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## PECULIARITIES DETECTED IN FORMATION OF SPECIFIC HAPTEN SENSITIZATION TO PHENOL IN CHILDREN

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*Phenol contamination in ambient air is a factor which creates health risks for children living in a zone influenced by emissions from a ferrous metallurgy enterprise. Our research goal was to assess specific hapten sensitization in children living under excessive aerogenic exposure to phenol.*

*We performed hygienic assessment of ambient air pollution on territories of pre-school children facilities located at various distances from a zone influenced by the examined enterprise (1 km and 5 km were the test territories No. 1 and 2 accordingly) which emitted phenol thus creating elevated concentrations of the chemical in ambient air being higher than single maximum MPC. Ambient air on a selected reference territory was not polluted with any industrial emissions. The test group No. 1 was made of 99 children (the test territory No. 1); the test group No. 2, 92 children (the test territory No. 2); and the reference group, 95 children (the reference territory). We analyzed phenol contents and levels of IgG specific to phenol in blood of all the examined children. Phenol concentrations in ambient air were higher than its permissible levels on the test territory No. 1, 1.7 single maximum MPC, and the test territory No. 2, 1.1 single maximum MPC.*

*We comparatively assessed phenol contents in blood of children from all three groups. The assessment revealed that children from the test group No. 1 had a hydroxybenzene concentration in their blood which was statistically significantly ( $p = 0.031$ ) by 1.9 times higher than in blood of children from the reference group. Production of specific G class antibodies was higher than the upper limit of the physiological standard in 60 % and 36 % children living and attending a preschool children facility in zones located accordingly at the minimal and maximum distance an emission source. The research results indicate that a hapten-associated increase in the level of IgG specific to phenol in preschool children is associated with excessive phenol contamination creating a substantial burden on biological media ( $OR = 14.75$ ; 95 %  $CI = 6.45-33.73$ ;  $p < 0.05$ ).*

**Key words:** phenol, aerogenic pollution, haptens, immunoglobulin G specific to phenol, preschool children, contaminant burden, sensitization, risk of developing allergic pathology.

Rapidly developing urbanization and growing industrialization make for considerable environmental pollution [1]. Anthropogenic sources make a substantial contribution to ambient air pollution with phenol and its derivatives [2, 3]. According to experts' estimates, ambient air in many megacities all over the world contains phenol in concentrations which are significantly higher than those stipulated by hygienic standards<sup>1</sup> [4–7]. Assessment of ambient air quality in residential areas in the RF in 2015–2020 revealed a growing share of

samples which deviated from hygienic standards as per contents of hydroxybenzene (phenol) and its derivatives. This share grew by 1.45 over the period, from 0.86 to 1.25<sup>1</sup>.

Phenol acts as a sensitizing agent in case it is inhaled and produces certain pro-allergic effects [8]. Developing IgG-specific sensitization to phenol creates a risk of bronchial asthma, allergic rhinitis, asthma-like bronchitis, pollen allergy, and hypertrophic changes in the respiratory tract mucosa. Children, as opposed to adults, are more sensitive to ef-

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<sup>1</sup>O sostoyanii sanitarno-epidemiologicheskogo blagopoluchiya naseleniya v Rossiiskoi Federatsii v 2020 godu: Gosudarstvennyi doklad [On sanitary-epidemiological welfare of the population in the Russian federation in 2020: The State Report]. Moscow, The Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, 2021 (in Russian).

fects produced by phenol. Higher concentrations of the pollutant are identified in children's biological media under exposure to it. This is due to anatomic and physiological peculiarities of their bodies (the respiratory surface of the lungs with respect to body weight is greater in children than in adults, their airways are more narrow, the detoxification system is underdeveloped, the immune system has certain age-related peculiarities, etc.)<sup>2</sup> [9]. A child's age from 4 to 6 years is a crucial period in formation of the immunity when Th-2 shift occurs in the cytokine profile and IgE antibodies are produced in the highest quantities in comparison with any other period in childhood [8, 10]. Besides, children are much shorter than adults and this leads to exposure to higher phenol concentrations since its vapors are identified in greater volumes closer to the ground<sup>2</sup>.

Obviously, ambient air pollution with hydroxybenzene creates risks of sensitization and allergic pathologies among pre-school children as the most susceptible population group. It is necessary to describe a group and an individual profile of IgG-specific sensitization to phenol if we want to detect susceptibility to technogenic chemicals as early as possible. In future this will make for implementing more effective protection activities aimed at reducing incidence associated with aerogenic exposure to phenol.

**Our research goal** was to assess specific hapten sensitization in children under excessive aerogenic exposure to phenol.

**Materials and methods.** We performed hygienic assessment of ambient air on areas around pre-school children faculties located at different distances from a ferrous metallurgy enterprise. It emitted phenol in hazardous concentrations exceeding maximum single MPC (the test territory No. 1 was located 1 km away from the enterprise; the test territory No. 2, 5 km away). Our reference terri-

tory was an area where any sources of phenol emissions were completely absent. Hygienic assessment of ambient air quality was performed in conformity with the methodical guidelines RD 52.04.186-89 "The Guide on control of ambient air pollution"<sup>3</sup>. We used two standard values: average daily concentration (MPC<sub>av.d.</sub>) and maximum single concentration (MPC<sub>m.s.</sub>). We also analyzed data on volumes and structure of emissions from stationary and mobile sources (Form No. 2-TP (air)).

All the diagnostic examinations were performed in accordance with requirements fixed by the WMA's Declaration of Helsinki (1964, last edited 2013). Our study involved assessing overall sensitization and specific sensitization to phenol. To do that, we examined 286 pre-school children who lived and attended pre-school children facilities on the examined territories. Our reference group was made up of 95 children who lived and attended pre-school children facilities on the reference territory which was considered "conditionally" clean. The test group No. 1 included 99 children who lived and attended pre-school children facilities on the test territory No. 1; the test group No. 2, 92 children who lived and attended pre-school children facilities on the test territory No. 2. We applied several criteria to include children into our study: their age was from 4 to 6 years and their family lived on the examined territory for not less than 5 years. Participation in another study or parents not being capable or willing to give their written informed consent to participation of their children were the reasons for excluding children from our study. All parents (legal guardians) of participating children gave their informed written consent to it.

Chemical analysis of children's blood involved identifying phenol concentrations with gas chromatography in accordance with the me-

<sup>2</sup> Medical management guidelines for phenol. *ATSDR*, 2014. Available at: <https://wwwn.cdc.gov/TSP/MMG/MMGDetails.aspx?mmgid=144&toxid=27> (March 01, 2022).

<sup>3</sup> RD 52.04.186-89. Rukovodstvo po kontrolyu zagryazneniya atmosfery [The Guide on control of ambient air pollution]. Moscow, USSR Goskomgidromet; USSR Public Healthcare Ministry, 1991, 695 p. Available at: <https://files.stroyinf.ru/Data2/1/4293854/4293854583.pdf> (March 01, 2022) (in Russian).

thodical guidelines MUK 4.1.2102-4.1.2116-06<sup>4</sup> on “Kristall 2000” capillary gas chromatograph (SKB “Chromatek” LLC, Russia).

We determined IgG specific to phenol using procedures for determining allergen adsorption. Total IgG was determined by ELISA tests on Sunrise analyzer (Tecan, Austria).

All the test results were statistically analyzed using Statistica 6.0 software package (StatSoft, USA). We applied Kolmogorov – Smirnov test as a criterion showing whether indicators in the children groups were distributed normally. Student’s two-sample test was applied to test zero hypotheses about equality of mean values in two independent groups with normal distribution. The research data were given as simple mean ( $M$ ), error of mean ( $m$ ) and 95 % confidence interval for simple mean (95 % CI). We compared sampling data with physiological standards using Wilcoxon one-sample test. To assess a correlation between health outcomes and exposure to the examined factor (phenol), we calculated odds ratio ( $OR$ ) and its 95 % confidence interval. Differences were considered statistically significant at  $p < 0.05$  for all the accomplished tests.

**Results.** Ambient air pollution occurred on the test territories due to emissions of pollutants from stationary sources. Thus, the total phenol (hydroxybenzene) (code 1071) emission was equal to 97.721626 tons/years; the maximum single emission, 3.0533076 g/sec.

Phenol concentration in ambient air was lower than  $MPC_{av.d.}$  (up to 0.68 MPC) on the examined territories (taken as per averaged values). We established that phenol  $MPC_{av.d.}$  in ambient air was on average by 2.4 times higher on the test territories influenced by emission from the aforementioned industrial enterprise than on the reference territory where there were no industrial emissions. Having assessed maximum single concentrations of pol-

lutants emitted by the ferrous metallurgy enterprise, we revealed that the relevant hygienic standards were violated both on the test territory No. 1 and No. 2, where phenol concentration was equal to 1.74  $MPC_{m.s.}$  and 1.09  $MPC_{m.s.}$  accordingly.

We detected that phenol contents were statistically significantly ( $p = 0.031$ ) by 1.9 times higher in biological media (blood) of children from the test group No. 1 against the reference group (Table 1). A share of samples with phenol concentrations that deviated from hygienic standards was equal to 88.9 % in the test group No. 1 against values detected in the reference group. Average phenol contents determined in biological media of children from the test group No. 2 didn’t have any statistically significant difference ( $p = 0.376$ ) against the reference group. A share of samples with phenol concentrations which deviated significantly from hygienic standards was equal to 75 % in children living on the test territory No. 2 against concentrations detected in children living on the reference territory.

We established that concentrations of the total immunoglobulin E were statistically significantly ( $p < 0.05$ ) higher than the physiological standard (0–49.9 IU/cm<sup>3</sup>) in all the examined children. We comparatively analyzed indicators which described specific sensitization to the priority factor and established that children who were not exposed to phenol had IgG specific to phenol in their blood in concentrations that were within physiologically normal ranges, 0–0.13 arbitrary units. The examined children from the test group No. 1 had concentrations of IgG specific to phenol which were statistically significantly ( $p = 0.003$ ) by 4 times higher than the same indicators in the reference group. Specific IgG sensitization to phenol was statistically significantly ( $p = 0.014$ ) by 3.5 times higher among children from the test group No. 2

<sup>4</sup> MUK 4.1.2102-4.1.2116-06. Opređenje vrednykh veshchestv v biologicheskikh sredakh: Sbornik metodicheskikh ukazaniy (utv. i vved. v deystvie Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebiteliy i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii 09.08.2006) [Identification of harmful chemicals in biological media: The collection of methodical guidelines (approved and introduced by the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, the RF Chief Sanitary Inspector on August 9, 2006)]. *KODEKS: electronic fund for legal and reference documentation*. Available at: <https://docs.cntd.ru/document/1200066799> (March 01, 2022) (in Russian).

Table 1

Chemical analysis of biological media and serum immunoglobulins profile in children exposed to phenol

Indicator	Reference group <i>n</i> = 95	Test group no. 1 <i>n</i> = 99	Test group no. 2 <i>n</i> = 92	$p^1$	$p^2$
Phenol in blood, mg/dm <sup>3</sup>					
<i>M</i> ( <i>m</i> )	0.0379 (0.0083)	0.0732 (0.014)	0.0563 (0.019)	<i>t</i> = 2.17	<i>t</i> = 0.89
95 % CI	0.02–0.05	0.07–0.08	0.05–0.06	<i>p</i> = 0.031	<i>p</i> = 0.376
Serum immunoglobulins profile					
Total IgE, IU/cm <sup>3</sup>					
<i>M</i> ( <i>m</i> )	75.37 (17.00)*	144.84 (33.10)*	87.76 (25.00)*	<i>t</i> = 1.87	<i>t</i> = 0.41
95 % CI	71.84–78.90	136.42–153.26	82.52–93.00	<i>p</i> = 0.634	<i>p</i> = 0.682
IgG specific to phenol, arb. units					
<i>M</i> ( <i>m</i> )	0.04 (0.005)	0.16 (0.04)*	0.14 (0.04)*	<i>t</i> = 2.98	<i>t</i> = 2.48
95 % CI	0.03–0.05	0.15–0.17	0.13–0.15	<i>p</i> = 0.003	<i>p</i> = 0.014

Note:  $p^1$  means differences between the reference group and the test group No. 1 are authentic according to Student's t-test;  $p^2$  means differences between the reference group and the test group No. 2 are authentic according to Student's t-test; \* means that differences from physiological standard are authentic as per Wilcoxon one-sample test, differences are considered statistically significant at  $p < 0.05$ .

Table 2

Frequency of allergy indicators deviating from physiological standards in children with different levels of phenol contamination in biological media

Indicator	Physiological standard	Reference group <i>n</i> = 95		Test group no. 1 <i>n</i> = 99		Test group no. 2 <i>n</i> = 92	
		A share of samples deviating from physiological standard, %					
		higher	lower	higher	lower	higher	lower
Total IgE	0–49.9	38.3	0	58	0	43.3	0
IgG specific to phenol	0–0.13	8.7	0	58	0	36.2	0

against those from the reference group. We also established that production of IgG specific to phenol was on average statistically significantly ( $p < 0.05$ ) by 1.2 times higher than the upper limit of the physiological standard in children who lived and attended preschool children facilities on the test territories (located at different distances from the source of industrial emissions).

A share of samples with total IgG concentration being significantly higher than the physiological standard amounted to 38.3, 58 and 43.3 % among children from the reference group, test group No. 1 and test group No. 2 accordingly (Table 2). Hyperproduction of IgG specific to phenol was detected in 58 % of analyzed samples taken in the test group No. 1 and this result was by 6.7 times higher than in the reference group. A share of samples with concentrations of IgG specific to phenol being

higher than the physiological standards equaled to 36.2 % in the test group No. 2 against 8.7 % in the reference group and this was by 4.2 times higher.

Odds ratio analysis indicated there was a correlation between phenol contamination and elevated specific sensitization to phenol in children from the test group No. 2 ( $OR = 6.08$ ; 95 % CI = 2.62–14.09;  $p < 0.05$ ). It was established that as hapten (phenol) loads grew, there was also a growth in risks of excessive production of total IgE and IgE specific to phenol in the examined children living on the test territory No. 1 ( $OR = 2.22$ ; 95 % CI = 1.25–3.95;  $p < 0.05$  and  $OR = 14.75$ ; 95 % CI = 6.45–33.73;  $p < 0.05$  accordingly).

**Discussion.** Negative effects produced by phenol on the immune system and associated with development of allergic reactions have been discussed over the last decades in many

research papers [9–11]. Immune-modulating effects produced by phenol are assumed to be mediated by the chemical being tropic to estrogen receptors (ER), peroxisome proliferator-activated receptors (PPAR), aryl hydrocarbon receptors (AhR), and its ability to induce Th2-shift in the cytokine profile [8, 12–15].

Estrogen receptors which are exhibited in significant quantities on many immune-competent cells play a most important role in regulating proliferative and functional activity of immunocytes. They also maintain the balance between Th1 and Th2-cytokines. Activation of estrogen receptors induces mast cells degranulation by altering intracellular calcium homeostasis. Additionally, estrogen-like chemicals stimulate rapid dose-dependent release of  $\beta$ -hexosaminidase from mast cells thus enhancing IgG-mediated release of histamine from them [15]. PPAR belongs to major regulators of the energy balance in a cell and activity performed by NF- $\kappa$ B transcription factor. It is also a significant participant in regulation of inflammation and fibrosis [16]. Several experimental and clinical studies established that phenol and its metabolites (hydroquinone) were able to induce hyperproduction of interleukin 4 and elevated levels of IgE [10, 12, 13]. Th2-dependent deviation in the immune response was studied using experimental models of asthma and turned out to make for generation of reactive oxygen species in considerable quantities thus making the inflammatory process more severe [16]. The role played by AhR in producing a protective response by the body to exposure to xenobiotics has been proven. Aryl hydrocarbon receptor acts as a protector in case an autoimmune pathology, an oncologic process or an allergy develops in the body. Indoleamine-pyrrole-2,3-dioxygenase enzyme (IDO) catalyzes degradation of the essential amino acid tryptophan (TRP) into N-formyl-kynurenine and produces protective effects when bronchial asthma develops. It was shown in *in vivo* systems (in animal models) that AhR and NF- $\kappa$ B participated in regulation of IDO expression

[17]. It was established that aryl hydrocarbon receptor also made a substantial contribution to production of immunoglobulins (IgA, IgG, IgM, IgE) and processes of their switching between different types (IgG – IgE) as well as production of IgG isotypes in a plasmatic cell<sup>5</sup>.

Intensive ambient air pollution with industrial emissions (hydroxybenzene (phenol) and its derivatives) results in poorer human health [18–20]. Children who live in zones influenced by emissions from industrial enterprises are the most sensitive risk group under exposure to substantial adverse environmental loads. It was established that excessive ambient air pollution with phenol resulted in apparent sensitization of the body. Meanwhile, we should remember about an existing danger associated with sensitization with low doses of an immune-tropic chemical. Phenol is also a chemical with high allergenic potential<sup>2</sup> [8]. Several allergenic diseases develop as per an IgE-dependent and IgG4-dependent scenario thus causing an elevated level of specific antibodies in blood serum. However, identification of total IgE and specific IgG within a physiological range doesn't mean there is no developing sensitization and / or an allergic reaction since we can't exclude that immunoglobulin G can be bound by tissues or that IgG is produced locally. Our research results are well in line with those produced by previous research works focusing on negative impacts exerted by aerogenic exposure to phenol on the immune system which involve developing sensitization associated with a level of exposure to an immune-tropic chemical<sup>2</sup> [10].

Therefore, children who live on territories where phenol is the priority anthropogenic pollutant are exposed to risks of developing specific sensitization. This induces occurrence and manifestation of allergic diseases associated with inhalation exposure to an immune-tropic chemical during a crucial period in childhood. Phenol was detected in excessive concentrations up to 1.7 MPC<sub>m.s.</sub> on the test territory No. 1 which was only 1 km away

<sup>5</sup> Kashgari B.F. Determining the role of the AhR in immunoglobulin expression and class switch recombination: diss. thesis for MS. *Wright State University*, 2015, 85 p. Available at: [https://corescholar.libraries.wright.edu/etd\\_all/1591](https://corescholar.libraries.wright.edu/etd_all/1591) (March 01, 2022).

from the industrial enterprise and this was higher than permissible levels. It was detected in concentrations up to 1.1 MPC<sub>m.s.</sub> on the test territory No. 2 which was located 5 km away from the source of industrial emissions. Average group phenol concentration was statistically significantly ( $p = 0.031$ ) by 1.9 times higher in blood of children who lived close to the emission source (the test group No. 1) against children from the reference group who were not exposed to phenol. There were no statistically significant differences in phenol concentrations in blood of children from the test group No. 2 (who lived 5 km away from the emission source) and children from the reference group. We established a statistically significantly ( $p = 0.003$ – $0.014$ ) higher level of IgG specific to phenol in blood of children living at the minimum and maximum distance from the industrial enterprise which emitted phenol into ambient air (1 km and 5 km), by 4 and 3.5 times accordingly. Hyperproduction of IgG specific to phenol was detected in 60 % children from the test group No. 1 and 36 % children from the test group No. 2. The results produced by mathematical modeling confirm the immunologically mediated increase in the body sensitivity to chronic exposure to phenol ( $OR = 6.08$ – $14.75$ ;  $p < 0.05$ ). The research re-

sults indicate that levels of aerogenic exposure to phenol influence contamination of biological media with this chemical thus determining frequency and severity of developing sensitization and autoimmune disorders.

Inhalation hapten chemical loads (phenol) on bodies of children aged 4–6 years make for developing specific sensitization to an anthropogenic immune-tropic chemical and create risks of developing allergic diseases. Comparative characteristics of group and individual profiles of IgG specific to phenol outlined in this paper confirms that a degree of sensitization under chronic aerogenic exposure to phenol is associated with a level to exposure to hapten (phenol) in doses lower than maximum permissible concentrations. We have shown that a hapten-associated level of IgG specific to phenol in pre-school children living under aerogenic exposure to the chemical in low doses is a criterion indicating early manifestations of sensitization and developing allergic pathology ( $OR = 14.75$ ; 95 %  $CI = 6.45$ – $33.73$ ;  $p < 0.05$ ).

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