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Research article

EXPOSURE TO AIRBORNE NICKEL AND PHENOL AND FEATURES OF THE IMMUNE RESPONSE MEDIATED BY E AND G IMMUNOGLOBULINS

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Ambient air pollution with potentially allergenic technogenic haptens facilitates occurrence of atopic reactions and creates favorable conditions for future development of allergic pathologies in exposed population.

The aim of this study was to estimate formation of an IgE-mediated and IgG-mediated specific immune response to low-molecular chemical compounds introduced into the body by inhalation (nickel and phenol used as examples).

The test groups were made of children (n = 99) and adults (n = 57) who lived under exposure to airborne nickel and phenol in levels not exceeding maximum permissible ones (up to 0.7 MPL). The reference groups included children (n = 95) and adults (n = 53) who lived on a conventionally clean territory.

In the test groups, average daily exposure doses of airborne nickel and phenol varied between $0.7 \cdot 10^{-6}$ and $9.3 \cdot 10^{-6}$ mg/(kg·day) for children and between $3.5 \cdot 10^{-6}$ and $5.0 \cdot 10^{-5}$ mg/(kg·day) for adults (the doses were created by emissions from a non-ferrous metallurgy plant); this was 1.5–3.0 times higher than the same indicators in the reference groups. Levels of IgG specific to nickel were more than two times higher in the exposed groups; the exposed children had elevated levels of IgG specific to phenol in their blood, practically three times higher than in the reference group ($p < 0.05$). By using logistic regression models, we established a significant probabilistic cause-effect relation between elevated nickel levels in children's blood and elevated levels of IgE-specific to nickel ($R^2 = 0.87$; $F = 468.58$; $p < 0.05$). The assessment of the odds ratio made it possible to verify the relationship between nickel levels in blood and the increase in the level of IgE specific to nickel in children (OR = 8.96; 95 % CI = 2.00–40.15) and in adults from the test group (OR = 3.12; 95 % CI = 1.10–9.40).

The study results indicate that exposure to low levels of airborne nickel and phenol induces hypersensitivity to technogenic haptens in the exposed children and adults. Its distinctive features are an IgE-mediated reaction to nickel and IgG-mediated reaction to phenol. Hyperproduction of immunoglobulin E specific to nickel as well as IgG-antibodies specific to phenol in the exposed children and adults reflects levels of exposure to airborne nickel and phenol and is a peculiarity of a hyperactive immune response developing in the analyzed children on the test territory.

Keywords: *nickel, phenol, airborne exposure, specific IgG, specific IgE, reagins, sensitivity to haptens, atopic reaction.*

Over the last 20 years, we have witnessed intensive urbanization, rapid industrialization and population growth; all these processes play a significant role in increasing anthropogenic environmental pollution and create elevated risks of allergic diseases [1]. According to The World Allergy Organization (WAO), allergic diseases are diagnosed in 30–40 % of the world population. Statistical data indicate that allergy is more widely spread among children and young people [2].

Hypersensitivity to technogenic haptens that penetrate the body by inhalation is a quite common immunological dysfunction. Thus, in our previous studies, we reported hapten-associated elevated levels of G class antibodies to phenol adducts in preschool children and schoolchildren of different age; these levels were related to excessive phenol in blood [3, 4]. Only IgG specific to formaldehyde are usually identified under exposure to airborne phenol and formaldehyde [5]. However, a di-

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rect relationship has been established between an increase in a bisphenol S (BPS) concentration in the body and IgG specific to BPS in women with bronchial asthma [6]. Women and children are more susceptible to phenol and its derivatives than men [7]. Phenol has been established to be able to stimulate deviation of the immune response towards Th2; the chemical has also been reported to be prone to affect aryl hydrocarbon and estrogen receptors [3]. Some authors have diagnosed respiratory dysfunctions (shortness of breath and wheeze) in preschool children caused by exposure to phenol; however, they have not identified and association between this exposure and the course of bronchial asthma [8]. At the same time, other researchers have established a relationship between development of bronchial asthma and phenol introduced by inhalation in adult patients [9]. Systemic effects produced by phenol have been reported to determine reproductive dysfunctions [10] and development of metabolic syndrome [11]. Phenol is highly likely to be able to deposit in fat tissues that induce inflammation by hyperproduction of cytokines; as a result, all these effects combined create elevated risks of allergy. A highly positive IgG-response to allergens has been shown to be three times more frequent in patients with obesity [6]. Regardless of introduction, the highest levels of many phenol compounds are identified in urine and lower levels are usually identified in blood serum or breast milk, which is due to the fact that phenols are mostly excreted by the kidneys [6]. Phenol has a relatively short half-life. However, persistent exposure creates relatively stable long-term levels of phenol compounds in biological media and this means it is fair to perform single estimation of phenol levels in the body [6]. Transition metals such as iron (Fe), zinc (Zn), copper (Cu), cobalt (Co), manganese (Mn), and nickel (Ni) are essential microelements and can be found in many enzymes participating in fundamental biological processes. Effects of nickel on the inborn and adaptive immunity when it is forming a response to a food or airborne allergen have been reported in some studies [12]. Nickel has been proven to be able to change metabolism of other metals [13]. Nickel is also an adjuvant for other metals [13]. When nickel penetrates the body by inhalation, it induces lung fibrosis; trachea, larynx and lung cancer; inflammatory non-communicable bronchopulmonary diseases; cardiovascular diseases; damage of the kidneys, and immunological dysfunctions. Inhalation exposure to nickel also facilitates its deposition in the brain and marrow, lung tissues, and the cardiac muscle [12–14]. Some researchers report that inhalation introduction of nickel causes asthma and rhinoconjunctivitis; at the same time, other authors have not established similar relationships. However, it has been noted that prevalence of bronchial asthma correlated with age and grew during pubescence [14]. Among young adults (aged 20–40 years), prevalence of nickel-associated sensitization is the highest and then the indicator starts to decline at an older age. The established trend is caused by declining hyperreactivity of the immune system with age. Allergy to nickel is more frequent among women than among men (15.7–22.9 and 4.3–6.65 % accordingly) [13]. Nickel has high allergenic potential and in some cases can act as an immunotoxic and carcinogenic agent [13]. Allergic contact dermatitis caused by exposure to nickel develops in 10–20 % of population [15]. Elevated levels of IL-6, IFN-γ и TNF-α, IL-2 in biological media (blood serum and bronchial secretion) were identified under nickel contamination [16]. When nickel penetrates the body through skin or the respiratory system, it induces the development of type I and IV allergic reactions mediated by reaginic antibodies and allergen-specific T-lymphocytes [17]. However, it is very difficult to describe how an allergic reaction develops and exact mechanisms of allergy to nickel have not yet been clarified [14]. Several authors insist that only such transition metals as nickel and chromium are allergenic [18–20]. Nickel and manganese can be found in particular matter; the latter have porous surfaces and electrostatic properties and are therefore able to interact with al-

lergens and induce a specific immune reaction [16, 21–23]. It has been established in experimental models *in vitro* and *in vivo* that manganese and nickel increase expression of the class II HLA-molecules, CD86-antigen, CD23-antigen and production of Th2-cytokines resulting in more intensive sensitization and allergic inflammation [24, 25].

Therefore, prevalence of allergic diseases and their dynamics being dependent on intensity of anthropogenic influence on the environment have been observed over the last decades. This confirms the necessity to search for updated diagnostic methodological approaches and to use them to timely identify how sensitive various population groups are to environmental pollutants. In future, these approaches will provide effectiveness of medical and preventive activities and reduce risks of developing allergic reactions to anthropogenic factors, including technogenic chemical ones.

In this study, our aim was to estimate the formation of an IgE-mediated and IgG-mediated specific immune response to low molecular weight compounds introduced into the body by inhalation (nickel and phenol used as examples).

Materials and methods. Biomedical tests were accomplished in conformity with the requirements fixed in the WMA Declaration of Helsinki (1964, 2013). An individual written informed consent to examinations and personal data processing was obtained from all the participants or their legal representatives. Overall, we examined 304 adults (aged 30–45 years) and children (aged 3–7 years) in both test and reference groups. The participants lived in areas with different anthropogenic loads in the Eastern Siberia. We applied the following criteria to include participants into the study: they had been living on the examined territories for at least five years prior to the examinations; they had not had any acute communicable diseases for at least two weeks prior to the examinations. Participation in another study was an exclusion criterion. The test groups included children (n = 99) and adults (n = 57) who lived under inhalation exposure to emissions from a non-ferrous metallurgy plant: airborne phenol and nickel (the test territories). The reference groups were made of children (n = 95) and adults (n = 53) who were not exposed to these chemicals in ambient air (the reference territories). We compared chemical levels in the collected air samples with the standards for ambient air quality. As a result, nickel levels were established to reach 0.03 average daily MPC (maximum permissible concentration) on the test territories; phenol levels, 0.68 average daily MPC. On the reference territories, nickel levels reached 0.02 average daily MPC; phenol levels, 0.22 average daily MPC. Chemical analysis of children's blood included phenol quantification by gas chromatography in accordance with the Methodical guidelines MUK 4.1.2102-4.1.2116-06[1] using the Kristall 2000 capillary gas chromatographer (JSC CDO CHROMATEC, Russia). Nickel levels were identified in biological media by mass-spectrometry with inductively coupled plasma (ISP-MS) using the Agilent 7500cx mass spectrometer in accordance with the Methodical guidelines MUK 4.1.3230-14[2]. Phenol and nickel levels in biological media of the children and adults from the test groups were estimated comparatively against the same indicators in the reference groups.

[1] Opredelenie vrednykh veshchestv v biologicheskikh sredakh: Sbornik metodicheskikh ukazanii MUK 4.1.2102–4.1.2116-06 [Determination of harmful chemicals in biological media: the collection of methodical guidelines MUK 4.1.2102–4.1.2116-06]. Moscow, the Federal Center for Hygiene and Epidemiology of Rospotrebnadzor, 2008, 183 p. (in Russian).

[2] MUK 4.1.3230-14. Metody kontrolya. Khimicheskie faktory. Izmerenie massovykh kontsentratsii khimicheskikh elementov v biosredakh (krov', mocha) metodom mass-spektrometrii s induktivno svyazannoi plazmoi; utv. Rukovoditelem Federal'noi sluzhby po nadzoru v sfere zashchity prav potrebitelei i blagopoluchiya cheloveka, Glavnym gosudarstvennym sanitarnym vrachom Rossiiskoi Federatsii A.Yu. Popovoi 19 dekabrya 2014 g. [Methodical guidelines MUK 4.1.3230-14. Control techniques. Chemical factors. Measurement of mass concentrations of chemical elements in biological media (blood, urine) with mass spectrometry with inductively coupled plasma; approved by A.Yu. Popova, the Head of the Federal Service for Surveillance over Consumer Rights Protection and Human Wellbeing, the RF Chief Sanitary Inspector on December 19, 2014]. *KODEKS: electronic fund for legal and reference documentation.* Available at: https://docs.cntd.ru/document/495856222 (January 19, 2023) (in Russian).

Levels of IgG specific to phenol, IgE specific to nickel were identified with the allergosorbent method; the total IgE level was identified with ELISA tests performed with the ELx808IU microplate reader (Bio-Tek, USA).

We checked the normality of distributions in the analyzed groups using the Kolmogorov – Smirnov test. To describe data that were distributed normally, we used the simple mean (*M*) and the standard error of the mean (*m*). We tested the null hypotheses that the simple means were equal in two independent groups with normal distribution using the two-sample Student's t-test. Sample data were compared with the reference values using the one-sample Wilcoxon signed rank test. We applied simple logistic regression analysis to predict probability of immune response dysfunctions. The odds ratio (OR) and its 95 % confidence interval were calculated to assess the relationship between the studied responses and the impact of factors. The null hypotheses were tested at the level of significance taken as equal to 0.05. Data were statistically analyzed using Statistica 6.0 software package (StatSoft, USA).

Results and discussion. We established that an average daily exposure to airborne nickel amounted to $0.7 \cdot 10^{-6}$ mg/(kg·day) and to airborne phenol $9.3 \cdot 10^{-6}$ mg(kg·day) for children in the test group; for the reference group, average daily exposure to airborne nickel equaled $0.4 \cdot 10^{-6}$ mg/(kg·day); phenol, $3.0 \cdot 10^{-6}$ mg/(kg·day). Average daily exposure doses were also established for the adults in the test group and equaled $3.5 \cdot 10^{-6}$ mg/(kg·day) for airborne nickel; $5.0 \cdot 10^{-5}$ mg/(kg·day) for airborne phenol. For the reference group, these exposure doses were equal to $2.3 \cdot 10^{-6}$ mg/(kg·day) for nickel and $1.62 \cdot 10^{-5}$ mg/(kg·day)[3] for phenol. Obviously, average daily intake of nickel and phenol was on average 1.5 and 3.1 times higher accordingly for the test groups against the reference ones.

Chemical and analytical tests established no statistically significant differences between nickel in blood of the children from the test group (0.1125 ± 0.0098 mg/dm^3) and the same indicator in the reference group (0.1143 ± 0.0069 mg/dm^3; p = 0.751 and 0.1088 ± 0.0065 mg/dm^3; p = 0.753). The share of blood samples with elevated nickel levels, higher than those identified in the reference groups, equaled 50 % in the test groups. Phenol levels were established to be statistically significantly (p = 0.026–0.048) 2 times higher in biological media of the children (0.0732 ± 0.0158 mg/dm^3) and adults (0.0490 ± 0.008 mg/dm^3) from the test groups against the same indicators in the reference ones (0.0379 ± 0.0083 mg/dm^3; p = 0.026 and 0.0249 ± 0.0099 mg/dm^3; p = 0.048). The share of samples with excess phenol in blood equaled 75.0 % in each test group against the same indicator in the corresponding reference group.

Comparative characteristics of the specific sensitization profile established that levels of IgE specific to nickel were statistically significantly (p = 0.002–0.021) 2.6 times higher on average in blood serum of the children and adults from the test groups against the same indicator in the corresponding reference ones. Estimation of the IgG-mediated reaction revealed that the children exposed to phenol had statistically significantly (p = 0.046) 2.8 times higher levels of IgG-antibodies specific to phenol against levels established in the unexposed children (Table). The adults from the test group had statistically significantly ($p < 0.05$) 2.3 times higher average group levels of IgG specific to phenol against the upper limit of the reference range.

[3] O sostoyanii i ob okhrane okruzhayushchei sredy Rossiiskoi Federatsii v 2018 godu: Gosudarstvennyi doklad [On the condition and protection of the environment in the Russian Federation in 2018: the State report]. Moscow, The Ministry of Natural Resources and Environment of the Russian Federation; SPO Kadastr, 2019 (in Russian); Sostoyanie zagryazneniya atmosfery v gorodakh na territorii Rossii za 2017 g.: Ezhegodnik [The ambient air pollution in cities in Russia over 2017: the annual data collection]. Saint Petersburg, Rosgidromet's Voeikov Main Geophysical Observatory, 2018, 234 p. (in Russian).

Table

Specific sensitization profile in the test and reference groups

Subjects	Test group	Reference group	*p*
IgE total, IU/cm^3 (% of samples above the reference range) *RR* 0–9.99, IU/cm^3			
Children	75.375 ± 17.567 (38.3 %)	87.767 ± 25.64 (43.3 %)	0.445
Adults	88.125 ± 27.137 (18.9 %)	88.943 ± 55.982 (11.8 %)	0.977
IgE spec. to nickel, IU/cm^3, (% of samples above the reference range) *RR* 0–1.55, IU/cm^3			
Children	0.387 ± 0.146 (2.1 %)	1.014 ± 0.349 (16.5 %)	0.002
Adults	0.465 ± 0.215 (8.6 %)	1.340 ± 0.703 (22.0 %)	0.021
IgG spec. to phenol, c.u. (% of samples above the reference range) *RR* 0–0.13, c.u.			
Children	0.049 ± 0.054 (8.7 %)	0.139 ± 0.069 (36.2 %)	0.046
Adults	0.126 ± 0.086 (32.0 %)	0.300 ± 0.188 (62.5 %)	0.091

The share of samples with elevated levels of G class antibodies to phenol adducts and class E antibodies to nickel adducts, higher than the reference levels, equaled 36.2 and 16.5 % accordingly in blood serum of the children from the test group against 8.7 and 2.1 % in the reference one (4.2 and 7.9 times higher accordingly). In the adults from the test group, the shares of samples with elevated levels of IgG specific to phenol and IgE specific to nickel that were higher than the reference levels equaled 62.5 and 22.0 % accordingly against 32.0 and 8.6 % in the reference group (2.0 and 2.6 times higher accordingly). The odds ratio assessment demonstrated an association of hapten load (nickel) with an increase in the level of nickel-specific IgE in children in the test group (OR = 8.96; 95 % CI = 2.00–40.15) and in adults in the test group (OR = 3.12, 95 % CI = 1.10–9.40).

We created mathematical logistic regression models that allowed establishing a statistically significant probabilistic cause-effect relation between growing levels of nickel and IgE-antibodies specific to nickel in children's blood ($b_0 = -5.53$; $b_1 = 28.44$; $R^2 = 0.87$; $F = 468.58$; $p < 0.001$).

Chronic exposure to phenol, and nickel in doses not higher than MPC (0.03–0.68 average daily MPC) clearly facilitates an immunologically mediated growth in sensitivity of the body to chemical factors (haptens) in children and adults. We established that IgE-mediated sensitization to nickel was more apparent in children living under possible exposure to priority airborne chemical factors than in adults living under the same conditions; production of immunoglobulin G specific to phenol was also much more intensive in children than in adults.

Persistent penetration of airborne low molecular weight compounds (LMWC) through the airways determines their accumulation in various biological media in the body and this is often associated with developing hypersensitivity. Under normal physiological conditions, cells of the adaptive immune system adequately recognize and remove antigens (haptens). However, an excessive immune reaction to usually harmless chemicals can be accompanied with allergy and inflammation. Permanent inflammation occurs in places that are repeatedly affected by allergens. Chronic allergic inflammation is associated with tissue remodeling and substantial changes in the barrier function of damaged epithelium, which increases a risk of infection. Mast cells, T-cells, eosinophils, basophils, neutrophils, monocytes / macrophages, thrombocytes, NK-cells, and Th-2 cytokines are basic participants responsible for development of chronic allergic inflammation. The immune system in children functions with a certain peculiarity which is Th-2-deviation of the immune response characterized with intensified production of allergen-specific IgE and eosinophilic inflammation as well as activation of the inborn immunity factors making inflammatory reactions

last longer [2]. A peculiarity of the adult immune system is an ability of the adaptive immune system to pose certain limitations on functioning of the inborn immune system in order to minimize immune-associated pathological damage to tissues.

The body response to LMWC, which are not recognized by TCR or antibodies, is associated with creation of a hapten-protein conjugate. Haptenization is obligatory for interactions between low molecular weight compounds and the adaptive immune system. Obviously, sensitization to LMWC can be considered an excessive adaptive immune response to a hapten [13]. Hyperreactivity to organic compounds and metals develops in a very different way. In case of sensitization to organic compounds (those having a phenyl ring), creation of a hapten-protein conjugate is determined by a covalent association. Metal ions (in particular, nickel) form spatially highly defined coordination bonds as per the donor-acceptor mechanism. It is these very specific coordination complexes that facilitate immune recognition and the triggering of an immune response culminating in the acquisition of sensitization to nickel [23]. Cross-reactivity between transition metals is quite possible since ion of one metal can be replaced with ion of another metal with the same charge and similar properties [13]. Inclusion of several metals (nickel, manganese, chromium, cobalt) of a carrier protein into the antigen determinant underlies creation of a new hapten determinants and this also explains occurrence of cross-reactions to these metals.

The linkage between an allergen and IgG and Fc-epsilon-receptor 1 (FcεRI) is necessary for induction of mast cell degranulation. $CD23^{+}$-receptor (FcεRII) is expressed on B- and T-lymphocytes and antigen-presenting cells. It controls the immune response, regulates IgE homeostasis and is responsible for transporting reaginic antibodies through the airway and intestinal epithelium [24, 25]. $CD23^{+}$-receptor binding on B-cell, on the one hand, prevents activation of effector cells; on the other hand, it facilitates presentation by delivering an antigen to dendritic cells. FcεRI was established to be able to bind free IgE thereby inducing allergic inflammation, and FcεRII, which has the low affinity with IgE, mostly binds the immune complex IgE-allergen (IgE-IC) [24]. Soluble CD23 (sCD23) show a range of sizes but all bind IgE. They are thought to promote or inhibit IgE synthesis, depending on their oligomerization state [26]. It is noteworthy that the airway and intestinal epithelium is a major participant in the development of allergic inflammation [27]. Epithelial cells directly activate antigen-presenting cells and indirectly activate type 2 innate lymphoid cells (ILC2). An allergen induces Th-2-polarization of the immune response together with hyperproduction of allergen-specific IgE and ILC2. The role played by ILC2 in developing allergic reactions and tissue reparation has been reported. Lesions of epithelium under the Th-2 shift in the cytokine profile make for IgM synthesis being switched to IgE [27]. A level of specific IgE in blood serum can persist for a long time after an exposure to an allergen ceases. Reagin reactions mediate promotion of inflammation and bronchial hyperreactivity. IgE has been assumed to possibly play a regulatory role. Excess non-specific IgE has been shown to be able to inhibit allergen-induced mast cell degranulation and basophils in skin [26]. Specific IgG antibodies enter cross-reactions with allergens and inhibit their binding to IgE due to competition between epitopes. Some experts believe that induction of such antibodies prevents allergic inflammation [27]. The role that the aryl hydrocarbon receptor plays in production of all types of antibodies and switching between their different classes (IgG – IgE) as well as IgG isotypes in a plasmatic cell has been evidenced [4]. The study results are clearly in line with previous reports by other authors stating that an excess immune response could possibly develop under exposure to LMWC in low doses; the results also confirm higher risks of allergic diseases for people exposed to technogenic chemical factors.

Conclusion. In the test groups, average daily exposure doses of airborne nickel and phenol varied between $0.7 \cdot 10^{-6}$ and $9.3 \cdot 10^{-6}$ mg/(kg·day)

for children and between $3.5 \cdot 10^{-6}$ and $5.0 \cdot 10^{-5}$ mg/(kg·day) for adults. This is 1.5–3.0 times higher than the same indicators in the reference groups. Comparative characteristics of the sensitization profile created for the children and adults living under exposure to airborne nickel and phenol in low doses revealed some peculiarities in the development of elevated sensitivity to haptens, namely, an IgE-mediated reaction to nickel and IgG-mediated reaction to phenol. The results reported in this study make it possible to recommend using IgE and IgG as indicators of susceptibility to allergic diseases in adults and children living under chronic exposure to low doses of nickel and phenol, chemicals with obvious allergenic potential.

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