In case dissemination is mixed (including lymphohematogenic one) a patient has foci with their diameter varying from 2 to 10 mm and CD4-lymphocytes contents in blood do not exceed 39–20 cells/μL. Patients who suffer from bronchial lobular caseous pneumonia have different foci but with large ones prevailing and tending to merge and create infiltrates with multiple cavities. It indicates there is combined lymphohematogenic and bronchogenic dissemination. CD4-lymohcytes contents being lower than 19 cells/μL mean that immune control over tuberculosis inflammation development and enclosure has been lost; it results in development of acute disseminated and miliary tuberculosis that cause death most frequently [10].

Patients with comorbid HIV/tuberculosis are more frequently males who have promiscuous sexual relations, smoke and abuse alcohol [11]. Recently there has been a significant growth in number of HIV-infected women in their reproductive age and it leads to growing number of children borne by HIV-infected mothers. Children with HIV-infection are also a risk group as per disseminated lung diseases [12].

J.P. Aguilar, M.B. Arriaga, M.N. Rodas, and E. Martins-Netto (2019) examined risks of fatal outcomes when tuberculosis was treated. Failure in treatment was primarily due to smoking and a patient's age and not due to sex, income, education, alcohol intake, or family status. Age older than 50 was established to increase fatal outcome probability among patients with tuberculosis by 2.8 times; smoking in case history, by 2.1 times [13]. Other authors considered smoking, alcohol abuse, as well as pancreatic diabetes and low body mass index to be the most significant individual risk factors that caused tuberculosis; their combination was assumed to result in 3–4 times higher risks of active tuberculosis [14].

Pneumocytic pneumonia has become the most common opportunistic HIV-related diseases in many countries since the first HIV-infection cases were registered. Its x-ray picture is quite similar to that of bilateral interstitial pneumonia or bilateral microfocal pneumonia; the disease develops in most patients in case CD4-lymphocytes content in blood is lower than 100 cells/μL; in rare cases it can occur even when it is more than 200 cells/μL [15–17]. Pneumonia pathogenesis includes three stages:

1) cysts and trophozoides attaching to type I alveolocytes;

2) alveolar epithelium desquamation and cysts growing bigger inside alveolar macrophages;

3) reactive alveolitis combined with clinical symptoms with respiratory failure signs.

The disease is diagnosed basing on detected etiological factor, namely *pneumocystis jirovecii,* but not all regions in the country are capable of performing such examinations [15].

Morbidity with bacterial pneumonias is 5–10 times higher among HIV-infected people than among population in general. Drug intake, smoking, HIV-associated immune suppression, cirrhosis, and absence or a break in anti-viral therapy are significant risk factors that can cause community-acquired pneumonia [18]. Clinical picture of bacterial pneumonia in a HIV-infected patient does not differ from that in a non-infected one; however, the disease develops more rapidly among HIV-infected patients, bacteremia occurs more frequently, and respiratory failure is also more common among them [19].

Social burdens such as low incomes, being homeless, unemployment, staying in a penal institution, or ecologically adverse living conditions are undoubted risk factors causing both tuberculosis and pneumonia [1, 20, 21].

Non-communicable disseminated lung diseases include tumor disseminations (bronchial alveolar cancer, metastatic tumors, lymphogioleiomyomatosis), interstitial lung diseases (alveolitis, granulematosis, systemic vasculitis with damage to lungs), and storage diseases (bronchopulmonary amyloidosis, alveolar microlithiasis, etc) [2, 3].

Bronchial alveolar cancer (BAC) as disseminated lung tumor is a variety of lung adenocarcinoma that spreads along interalveolar septa without any signs of vascular, pleural, or stromal invasion. A tumor doesn't create its own stroma and uses alveolar septa instead. BAC occurs out of bronchial and alveolar epithelium cells that underwent mucinous metaplasia (chalice cells) and type II pneumocytes [22]. Smoking and type 1 human T-cell leukemia virus (HTLV-I) are considered to be risk factors that can cause BAC [23, 24]. Smoking can be considered a significant risk factor common for multiple lung diseases, both non-communicable (BAC, for example) and communicable ones (tuberculosis) since tobacco smoke changes susceptibility of respiratory mucosa [13, 14, 25]. Common risk factors make differential diagnostics of disseminated diseases even more difficult.

Interstitial lung diseases are a heterogeneous group that includes variable diseases and pathologic states characterized with different parenchymatous non-infectious inflammation (as per alveolitis and/or granulematosis type) with the following fibrosis development. Conventionally experts distinguish interstitial lung diseases with unknown etiology (idiopathic lung fibrosis, other idiopathic interstitial pneumonias, lung vasculitis, eosinophilic pneumonia, etc.) and with known etiology (diffuse diseases of the connective tissue with damage to lungs, exogenous allergic alveolitis, medication-induced damage, pneumoconiosis, etc.) [3]. Risk factors are individual for each nosology that has known etiology, for example, long-term and intense contacts with an allergen as a risk factor causing exogenous allergic alveolitis («farmer's kung», «cheese-maker's lung»); amiodarone intake («amiodarone lung») [3, 26, 27]. Long-term contacts with high-fibrogenic industrial aerosols or fine-dispersed welding aerosols result in high occupational risks of pneumoconiosis [28, 29].

Bronchopulmonary amyloidosis is the most frequent among storage diseases. Etiology of primary amyloidosis is still unclear. There are three types of the disease, idiopathic, hereditary, and senile one. Pathogenesis is related to elevated secretion of immunoglobulin and amyloid fibrils that get bonded to proteins in blood serum, absorbed with macrophages, and deposit in organs and tissues as amyloid [29, 30]. Secondary amyloidosis usually involves amyloid fibrils that contain so called amyloid protein (amyloid A-protein). Risk factors that can cause secondary amyloidosis include chronic purulent-destructive processes (multiple bronchiectasis osteomyelitis), rheumatic diseases, and chronic diseases in the intestines (non-specific ulcerative colitis and Crohn's disease) [31, 32].

Therefore, despite multiple research works performed all over the world, comprehensive studies that focus on disseminated lung diseases remain vital. Patients with disseminated damage to their lungs tend to have similar x-ray picture of a disease and common clinical analyses also do not have any pathognomic peculiarities. Biopsy is a truly reliable procedure for lung dissemination verification as it allows determining what lung structures and to what extent are involved into processes that are shown as dissemination on an x-ray picture.

Lung disseminations have different pathogenesis; still, we can spot out risk factors that are common for communicable disseminations. They are concomitant HIV-infection, smoking, alcohol abuse, staying in a penal institution, low income, and adverse ecological situation. Certain risk factors can be revealed by physician even at the 1st meeting and used to perform differential diagnostics of communicable and non-communicable lung disseminations. Such factors are usually among those related to a patient's case history and include his or her lifestyle, bad habits, occupational or communal contacts with dusts and allergens, and medications he or she is taking at the moment (corrigible risk factors) as well as concomitant diseases and hereditary predisposition (incorrigible risk factors).

Development of preventive activities aimed at reducing risks of disseminated lung diseases will allow preventing morbidity and mortality among patients with lung disseminations caused by corrigible risk factors.

Funding. The research was not granted any sponsor support.

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

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Borodulina E.A., Yakovleva E.V. Contemporary risk factors that cause disseminated lung diseases. Health Risk Analysis, 2020, no. 4, pp. 179–184. DOI: 10.21668/health.risk/2020.4.20.eng

Received: 06.05.2020
Accepted: 11.11.2020
Published: 30.12.2020

UDC 614.894
DOI: 10.21668/health.risk/2020.4.21.eng

Read online

Review

REQUIREMENTS TO RESPIRATORY PROTECTION FOR WORKERS (WORLD PRACTICES REVIEWED)

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A great number of workplaces in Russia do not conform to sanitary-hygienic requirements and it results in wide use of personal respiratory protective equipment (PRPE). Choice on such equipment and its application are not regulated by the existing legislation in the RF in great detail as it is the case in developed countries. As a result, employers apply PRPE that is not efficient enough, or such equipment is not used properly, and it leads to diseases occurrence.

Our research goal was to reveal requirements to PRPE application which, when met, would reduce risks for workers' life and health as greatly as it is only possible.

Our research object was personal respiratory protective equipment (PRPE).

We compared requirements to selecting and applying PRPE in the USA, Australia, Great Britain, Canada, and West Germany and also took into account requirement and experts' recommendations existing in several other countries. When comparing, we tried to focus on key elements that determined whether PRPE applied in due time was able to prevent exposure to air contamination. Such key elements included choice on PRPE suitable for work under extremely hazardous conditions; permissible application of PRPE with different structure (expected protective efficiency); individual selection and testing whether a mask is fit for a face; timely replacement of respirator filters; requirements to skills of workers and their supervisors.

Our research revealed that results of PRPE application and requirements fixed for employers were most comprehensively estimated and well-grounded in the USA. The most favorable situation with quality and availability of materials on how to select and apply PRPE for workers, specialists, and supervisors is also in the USA. Results obtained via the performed comparison allow recommending US Standard 29 CFR 1910.134 as a basis for developing similar requirements in Russia.

Key words: *PRPE, efficiency of personal protective equipment, protective efficiency, respirators, prompt-hazardous concentration, insulating properties of a mask, respirator filters, health risk reduction.*

There are different methods used to protect workers from contaminants in the air; if we rank them in a descending order as per their efficiency, we get the following: changes in a technology aimed at eliminating/reducing contamination; equipment being placed into sealed casing; automation and remote control; ventilation; protection with time. Should exposure exceed MPC even in case these methods are used, then employers usually avail to the last and the least reliable protection means, namely personal respiratory protective equipment (PRPE). In order to achieve maximum possible effects produced by their use, there are requirements to them fixed in developed countries. These requirements regulate PRPE selection and procedures on their proper use. Requirements applied in the USA or the European Union (EU) were used as basic ones when national requirements in many countries were developed.

A growth in number of workplaces where air contamination exceeds MPC has resulted in wider PRPE use in the Russian Federation. Their distribution among workers is regulated by «Typical branch standards for free distribution of protective clothing», results obtained via special assessment of working conditions (The Federal Law 426-FZ), and «Methodology for assigning lower hazard categories for

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working conditions»[1, 2, 3]. But these documents don't take into account either protective efficiency of PRPE with different structure (different types) or the necessity to apply this equipment properly. Absence of specific requirements to PRPE selection and application makes errors more probable and results in elevated health risks for workers.

The present work focuses on comparing requirements an employer has to meet in Australia (AS), Bulgaria (BG), the United Kingdom (UK), Canada (CA), the USA (US), France, Germany (DE), China (CH), Ukraine (UA), and Japan (JP) as well as recommendations for an employer provided in South Korea (SK). We also gave certain recommendations on developing a document that would regulate PRPE selection and application in the RF. Links to requirements are given as per an abbreviation given in brackets after a country name or as per any other source[4].

We compared all these requirements as per certain key moments that determined how efficiently applied PRPE protected respiratory organs; it allowed us to spot out basic differences in regulatory documents existing in different countries.

When it comes down to application conditions and requirements to an employer we should note the following**.** The Standard applied in the USA (US) was developed to be used everywhere in a country where there was unified state legislation on labor protection. The EU standard was developed to be applied in some countries (DE, BG, and UA) with certain differences in their national legislations as regards labor protection requirements. Therefore, certain key moments that influence efficiency of protection provided for workers (who use PRPE properly and in due time) are much more strict and concrete in (US) than in the EU. Besides, to control whether the requirements are met in (US), an instruction for inspectors was developed; it describes in detail what should be inspected and how an inspection should be accomplished when assessing workers' provision with PRPE as well as how to make legal claims on the matter[5].

There are also differences in requirements applied in the USA and EU as regards *protection for workers employed at workplaces with extremely hazardous working conditions*. Workers who are exposed to contaminants concentration that is immediately dangerous

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[1] On Approval of the Typical standards for free distribution of protective clothing, protective foot wear, and other personal protective equipment for workers employed at any industry and/or at any workplace with adverse and(or) hazardous working conditions, as well as workers who have to perform their work tasks under specific temperature conditions or under exposure to contamination: The Order by the RF labor Ministry issued on December 09, 2014 No. 997n (Registered in the RF Ministry of Justice on February 26, 2015 No. 36213). *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_175841/ (18.06.2020) (in Russian).

[2] On special assessment of working conditions: The Federal Law issued on December 28, 2013 No. 426-FZ (last edited on December 08, 2020). *KonsultantPlus*. Available at: http://www.consultant.ru/document/cons_doc_LAW_156555/a2d1f36be57aa07bb3d5a9867a8200ff79552c6e/ (18.06. 2020) (in Russian).

[3] The Methodology for assigning lower hazard categories for working conditions in case workers employed at workplaces with adverse working conditions use efficient personal protective equipment that was certified as per obligatory certification procedures corresponding to relevant technical regulations. Moscow, 2015, 13 p. (in Russian).

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BG – BDS EN 529:2006. Respiratory protection. Recommendations for selection, use, care and maintenance. Guide. Sofia, The Bulgarian Institute for Standardization Publ., 2010, 54 p.

CA – Z94.4-11. Selection, use, and care of respirators. Ottawa, Canadian Standards Association Publ., 2012, 126 p.

DE – DIN EN 529:2006 Atemschutzgeräte – Empfehlungen für Auswahl, Einsatz, Pflege und Instandhaltung – Leitfaden, Brüssel, Europäisches Komitee für Normung Publ., 2005, 51 p.

JP – JIS T 8150:2006. 保守管理方法び使用及，選択の呼吸用保護具. Tokyo, JSA Publ., 2006, 22 p.

SK – Guide H-82–2012. Ulsan, Korea Occupational Safety and Health Agency (KOSHA) Publ., 2012, 24 p.

UA – DSTU EN 529:2006 PRPE. Recommendations on selection, use, maintenance and service. Labor code 135. Kiev, 2008, 47 p.

UK – BS 4275:1997. Guide to implementing an effective respiratory protective device programme. London, Technical Committee PH/4, BSI Publ., 1997, 64 p.

US – OSHA Standard 29 CFR 1910.134. Respiratory Protection. Cornell Law School Publ. Available at: https://www.law.cornell.edu/cfr/text/29/1910.134 (08.08.2020).

[5] CPL 2-0.120. Inspection procedures for the Respiratory Protection Standard. Occupational Safety and Health Administration, 1998. Available at: https://www.osha.gov/pls/oshaweb/owadisp.show_document?p_id=2275&p_table=DIRECTIVES (18.08.2020).

for life or health (IDHL or a situation when PRPE absence for ~ 30 minutes results in death or significant irreversible damage to health) should be properly protected. To provide such protection, the US legislation allows using only insulating PRPE (that protect from any contamination for a predictable period of time) with full face masks (they protect eyes and face skin and contaminated air can penetrate into gaps between a full face mask and a face not so efficiently as it is the case with half masks). Air should be fed into a mask in such PRPE in such way so that there is excessive pressure in it when a person breathes in (it reduces risks that contaminations penetrate into a mask when there are gaps between it and a face it protects). IDLH concentrations were estimated for approximately 400 substances [1].

Requirements applied in other countries are quite similar but there are no estimated IDHL concentrations in AS, BG, DE, UA, UK, SK, and JP. AS, CA, and UK apply concentrations estimated in the USA. When (basic) hose-equipped PRPE is used in Canada or the USA, it is required to be also equipped with auxiliary autonomous respirator in case air-feeding though a hose is distorted during evacuation. AS and BS legislation also requires basic hose PRPE to be equipped with auxiliary one (for evacuation) but it is not necessarily a respirator (as it is in the USA) but it can also be filtrating PRPE in certain cases.

When it comes to *assigned protection factors* we can mention the following. Should concentration be lower than immediately dangerous for life or health one, PRPE with different constructions can be applied (provided they truly protect from exposure). To assess protective PRPE capabilities, experts usually apply protection factors (PF) as a ratio between substances concentrations in the air outside and concentrations in inhaled air. When a PRPE type is selected, Assigned PF or APF are usually applied. These PF were developed by experts for PRPE with any construction; when PRPE are selected correctly and they are certified according to the existing legislation, these PF should be reached at *workplaces* in most cases. Studies on PRPE PF performed in laboratories and at workplaces revealed that they tended to be lower in the latter case and laboratory values should not be used to assess efficiency at workplaces [2]. When developing assigned PF in the USA, experts analyzed results obtained via PF measuring at workplaces and due to it they managed to take into account significantly lower actual PRPE efficiency (US) [3]. The same approach was applied in BS and similar values were obtained (Table 1).

To take into account differences between laboratory efficiency and actual one, experts in (UK) used the best available data obtained via 32 studies focusing on PF at workplaces, ¾ out of them having been performed in the USA. Therefore, assigned PF values for filtrating PRPE without air-feeding (with full face masks and half masks) and with air-feeding (into a helmet/hood) are similar in the UK and the USA.

The difference is partially due to experts in the USA relying on «the worst case» in their estimations and experts in the UK considering that it was impossible to wear a mask for 8 hours so their PF were estimated for working under exposure to contaminated air only during a part of a shift (up to 1 hour without air-feeding). Overall, small assigned PF values are due to detected low PF when they were measured at workplaces [6–10]. High PF can be obtained for PRPE with air-feeding into full face masks. But it was shown in several studies that efficiency could go down significantly [10]. As a result, in the UK assigned PF was reduced from 2,000 to 40. Efficiency of such PRPE at workplaces was not studied at all in the USA and Canada and it can explain why APF value is significantly high (=1,000).

In other countries labor-consuming and expensive PF measurements at workplaces were either not accomplished or they were rather rare; as for results obtained in foreign studies, they were sometimes neglected [5–10]. As a result, assigned PF are significantly higher in many countries than in the UK or the USA, and differences in efficiency estimated in laboratories and at actual workplaces are also neglected (to a various extent).

Table 1

Assigned PF (APF, maximum values[1])

Country[2] → / Face ↓	US	UK	CA	AS	China	JP	SK	France	DE	Min PF[3]
Filtrating without air-feeding										
Half masks	10	10/20[4]	10	10	10	10	10	20	30	2.2
Full face masks	50	20/40[4]	50	100	100	50	100	40	400	11; 17
Filtrating with forced air-feeding										
Half masks	50	–	50	–	50	50	50	40	500	16; 19
Full face masks	1000	40	1000	> 100	1,000	100	200	40	500	12; 15
Helmet / hood	25/1,000	40	25/1,000	> 100	25/ 1,000	25	200	40	100	23; 28
Insulating with forced air-feeding										
Half masks	1,000	–	50	50	50	50	50	200	100	–
Full face masks	2,000	2,000	1,000	> 100	1,000	1,000	1,000	~250	1,000	–
Helmet / hood	25/1,000	40	1,000	> 100	25/1,000	25	1,000	100	–	–
Autonomous respirator	10,000	2,000	10,000	> 100	> 1,000	5,000	2,000	Max	≥ 1,000	–

Note:

1 – means values for cases in which: efficient filters are used; air is fed when needed under pressure, or permanently. When selecting PRPE, one should remember that its assigned PF should be higher than MPC excess ratio;

2 – data on China were obtained via research; data on France, from a manual[6] [4];

3 – means they are minimal PF obtained for this PRPE at workplaces [5–10];

4 – means that the 1st value is given for protection from gases; the 2nd, from aerosols.

When EU (DE) standard was accepted in former socialist countries in Europe, it brought some interesting results. Experts in BG or UA didn't know that efficiency at workplaces was lower than laboratory efficiency and they failed to understand why the same PRPE had different assigned PF in different EU countries[7]. As a result, assigned PF values were not fixed in Bulgaria or Ukraine at all, and a relevant text from DE standard was just translated mechanically without any proper understanding. Developed requirements to employers do not prevent them from selecting non-efficient PRPE. When the State standard GOST 12.4.299-2015 was developed in the RF by «Roskhimzashchita Corporation» JSC, a section with data on assigned PF was deleted completely[8].

Aspects related to a mast being fit for a face are included into regulatory documents. The most widely spread filtrating PRPE pump air through a filter due to rarefying under a mask when inhaling. And still a part of inhaled air is contaminated as it penetrates respiratory organs via gaps between a mask and a face. Should filters be selected properly, this penetration becomes a basic way for contaminations introduction into a mask and determined overall PRPE efficiency. To reduce risks that contaminated air may penetrate through gaps due to a mask being unfit for a face or a worker not knowing how to wear a mask properly, it is required in the USA that a mask should be selected individually to fit a face and penetration should be estimated with *Fit test* devices [11]. There are 6 check-ups for the matter that are described in detail in US and CA. In other countries such check-ups are either not described (UK) or they are not obligatory (only recommended).

When *PRPE are certified* in the USA and China, testers' faces should be similar to faces

[6] M. Gumon. Les appareils de protection respiratoire. Choix et utilisation. 2-th edition. Paris, Institut National de Recherche et de Securite (INRS), 2017, 68 p. (in Russian).

[7] For reference: DE standard contains data on APF in 5 countries.

[8] State Standard GOST 12.4.299-2015. PRPE. Recommendations on selection, application, and technical maintenance. *Internet i Pravo*. Available at: https://internet-law.ru/gosts/gost/60298/ (18.09.2020) (in Russian).

Figure. Changes in End-of-Service Life Indicators (ESLI) when filters are applied to protect from: mercury (to the left) and acetone (to the right)

of most workers [12, 13]. To select testers properly, anthropometric examinations were performed and approximately 4 thousand workers were examined including three-dimensional scanning of a head and face. When certification is performed in the EU and RF, it is recommended to exclude testers with their faces not being fit to masks. The US market is better protected from low quality products.

Timely *gas mask filters replacement* is an obligatory component in providing workers' safety. Durability of any gas mask filter that purifies contaminated air is limited and greatly depends on application conditions[9]. In the last century a moment for timely filters replacement was usually determined by olfactory organs reaction to gas smell in a mask. However, people react to smells of some gases only in case their concentration is significantly higher than MPC; we should also remember that people tend to have different sensitivity to smells (for example, data from 32 different sources gave the following range for acetic acid: from 0.001 to 500 mg/m^3, and its single maximum MPC is 5 mg/m^3) [14]. If gas concentration is growing steadily (as sorbent in a filter becomes saturated), then olfactory organs sensitivity can go down (hydrogen sulphide). Adaptation to a smell due to long-term work under exposure to it, respiratory diseases, and attention being focused on a work task make filter replacement «as per smell factor» rather unreliable. In the USA an employer should replace filters according to schedules (when their durability is calculated or measured for known working conditions) or with ESLI indicator use (Figure) [15, 16].

In other countries there are similar requirements but they can be not so strict or specific. For example, in 2017 a program that is used in Germany to calculate filters durability was available at Dräger web-site[10] but only in English.

As for requirements to training provided for workers it is specifically defined in US and CA what kind of training should be provided for workers. Employers in the EU are obliged to train workers but training contents and learning procedures are clearly not specified; requirements to training are more specific in the USA.

Feedback or assessing effects produced by PRPE application was actually accomplished only in the USA. In 2001–2002 there was a wide-scale questioning performed in the country that focused on how PRPE was selected and applied (the questioning contained 37 questions and more than 30 thousand organizations gave their replies to them) [17]. Requirements that had been valid for more than 30 years turned out to be violated; in small organizations violations were rather frequent and sometimes also rather serious. Questioning results were applied in planning activities aimed at improving PRPE construction and requirements to their application. We haven't been able to find any data on similar research in other countries.

Results and discussion. High quality PRPE (provided they don't have any defects and are selected and applied properly) can protect a worker in case they are applied in due time. The best requirements out of all the examined ones stipulate that PRPE should corre-

[9] Kaptsov V.A., Chirkin A.V. Gas mask filters replacement (lecture). *Wikibook*. Available at: https://ru.wikibooks.org/wiki/Замена_противогазных_фильтров_СИЗОД_(лекция) (18.06.2020) (in Russian).

[10] Dräeger, Hazardous substances database VOICE. *Dräeger*. Available at: https://www.draeger.com/en-us_us/Chemical-Industry/Onlineservices/Draeger-VOICE (18.06.2020).

spond to working conditions as per both their protective properties and acceptability (physiological loads on a worker). Protective properties of any PRPE can be easily estimated but it is not the case with acceptability. There are only sporadic recommendations on the matter given in several documents. It partly explains why PRPE are frequently neglected even when air is contaminated. Requirements to PRPE application, even high quality ones, do not guarantee that extreme exposure is eliminated completely; they only reduce its probability.

Requirements existing in the USA and UK take into account differences between PRPE protective properties at workplaces and in laboratory conditions to the maximum possible extent. But filtrating PRPE with air-feeding into a full face mask are better examined in the UK. Bearing that in mind, application of such PRPE should be limited in the RF in the same manner as it is the case with filtrating PRPE without forced air-feeding into a mask.

According to western experts' common opinion that was reflected in standards, PRPE is not a reliable means for health protection but it still reduces exposure and risks of occupational diseases (but it is still unclear to what extent). In the RF PRPE is selected and applied in a different way. There are no specific requirements to PRPE selection and application, and suppliers tend to constantly overestimate their efficiency; workers are provided with PRPE that do not correspond to working conditions and are not fit for workers' faces; gas mask filters can be replaced later than they should be. It results in elevated risks of extreme exposure and occupational diseases are rarely prevented due to PRPE use [18]. It is necessary to provide better motivation for employers to improve working conditions for their workers. To enhance effects produced by PRPE as auxiliary protection means, there should be requirements to their application developed in the country using the most complete and scientifically well-grounded foreign ones (US, UK).

By coincidence, concrete and scientifically grounded requirements to protection from biological aerosols exist only in CA. They should be used when developing a relevant section in requirements to PRPE selection in the RF.

PF measurements at workplaces allowed revealing that efficiency of certain PRPE at workplaces was significantly lower than that estimated in laboratory conditions. It allowed calculating such assigned PF that would be obtained at workplaces provided their proper and timely use; still they would be obtained not for all workers but for most of them, and not in all cases, but in most of them. It is still impossible to predict or measure exposure for each individual who uses PRPE. Biological monitoring procedures can be used to reveal extreme exposure for each individual worker. But Biological MPC are being developed rather slowly in the RF (in 2014 biological MPC were developed for 5 substances and none of them has been implemented so far; 50 biological MPC are developed in the USA; and even in Bulgaria 17 biological MPC are developed and implemented) and it should be accelerated[11,12].

Finally, use of the most widely spread PRPE (without forced air-feeding into a mask) results in a worker being exposed to carbon dioxide in a concentration that can be up to 2 times higher than maximum single MPC. It makes timely and proper PRPE use physiologically impossible for some workers as it can lead to diseases [19, 20]. In some countries employers are not recommended to select PRPE without air-feeding for long-term work but there are no specific requirements on the matter. It is necessary to make employers take these risks into account via developing requirements to medical examinations and work and leisure regimes for workers. Accordingly, certification tests for PRPE should include CO_2 concentration measurements for different

[11] ACGIH Threshold Limit Values & Biological Exposure Indices for Chemical Substances and Physical Agents. – Ohio: ACGIH, Cincinnati, 2016, 276 p.

[12] Ordinance № 13 of 30 December 2003 on the protection of workers from the risks associated with exposure to chemical agents at work. Effective from 31.01.2005. Appendix № 2. *The Bulgarian Legal Portal*. Available at: https://www.lex.bg/bg/laws/ldoc/2135477597 (18.09.2020).

air expenditure (inhaling volumes), and these data should be included into a certificate and be available to an employer.

Our analysis allowed us to come to the following **conclusions**.

1. Even the best existing foreign requirements to PRPE selection and application do not allow either taking into account their negative physiological effects on workers or preventing workers from neglecting them when they are exposed to contaminated air.

2. Requirements existing in the USA are the most acceptable ones as a basis for developing similar requirements in the RF since they are the most comprehensive ones when it comes to all key moments that determine protection efficiency and conditions of their application (they were developed for just one state).

3. According to western experts, PRPE application induces spontaneous occupational selection since those workers who can't adapt to wearing PRPE just change their job. It is advisable to have this selection prior to workers start performing their work tasks in contaminated air. When a worker has his or her probation period and is not exposed to contamination, he or she should constantly wear PRPE with a register that records down periods of PRPE use. And if it turns out that a worker is able to permanently use PRPE in safe conditions, he or she can be moved to a workplace with exposure to contaminated air.

4. To better reveal extreme exposure cases, it is necessary to use biological monitoring procedures more widely; to speed up biological MPC development, experts can use BEI ACGIH as a basis for their development.

5. To improve control over working conditions, it seems advisable to return to use of public sanitary inspectors. It is necessary to develop requirements to this occupation, their responsibilities, and relevant legal grounds for their activities.

6. To reduce a number of situations in which PRPE is not used in contaminated environment, it is necessary to start using PRPE that is integrated into technological processes; for example, when a worker puts a mask off, a gauge gives a relevant signal and production equipment is stopped and blocked.

Certification system in the RF allows several organizations to issue certificates for PRPE (it can be done by only one organization in the USA). Certificates contents can be completely incorrect[13]. It is necessary to give the right to certify PRPE to only one organization (for example, any scientific research institute that deals with occupational diseases). All kinds of tests that can't be accomplished in such an institute can be performed, for example, by PPE laboratories at A.I. Burbazyan's Federal Medical Biophysical Center (and it is well in line with existing practices when a certifying organization delegates actual tests to the third party and only issues certificates). It will allow ceasing anti-gas filters certification in such cases when their manufacturer doesn't provide them with data that allow establishing a period of time during which filters provide actual protection without using subjective reactions from workers' olfactory organs. It will also allow revoking certificates or not granting them in case manufacturers provide consumers with false information overestimating PRPE efficiency. It is necessary to expand test procedures and add measuring exposure to carbon dioxide for a worker given different volumes of air expenditure.

Funding. The research was not granted any sponsor support.

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

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[13] «Test-S – Petersburg» tested several filtrating half masks (manufactured by «Respiratorniy complex» LLC with added sorbent). They were tested just as anti-aerosol ones but it was stated in a certificate that PRPE could be used for protection from gases. «ProdMashTest» certified «Lepestok-200» as an elastomer full face mask with panoramic glass.

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Received: 05.07.2020
Accepted: 29.11.2020
Published: 30.12.2020