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Research article

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

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

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

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

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

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

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

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

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

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relevant activities aimed at promoting healthy lifestyles.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[1] SanPiN 1.2.3685-21. Gigienicheskie normativy i trebovaniya k obespecheniyu bezopasnosti i (ili) bezvrednosti dlya cheloveka faktorov sredy obitaniya; utv. postanovleniem Glavnogo gosudarstvennogo sanitarnogo vracha Rossiiskoi Federatsii ot 28 yanvarya 2021 goda № 2 (s izmeneniyami na 30 dekabrya 2022 goda) [Hygienic Standards and Requirements to Providing Safety and (or) Harmlessness of Environmental Factors for People; approved by the Order of the RF Chief Sanitary Inspector on January 28, 2021 No. 2 (last altered as of December 30, 2022)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: https://docs.cntd.ru/document/573500115 (April 13, 2024) (in Russian).

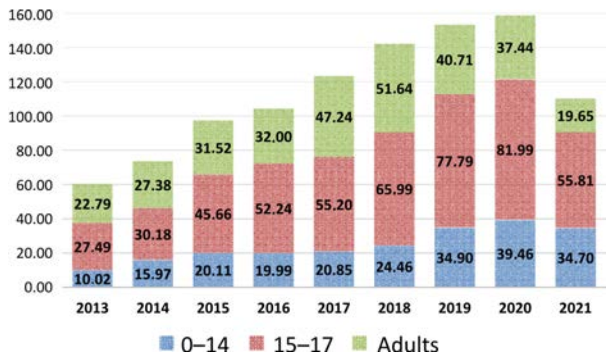

Figure 1. Primary obesity incidence among the Orenburg region population (cases per 1000 people)

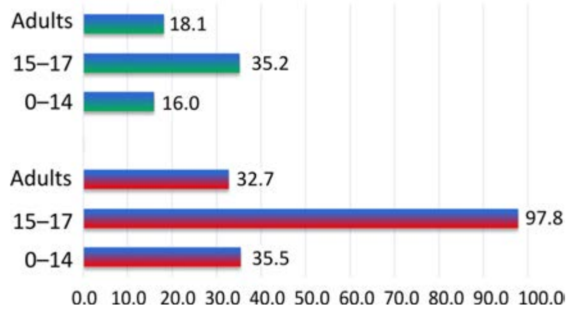

Figure 2. Primary obesity incidence among the population in the observation and reference areas (cases per 1000 people)

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

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

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

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

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

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

Dendrogram for 40 observations
Ward's method
Euclidian distance

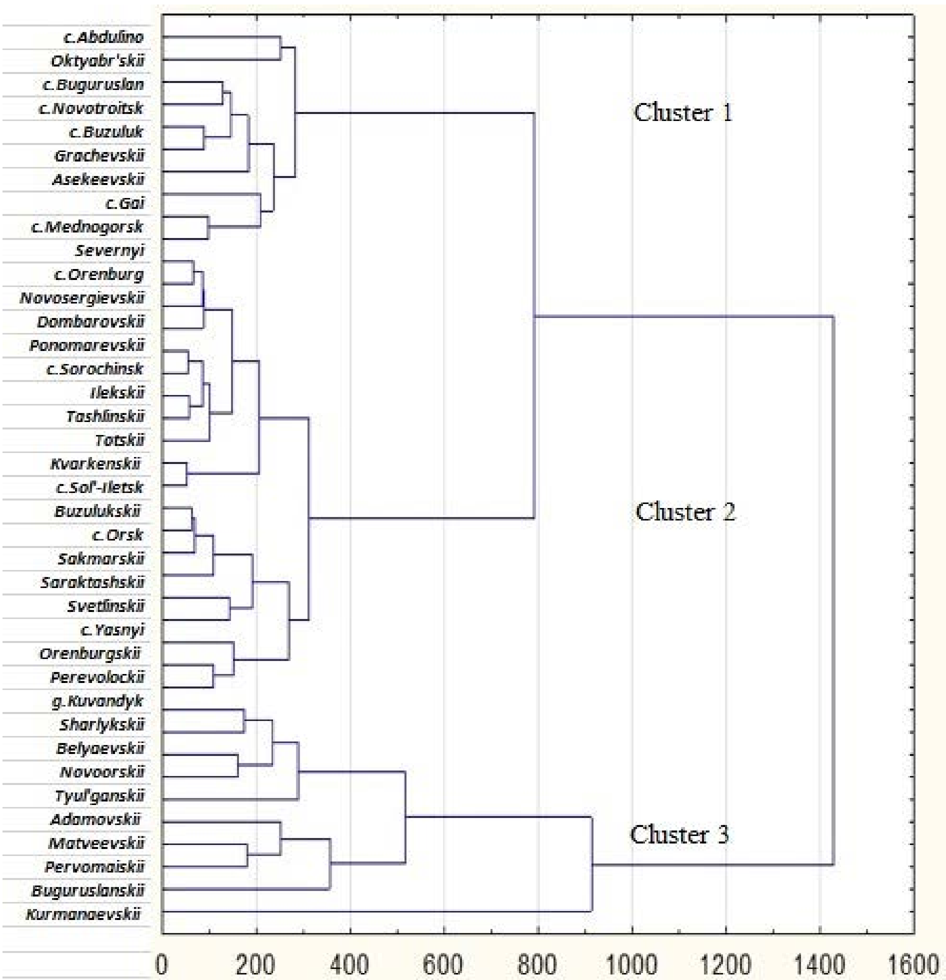

Figure 3. Three clusters of the areas in the Orenburg region per obesity incidence

Table 1

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

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

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

Table 2

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

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

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

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

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

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

Table 3

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

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

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

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

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

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

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

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

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

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

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

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

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