Research article

COMBINED EXPOSURE TO CHEMICAL FACTORS AND FACTORS RELATED TO EDUCATIONAL PROCESS

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Hygienic assessment of combined effects produced by heterogeneous factors on comorbid diseases in the nervous system and digestive organs in children is vital for early detection and prevention of health disorders given existing risks and threats.

Our research goal was to estimate probability of comorbid diseases in the nervous system and digestive organs in children attending primary schools under combined exposure to chemical factors and factors related to the educational process.

Our research objects were factors related to the educational process that produced their effects on children aged 7–10 who attended primary schools with different educational programs; chemicals contents in ambient air and air inside classrooms as well as in children's blood; biochemical parameters of negative effects; models showing cause-and-effect relations.

Our research results allowed us to identify priority influencing factors and their share contributions into negative effects development in case there was comorbidity with nervous system diseases and digestive organs diseases; to give grounds for biological markers of negative effects applied for early diagnostics and development of activities aimed at preventing comorbid disorders for schoolchildren. Implementation of an algorithm for calculating and estimating probability of comorbid diseases in the nervous system and digestive organs under combined exposure to heterogeneous factors involves determining additional comorbidity cases among children who attend schools with more comprehensive educational programs in comparison with children attending ordinary schools.

Timely and adequate correction of detected influencing factors and development of activities aimed at preventing comorbid health disorders will allow minimizing risks of comorbid diseases in the nervous system and digestive organs in school children under combined exposure to chemical factors existing in the environment and inside classroom and factors related to the educational process.

Key words: chemical environmental factors, factors related to the educational process, comorbidity of diseases, biomarkers of negative effects, cause-and-effect relations.

At present environmental objects tend to be of poor quality and educational processes at schools are rather stressful and intense; they involve much less physical activity than they used to. All this can exert combined negative impacts on the state of schoolchildren's leading vital systems. It can result in functional disorders in the digestive organs, first of all, motility disorders due to changes in nervous regulation caused by vegetative dysfunction as a pathogenic mechanism of diseases occurrence is common in this case (comorbidity) [1–5].

Results obtain in several Russian research works indicate that children living in industrially developed regions have technogenic chemicals in their blood that are simultaneously tropic to the central and vegetative nervous system and digestive organs [6, 7]. And such negative effects as functional disorders of the nervous system and motility disorders in the gastroduodenal and biliary systems occur

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together with oxidative stress and lower non-specific resistance of the gastrointestinal tract mucosa [8–11].

Health of children who attend primary schools operating in the contemporary innovative educational space is influenced not only by environmental factors but also by prevailing mental work together with lower physical activity, high static loads, and combined basic and additional education without taking into account aggregated volumes of studying a primary school child has to face [12, 13]. Children have to spend a lot of time under excessive educational loads and it creates neurotic disorders with the subsequent clinical manifestation, functional disorders in the gastrointestinal tract and other critical organs and systems [14].

As a result, there are additional diseases cases among children simultaneously in the gastrointestinal tract and nervous system, and this comorbid pathology tends to become chronic more frequently [15, 16]. There are rather alerting negative trends such as a 2-time growth in prevalence of gastric diseases among children, especially those who attend primary school; these diseases are chronic gastroduodenitis, stomach ulcer, and biliary dysfunction combined with functional disorders of the nervous system such as neurotic and asthenic disorders and vegetative-vascular dystonia [17–20].

Chronic somatic pathology in adults can actually occur as early as at pre-school age or during primary school years and later on it results in poorer life quality and lower labor activity. Bearing that in mind, it seems vital to detect and prevent additional comorbidity of the nervous system and digestive organs in primary school children under combined exposure to heterogeneous factors. In this relation it is especially important to substantiate biological markers showing negative effects produced by comorbidity among schoolchildren in order to provide early diagnostics and prevent health disorders caused by the existing risks and threats.

Our research goal was to assess probability of comorbid diseases in the nervous system and digestive organs in children attending primary school under combined exposure to chemical factors and factors related to educational process.

Data and methods. To achieve this goal, we performed a profound examination of 60 schoolchildren (boys) aged 7–10 who attended the 1st–4th grades. Our test group was made up of 34 children who simultaneously had a disease of the nervous system and digestive organs as a basic or a concomitant disease (ICD–10: G00–G99; K00–K93); they attended a primary school with additional educational programs involving intense physical and military training. Our reference group included 26 children with the same diseases who attended a primary school providing only basic educational programs without any additional training. Children's samplings were comparable in terms of sex and age, psychological climate in a family, social conditions at home, welfare, and frequency and types of bad habits and occupational hazards their parents had.

We hygienically assessed ambient air as per data collected via field observations at school territories and inside classrooms and also used a direct relevant model showing dependence between a chemical concentration in blood and its concentration in environmental objects. It allowed us to select phenol out of 11 analyzed chemical factors and to substantiate its concentration in blood being higher than 0.014 mg/dm^3 as aerogenic exposure marker.

We revealed that educational processes at the examined schools deviated considerably from the Sanitary-Epidemiologic Requirements 2.4.2.2821-10 and they were much more intense than it was fixed by the Federal recommendations FR ROSHUMZ-16-2015; and we also used a model that revealed direct dependence between nervous system and digestive organs diseases in children and exposure to factors related to educational processes. It allowed us to analyze 18 factors and select 4 of them as exposure markers related to educational process, namely intellectual loads, emotional loads, monotony of loads, and a period during

which technical teaching aids (TTA) were used uninterruptedly[1, 2].

We created a list of approximately 30 laboratory parameters as per data taken from scientific literature; these parameters showed a pathogenetic mechanism of negative effects occurrence in the nervous system and digestive organs. We modeled the following dependence: «exposure marker – response indicator – a negative effects as a disease of the nervous system and digestive organs»; it allowed us to substantiate increased acetyl cholinesterase and pepsinogen I contents in blood serum as biomarkers showing comorbidity in schoolchildren under combined exposure to phenol, intellectual, emotional, and monotonous loads and a period during which TTA were used uninterruptedly.

We calculated total probability of comorbid diseases in the nervous system and digestive organs with subsequent quantitative assessment of an extent to which they were caused by combined exposure to heterogeneous factors. The procedure was performed according to an algorithm developed together with experts from the Department for mathematical modeling of systems and processes.

The calculation algorithm included several stages. The 1st stage involved calculating a probability of k-th biomarker of an effect related to increased phenol contents in blood and exposure to educational process factors deviating from the physiological standard. The calculation was based on estimating «exposure marker – biomarker of an effect» dependence which was established separately for each k-th biomarker with each influencing i-th factor as per the following formula:

$$P_i^k = \frac{1}{1 + e^{-(b_0^k + b_1^k x)}}, \text{ where} \qquad (1)$$

P_i^k is a calculated probability that there is a deviation from physiological standard in k-th

biomarker of an effect related to increased phenol contents in blood and exposure to educational process factors;

x is phenol concentration in blood (mg/dm^3) or a factor related to educational process (arbitrary units);

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

b_0^k, b_1^k are mathematical model parameters determined via least square technique with applied software for statistical data analysis (Statistica, SPSS, SAS etc.).

The 2nd stage involved calculating a probability of a negative effect occurrence as syntrophy in the nervous system and digestive organs (as a disease) when k-th biomarker of an effect deviated from physiological standard; the calculation was performed as per the following formula:

$$P_k^n = \frac{1}{1 + e^{-(b_0^n + b_1^n x)}}, \text{ where} \qquad (2)$$

P_k^n is a calculated probability of a negative effect occurrence as syntrophy in the nervous system and digestive organs (as a disease) when k-th biomarker of an effect deviated from physiological standard;

x is a value of k-th biomarker of an effect (ng/ml or µg/L);

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

b_0^n, b_1^n are mathematical model parameters.

The 3rd stage involved calculating an overall probability that comorbid diseases occurred in the nervous system and digestive organs under isolated exposure to phenol, intellectual loads, monotonous loads, emotional loads, and uninterrupted use of technical teaching aids; the calculation was performed as per the following formula:

$$P_i^n = 1 - \prod_k (1 - P_k^n \cdot P_i^k), \text{ where} \qquad (3)$$

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[1] SER 2.4.2.2821-10. Sanitary-epidemiologic requirements to educational process conditions and organization in secondary schools. Approved by the RF Chief Sanitary Inspector on December 29, 2010 No. 189. *KODEKS: an electronic fund for legal and reference documentation.* Available at: http://docs.cntd.ru/document/901765645 (20.04.2020) (in Russian).

[2] FR ROSHUMZ-16-2015. Hygienic assessment of educational activities intensity for students: federal recommendations on providing medical aid to students. Moscow, 2015, 18 p. (in Russian).

P_i^n is an overall probability that comorbid diseases occurred in the nervous system and digestive organs under isolated exposure to a factor;

P_i^k is a probability that k-th biomarker deviates from physiological standard in case there is elevated phenol contents in blood or under exposure to one of the analyzed factors related to educational process;

P_k^n is a probability of a negative effect occurrence as syntrophy in the nervous system and digestive organs (as a disease) at an established values of k-th biomarker of an effect;

$\prod\limits_{k}$ is a product of values obtained via an operation $(1 - P_k^n \cdot P_i^k)$, that is, the formula looks as follows for k biomarkers ($k = 2$):

$$\prod\limits_{k=1}^{2} = (1 - P_{k_1}^n \cdot P_i^{k_1}) \cdot (1 - P_{k_2}^n \cdot P_i^{k_2})$$

The 4th stage involved calculating total probability that comorbid diseases occurred in the nervous system and digestive organs under combined exposure to the analyzed factors as per the following formula:

$$\sum P_i = 1 - (1 - P_{i_1}^n) \cdot (1 - P_{i_2}^n) \times$$

$$\times (1 - P_{i_3}^n) \cdot (1 - P_{i_4}^n) \cdot (1 - P_{i_5}^n), \text{ where} \quad (4)$$

$\sum P_i$ is total probability that comorbid diseases occurred in the nervous system and digestive organs under combined exposure to heterogeneous factors;

$P_{i_1}^n$ is an overall probability that comorbid diseases occurred in the nervous system and digestive organs under isolated exposure to phenol;

$P_{i_2}^n$ is an overall probability that comorbid diseases occurred in the nervous system and digestive organs under isolated exposure to intellectual loads;

$P_{i_3}^n$ is an overall probability that comorbid diseases occurred in the nervous system and digestive organs under isolated exposure to monotonous loads;

$P_{i_4}^n$ is an overall probability that comorbid diseases occurred in the nervous system and digestive organs under isolated exposure to emotional loads;

$P_{i_5}^n$ is an overall probability that comorbid diseases occurred in the nervous system and digestive organs under isolated exposure to uninterrupted use of technical teaching aids.

Calculated values, such as overall probability under isolated exposure ($P_i^n > 0,05$) and total exposure under combined exposure ($\sum P_i > 0,05$), were taken as criteria showing that such negative effects as comorbid diseases of the nervous system and digestive organs were caused by long-term aerogenic exposure to phenol and impacts exerted by intellectual, emotional, and monotonous loads and a period of time during which technical teaching aids were used uninterruptedly. An extent to which the negative effects were caused by the combined exposure to the analyzed factors was estimated according to the following scale: $0.05 \leq \Sigma P_i$ or $P_i^n \leq 0.3$ meant weak causality; $0.31 \leq \Sigma P_i$ or $P_i^n \leq 0.6$, average causality; $0.61 \leq \Sigma P_i$ or $P_i^n \leq 1.0$, strong causality.

Results and discussion. We assessed «exposure marker – biomarker of an effect» dependence and determined its parameters; it allowed us to establish how probable was a deviation in each biomarker of an effect (acetyl cholinesterase and pepsinogen I) from its physiological standards caused by increased phenol contents in blood and exposure to intellectual, emotional, and monotonous loads, as well as a period of time during which technical teaching aids wee used uninterruptedly (P_i^k) (Table 1). We also assessed «biomarker of a negative effect – syntrophy negative effect» dependence and determined its parameters; it allowed us to establish how probable was a syntrophic negative effect (P_k^n) in the nervous system or digestive organs in case acetyl cholinesterase and pepsinogen I contents exceeded their physiological (Table 2).

Overall probability that comorbid diseases of the nervous system and digestive organs would occur under isolated aerogenic exposure to phenol in school children attending a school

Table 1

Parameters b_0^k and b_1^k used for calculating probability (P_i^k) that a negative effect biomarker deviated from its physiological standard under increased phenol concentrations and exposure to factors related to educational process

Exposure marker (i)	Biomarker of a negative effect in blood serum (k)	Parameters of «exposure marker – negative effect biomarker» model		Probability (P_i^k) that a negative effect biomarker deviates from its physiological standard
		b_0^k	b_1^k	
Phenol in blood	Acetyl cholinesterase	–5.22	89.14	0.022
	Pepsinogen I	–6.43	184.73	0.030
Intellectual loads	Acetyl cholinesterase	–4.49	1.35	0.200
	Pepsinogen I	–3.05	1.11	0.379
Monotonous loads	Acetyl cholinesterase	–4.22	1.35	0.200
	Pepsinogen I	–2.94	0.74	0.200
Emotional loads	Acetyl cholinesterase	–4.22	2.02	0.200
	Pepsinogen I	–2.94	1.11	0.200
Duration of TTA uninterrupted use	Acetyl cholinesterase	–2.59	0.74	0.250
	Pepsinogen I	–2.42	0.34	0.150

Table 2

Parameters b_0^n and b_1^n used to calculate a probability (P_k^n) that a syntrophic negative effect would occur in case of deviation in each k-th biomarker of an effect

Biomarker of a negative effect in blood serum (k)	Negative effect (n)	Parameters of «biomarker of an effect – negative effect (disease model)»		Probability (P_k^n) that a syntrophic negative effect would occur
		b_0^n	b_1^n	
Acetyl cholinesterase	Comorbidity of the nervous system diseases (G00-99) and digestive organs diseases (K00-93)	–0.38	0.09	0.844
Pepsinogen I		–4.38	0.03	0.320

with additional training programs amounted to 0.028; overall probability under exposure to isolated influence exerted by specific factors related to educational process varied from 0.221 to 0.248 depending on an analyzed factor. We assessed calculated values and determined that causality was rather weak. A share contribution made into negative effects occurrence solely by a chemical factor (phenol) amounted to 2.8 %, and that made by exposure to factors related o educational process varied from 22.4 % to 27.2 %.

We comparatively analyzed total probability that comorbid diseases of the nervous system and digestive organs would occur in children attending primary schools under combined exposure to chemical environmental factors and factors re-lated to educational processes. The comparative analysis revealed that the total probability amounted to $\sum P_i = 0.55$ for school children attending ordinary primary schools without any additional training programs and it meant that causality was average. The total probability amounted to $\sum P_i = 0.68$ for schoolchildren attending primary schools with additional physical and military training and it meant strong dependence between the analyzed factors and comorbid diseases occurrence. A probability that comorbid diseases of the nervous system and digestive organs would occur in schoolchildren without exposure to any factor (P_0^n) amounted to 0.38, in other words, causality was weak. This causality value was the lowest one and it allowed us to consider it as «background causality».

Table 3

Additional cases of cop morbid diseases in the nervous system and digestive organs under combined exposure to environmental factors and factor related to educational process among schoolchildren in Perm region

Parameter	Additional physical and/or military training	Ordinary educational programs
Number of schools[*]	2	8
Average number of children in a class[**]	20	25
Overall number of classes in primary school	4	4
Number of classes belonging to the same grade	3	5
Overall number of children in primary school	480	4,000
Additional calculated probability of comorbid diseases in the nervous system and digestive organs under combined exposure to examined factors (ΔP_i^n)	0.298	0.172
Number of additional comorbid diseases cases	143	688
Number of additional comorbid diseases cases, cases/1,000 primary school children per year	298	172

Note:

[*]data on a number of primary schools with different educational programs are taken from the Unified information-analytical system (UIAS) on education;

[**]data on an average number of children in a class are given according to the Order issued by the Perm Regional Educational Department on June 29, 2001 No. 509 «On approval of typical staff standards for administrative, educational, auxiliary, and junior maintenance staff in educational establishments in Perm»[3].

The suggested algorithm for calculating and assessing probability that comorbid diseases in the nervous system and digestive organs in children were caused by combined exposure to heterogeneous factors allowed determining a number of additional co-morbid diseases cases in children attending primary schools with different educational programs. We comparatively analyzed comorbidity among children who attended primary schools in Perm region; the analysis allowed revealing that there were 0.2 additional disease cases among children attending primary schools with ordinary educational programs without any additional training and 0.3 additional diseases cases among children who attended schools with additional physical and military training (a 1.5-time discrepancy) (Table 3).

Therefore, we can predict approximately 298 additional cases of comorbid diseases in the nervous system and digestive organs per 1,000 people per year under combined exposure to heterogeneous factors among children attending schools with additional physical and military training; there can be up to 172 additional cases of comorbid diseases per 1,000 persons per year among children attending schools with ordinary educational programs.

Conclusion. If we want to reduce number of comorbid diseases in schoolchildren under combined exposure to environmental factors and factors related to educational process, we should determine and substantiate priority exposure factors and their share contribution into negative effects occurring simultaneously in the nervous system and digestive organs. These factors are subject to relevant correction depending on an extent to which comorbid diseases are caused by heterogeneous factors; substantiated biomarkers of negative effects are to be taken into account in order to make early diagnostics more efficient and to develop relevant prevention activities.

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

[3] On approval of typical «staff standards for administrative, educational, auxiliary, and junior maintenance staff in educational establishments in Perm: the Order issued by the Perm Regional Educational Department on June 29, 2001 No. 509. *Garant: information and legal support.* Available at: http://base.garant.ru/43079860/#friends (20.04.2020) (in Russian).

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