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THE LONG-TERM INFLUENCE OF OXYETHYLIZED NONYLPHENOLS AND THEIR DERIVATIVES ON THE CELLULAR AND HUMORAL FACTORS OF NONSPECIFIC IMMUNE RESISTANCE OF THE RATS ORGANISM

The research of xenobiotics mechanisms of action, development of the scientifically grounded diagnostic programs and detection of the objective prognostic criteria of pathological processes is one of the priority tasks of modern medicine [1, 2]. It is refered in a full degree to oxyethylized nonylphenols (OENP) and their derivatives – sodium salts of carboxymethylates of oxyethylized isononylphenols (CM-OENP), which have physical and chemical properties and features of structure of molecules like ionogenic detergents. These substances are characterized by considerable output volumes of synthesis, wide usage in different industries of national economy (as basis of industrial issue of plastics, polyurethanes, cleaning agents, emulsifying agents, anticorroding preparations, hydraulic and cooling fluids, and others like that), entry to the sources of water consumption and due to it possible influence on the organism of man [3, 4]. Mechanisms of OENP and their derivatives action are studied not enough. Their revelation is the base for explanation of measures on the conservation of the environment and health activities.

In the scientific literature there is no data about OENP and their derivatives influence on the state of the immune system, which is one of the first that responses on the influence of extreme environmental factors. The interest to this group of detergents is also caused by a large turnout, a wide range of the production output and absence of any prognostic assessment of a potential danger for homoitherms and human beings.

The purpose of the present work was to estimate the state of nonspecific immune resistance of the rats organism in conditions of the long-term influence of oxyethylized nonylphenols and their derivatives in doses 1/10 and 1/100 DL_{50} by determination of leukogram, activity of phagocytosis, content of acute phase proteins and lysozyme.

Materials and research methods.

The standards compounds with scheduled physical-chemical properties were used in the work: OENP with number of oxyethylized groups 4, 6, 8, 10, 12 ($OENP_{4-12}$) and CM-OENP with number of oxyethylized groups 4, 5, 6, 10 ($CM\text{-}OENP_{4-10}$). The experimental part of the research was performed on white rats of WAG population, with mass (180-220) g. The experiments on white rats were performed in com-

pliance with the international principles of the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, 1986). Every day before feeding they received orally, through a metal probe, aqueous solutions of xenobiotics with 1/10 and 1/100 of LD_{50}. The duration of subacute influence was 45 days. Half-lethal doses (LD_{50}) were determined at the levels: $OENP_4$ – 5,8 g/kg; $OENP_6$ – 4,2 g/kg; $OENP_8$ – 5,1 g/kg; $OENP_{10}$ – 4,3 g/kg; $OENP_{12}$ – 3,4 g/kg; CM-$OENP_4$ – 6,1 g/kg; CM-$OENP_5$ – 2,8 g/kg; CM-$OENP_6$ – 2,2 g/kg; CM-$OENP_{10}$ – 3,2 g/kg of the animal weight. The proper volumes of water were entered to the animals of control group.

Haematological researches were conducted, using standard methods. The leucocyte count of blood was carried out in an ***Goryaev*** counting ***chamber***. For the differential count of leucocytes the blood smears were prepared from a heparinized whole blood, fixed them by an ethanol and stained with Romanovsky dyes [5]. Phagocytic activity of neutrophils was estimated by phagocytic index (the average number of latex particles, ingested by one phagocyte), absorption index and digestion index in relation to Staphylococcus aureus (culture 209). In every blood smear 100 neutrophils were observed and marked the quantity of cells which were phagocyted [6]. Determination of haptoglobin content in the blood was performed by a photoelectrocalorimetric method [7]. Content of ceruloplasmin in the blood was determined by Ravin method in Moshkov modification [8]. Content of fibrinogen in the blood was determined by Clauss method using of reagents sets «Fibrinogen-test» («RENAM SPU», Russia), which is based on the measuring of clotting time of diluted plasma by thrombin. Determination of lysozyme activity was determined by a photoelectrocalorimetric method with the changes of temperature regimen of blood reaction with M. lisodecticus culture [9]. The statistical data analysis was performed with the usage of computer programs for statistical data handling Statistica 6.1 (StatSoft, Inc., the USA). The primary statistical data processing begun from verification of hypothesis about correspondence of sample to Gaussian distribution law, using Shapiro-Wilk test. The rightness of conclusion in relation to normality of sample distribution was additionally controlled by the instrumentality of the asymmetry and excess coefficients. Quantitative signs, that had normal distribution, were described by parametric descriptions – mean value of index (M) and standard deviation (s); in the case of absence of normal distribution – nonparametric: median (Me) and interquartile range. The Student`s t-test is used for comparison of two normal distributions. If at least one of distribution was not normal, for comparison of independent samples the Mann-Whitney U test was used. For the critical level of statistical significance at verification of statistical hypotheses took $p<0,05$.

Results and their discussions.

The indexes of leukogram were estimated in the conditions of the long-term influence of the researched compounds. Our results revealed statistically significant ($p<0,001$), comparatively with the control, reduction in the content of lymphocytes in

blood serum on 45-day of the influence of OENP and their derivatives in a dose 1/10 DL_{50} (tabl. 1). The most expressive it was for CM-$OENP_{10}$ (almost by 2 times), CM-$OENP_6$ (by 1,7 times), CM-$OENP_5$ and $OENP_{12}$ (at the average by 1,5 times), and the least – for CM-$OENP_4$, $OENP_4$, $OENP_8$, $OENP_{10}$ (at the average by 1,3 times). The same tendency, but less expressive, was observed in a dose 1/100 DL_{50} (tabl. 2). In this case most toxic were CM-$OENP_5$, CM-$OENP_6$, CM-$OENP_{10}$ and $OENP_{12}$: the contents of lymphocytes was diminished at the average by 1,3 times. The detected lymphocytopenia testifies about the development of immunodeficiency state in the rats organism in conditions of the long-term influence of compounds.

A neutrophilic link is the basic criterion of the organism intoxication. It is revealed statistically significant ($p<0,001$), comparatively with the control, increase in the content of stab neutrophils only for $OENP_4$ (by 1,5 times, $p<0,001$) and $OENP_8$ (by 1,2 times, $p=0,036$), while for $OENP_{12}$ and CM-$OENP_{10}$ was observed, opposite, their reduction ($p<0,001$) almost by 2 times (tabl. 1).

Table 1 **Indices of leukogram of rats on 45-day of the influence of oxyethylized nonylphenols and their derivatives in a dose 1/10 DL_{50} (%, n=15; Me [25%; 75%] or M±s)**

Indices	Neutrophils		Lympho-cytes	Monocytes	Eosinophils
	Stab	segmented			
$OENP_4$	3,1±1,19 p=0,03	28,9±7,74 p=0,01	62,9±7,55 p<0,001	3 [3; 4] p=0,76	1,7±0,88 p=0,73
$OENP_6$	3,5±1,46 p=0,21	29,8±7,33 p<0,001	59 [58; 65] p<0,001	4,0±1,07 p=0,58	1,9±0,80 p=0,84
$OENP_8$	4,8±1,42 p=0,09	30,6±7,32 p<0,001	60,3±6,40 p<0,001	4 [3; 5] p=0,72	2,0±1,07 p=0,73
$OENP_{10}$	5,3±1,40 p=0,01	29,2±8,71 p<0,001	58 [52; 65] p<0,001	4,3±1,39 p=0,33	1,5±0,74 p=0,31
$OENP_{12}$	2,7±1,10 p<0,001	32,5±7,04 p<0,001	56,4±6,23 p<0,001	5,9±1,67 p<0,001	3,2±1,01 p=0,001
CM-$OENP_4$	4,1±1,13 p=0,87	30,4±7,63 p<0,001	60 [55; 61] p<0,001	3,7±1,05 p=0,89	1,2±1,01 p=0,08
CM-$OENP_5$	4,6±1,55 p=0,29	31 [26; 42] p<0,001	55,1±5,64 p<0,001	4,8±1,74 p=0,09	3,6±1,24 p<0,001
CM-$OENP_6$	5 [4; 7] p=0,24	31,1±7,16 p<0,001	52,1±4,93 p<0,001	5,3±1,50 p=0,07	3,1±1,06 p=0,002
CM-$OENP_{10}$	3,7±1,33 p=0,46	36 [27; 40] p<0,001	57,5±8,18 p<0,001	5,4±1,48 p=0,05	2,7±1,03 p=0,026
Control	4,1±1,11	23 [17; 25]	69,5±5,41	3,7±1,53	2 [1; 3]

Note: p – level of statistical significance comparatively with the control

In cases of influence of 1/100 of DL_{50} we observed a reduction ($p<0,001$) in the concentration of stab neutrophils for $OENP_4$ and $OENP_{12}$ at the average by 1,4 times, comparatively with the control, and for $OENP_{10}$ – insignificant increase by 1,3 times

(tabl. 2). The influence of other compounds in doses 1/10 and 1/100 DL_{50} did not cause the changes from the side of stab neutrophils. It should be noted that all investigated compounds in a dose 1/10 DL_{50} caused on 45-day of influence to an increase ($p<0,001$) of segmented neutrophils content (tabl. 1). Most toxic compounds were CM-$OENP_5$, CM-$OENP_6$ and $OENP_{12}$ (increase by 2 times at the average), and least – $OENP_4$ and CM-$OENP_4$ (by 1,4 times). For a dose 1/100 DL_{50} this tendency was saved, especially for CM-$OENP_{10}$ (by 1,6 times), CM-$OENP_5$, CM-$OENP_6$, $OENP_6$, $OENP_{10}$ and $OENP_{12}$ (at the average by 1,3 times) (tabl. 2). The increase of neutrophils probably testifies about the presence of intoxication of the rats organism, and its decrease is ensured due to depression of hematopoietic processes or as a result of exhaustion of an organism against a background of the long-term intoxication by the chemical compounds.

Table 2 **Indices of leukogram of rats on 45-day of the influence of oxyethylized nonylphenols and their derivatives in a dose 1/100 DL_{50} (%, n=15; Me [25%; 75%] or M±s)**

Indices	Neutrophils		Lympho-cytes	Monocytes	Eosinophils
	stab	segmented			
$OENP_4$	3,1±1,19 p=0,03	28,9±7,74 p=0,01	62,9±7,55 p<0,001	3 [3; 4] p=0,76	1,7±0,88 p=0,73
$OENP_6$	3,5±1,46 p=0,21	29,8±7,33 p<0,001	59 [58; 65] p<0,001	4,0±1,07 p=0,58	1,9±0,80 p=0,84
$OENP_8$	4,8±1,42 p=0,09	30,6±7,32 p<0,001	60,3±6,40 p<0,001	4 [3; 5] p=0,72	2,0±1,07 p=0,73
$OENP_{10}$	5,3±1,40 p=0,01	29,2±8,71 p<0,001	58 [52; 65] p<0,001	4,3±1,39 p=0,33	1,5±0,74 p=0,31
$OENP_{12}$	2,7±1,10 p<0,001	32,5±7,04 p<0,001	56,4±6,23 p<0,001	5,9±1,67 p<0,001	3,2±1,01 p=0,001
CM-$OENP_4$	4,1±1,13 p=0,87	30,4±7,63 p<0,001	60 [55; 61] p<0,001	3,7±1,05 p=0,89	1,2±1,01 p=0,08
CM-$OENP_5$	4,6±1,55 p=0,29	31 [26; 42] p<0,001	55,1±5,64 p<0,001	4,8±1,74 p=0,09	3,6±1,24 p<0,001
CM-$OENP_6$	5 [4; 7] p=0,24	31,1±7,16 p<0,001	52,1±4,93 p<0,001	5,3±1,50 p=0,07	3,1±1,06 p=0,002
CM-$OENP_{10}$	3,7±1,33 p=0,46	36 [27; 40] p<0,001	57,5±8,18 p<0,001	5,4±1,48 p=0,05	2,7±1,03 p=0,026
Control	4,1±1,11	23 [17; 25]	69,5±5,41	3,7±1,53	2 [1; 3]

Note: p – level of statistical significance comparatively with the control

Next to neutrophils the most phylogenetically old element of cellular immunity is monocyte. Chemical compounds in doses 1/10 and 1/100 DL_{50} in whole did not affect on this index (tabl. 1, 2). On 45-day of monitoring only for CM-$OENP_{10}$, $OENP_4$, $OENP_6$, $OENP_{12}$ in a dose 1/10 DL_{50} and for $OENP_{12}$, CM-$OENP_{10}$ in a dose 1/100 DL_{50} it is revealed the statistically significant ($p<0,05$), comparatively with the con-

trol, an increase of its content, but the last was within the limits of physiological norm. The revealed tendency to some increase of monocytes it is possible to consider as a protective reaction of the rats organism on the long-term influence of OENP and their derivatives. The content of eosinophils was within the limits of physiological norm in the conditions of the long-term influence of all chemical compounds in doses a 1/10 and 1/100 DL_{50}. Besides, we observed, compa-ratively with the control, an increase in its concentration in the case of the ifluence of CM-$OENP_4$ ($p=0,003$), CM-$OENP_5$ ($p<0,001$), CM-$OENP_6$ ($p<0,001$), $OENP_4$ ($p=0,01$), $OENP_{12}$ ($p=0,03$) in a dose 1/10 DL_{50} that CM-$OENP_5$ ($p<0,001$), CM-$OENP_6$ ($p=0,002$), CM-$OENP_{10}$ ($p=0,026$), $OENP_{12}$ ($p<0,001$) in a dose 1/100 DL_{50}.

The phagocytic activity of neutrophils in the peripheral blood of rats was estimated in the conditions of the long-term influence in doses 1/10 and 1/100 DL_{50} most toxic, according to previous results, CM-$OENP_5$ and CM-$OENP_6$ and least toxic – $OENP_4$ and CM-$OENP_4$. These compounds on 45-day of influence in a dose 1/10 DL_{50} statistically significant ($p<0,05$), comparatively with the control, have decreased this index, that was confirmed by reduction of phagocytic index, index of absorption and digestion index, absolute indexes of absorption and digestion of staphylococci (tabl. 3). For a dose 1/100 DL_{50} we observed other dynamics (tabl. 4).

Table 3 **The phagocytic activity of neutrophils of rats on 45-day of the influence of oxyethylized nonylphenols and their derivatives in a dose 1/10 DL_{50} (n=15; Me [25%; 75%] or M±s)**

Indices	Phagocytic index %	Absorption index, arbitrary units	Digestion index, arbitrary units	Absorption of staphylococci on active neutrophil, arbitrary units	Digestion of staphylococci on active neutrophil, arbitrary units
CM-$OENP_5$	60,2±7,15 p<0,001	3,4±1,05 p<0,001	0,4 [0,3; 0,4] p<0,001	4,3±0,73 p<0,001	1,0±0,39 p<0,001
CM-$OENP_6$	50,5±10,39 p<0,001	2,2 [1,8; 4,1] p<0,001	0,3±0,14 p<0,001	3,9 [3,5; 4,6] p<0,001	0,9±0,31 p<0,001
$OENP_4$	69,3 [59,9; 75,3] p<0,001	4,2 [3,0; 5,0] p=0,001	0,6±0,15 p<0,001	6,0 [5,0; 7,0] p<0,001	1,2±0,33 p<0,001
CM-$OENP_4$	72,5 [62,5; 77,4] p<0,001	4,8 [4,2; 5,4] p=0,009	0,8 [0,5; 0,8] p=0,054	6,9 [6,0; 7,7] p=0,009	1,3 [1,0; 1,5] p<0,001
Control	79,4±4,42	5,9±1,36	0,9±0,26	8,8 [6,7; 10,0]	1,9±0,46

Note: p – level of statistical significance comparatively with the control

Table 4 **The phagocytic activity of neutrophils of rats on 45-day of the influence of oxyethylized nonylphenols and their derivatives in a dose 1/100 DL_{50} (%, n=15; Me [25%; 75%] or M±s)**

Indices	Phagocytic index %	Absorption index, arbitrary units	Digestion index, arbitrary units	Absorption of staphylococci on active neutrophil, arbitrary units	Digestion of staphylococci on active neutrophil, arbitrary units
CM-OENF5	69,4±6,83 p<0,001	4,2 [3,8; 5,0] p=0,001	0,6±0,14 p=0,001	5,9±0,72 p<0,001	1,4 [1,0; 1,5] p<0,001
CM-OENF6	64,7±7,34 p<0,001	3,7±0,83 p<0,001	0,5±0,16 p<0,001	6,4±1,12 p=0,003	1,3 [0,9; 1,6] p<0,001
OENF4	92,5±5,09 p<0,001	6,8±1,08 p=0,06	1,4±0,47 p<0,001	10,3±1,19 p=0,016	2,8±0,56 p<0,001
CM-OENF4	99,1±8,61 p<0,001	7,3±0,92 p=0,002	1,6±0,52 p<0,001	12,0 [9,8; 12,5] p<0,001	2,6±0,53 p=0,002
Control	79,4±4,42	5,9±1,36	0,9±0,26	8,8 [6,7; 10,0]	1,9±0,46

Note: p – level of statistical significance comparatively with the control

$CM\text{-}OENP_5$ and $CM\text{-}OENP_6$ decrease (p<0,001) a phagocytic index at the average by 1,2 times, absorption index – by 1,5 times, digestion index by 1,7 times, absolute indexes of absorption and digestion of staphylococci – by 1,5 times. It was determined for least toxic $OENP_4$ and $CM\text{-}OENP_4$, opposite, statistically significant, comparatively with the control, increase of phagocytic activity of neutrophils in the peripheral blood of rats. This is associated with increase of phagocytic index at the average by 1,2 times, absorption index and digestion index – accordingly by 1,2 and 1,7 times, absolute indexes of absorption and digestion of staphylococci – accordingly by 1,3 and 1,5 times, that may be considered as a protectivly-compensatory reaction under the long-term influence of the compounds.

It is showed, that the long-term influence of $CM\text{-}OENP_5$, $CM\text{-}OENP_6$, $OENP_4$ and $CM\text{-}OENP_4$ in a dose 1/10 DL_{50} is accompanied by statistically significant (p<0,016), comparatively with the control, by the decrease of ***acute-phase proteins***: haptoglobin at the average almost by 2 times, ceruloplasmin – 1,7 times and fibrinogen – 1,5 times (tabl. 5). The influence of $CM\text{-}OENP_5$ and $CM\text{-}OENP_6$ in a dose 1/100 DL_{50} caused on 45-day of experiment also to the decrease of haptoglobin content (p<0,009) at the average by 1,5 times, ceruloplasmin (p<0,011) – 1,4 times and fibrinogen (p<0,01) – 1,3 times. For least toxic $OENP_4$ and $CM\text{-}OENP_4$ in that dose, opposite, caused the statistically significant, comparatively with the control, increase of haptoglobin content (p<0,039) by 1,3 times, ceruloplasmin (p<0,002) – 1,5 times. The content of fibrinogen in blood plasma of rats in the conditions of influence 1/100 DL_{50} $OENP_4$ practically was not changed (p=0,21), and $CM\text{-}OENP_4$ – was increased (p=0,014) by 1,2 times. The revealed decrease of ***acute-phase proteins content*** in blood of rats in the conditions of the long-term influence of the researched compounds testifies about violation of protein synthesis of the liver. The last plays an

important role in formation of the cellular and humoral links of the immune system. Its affection causes considerable changes in decrease of activity of nonspecific reactivity and development of immune distress [10,11]. The revealed increase of a*cute-phase proteins content may be considered as* an adaptation reaction of an organism on the long-term influence of chemical compounds in a dose 1/100 DL_{50}.

Table 5 **The a*cute-phase proteins content* in blood of rats on 45-day of the influence of oxyethylized nonylphenols and their derivatives in doses 1/10 and 1/100 DL_{50} (n=15; Me [25%; 75%] or M±s)**

Indices	Haptoglobin g/l		Ceruloplasmin, mcmol/l		Fibrinogen g/l	
	dose, DL_{50}					
	1/10	1/100	1/10	1/100	1/10	1/100
CM-$OENP_5$	0,15 [0,1; 0,18] p<0,001	0,19±0,033 p<0,001	1,0±0,27 p<0,001	1,5 [0,9; 1,6] p=0,011	1,7 [1,1; 1,9] p<0,001	1,9 [1,5; 2,0] p=0,01
CM-$OENP_6$	0,11 [0,1; 0,2] p<0,001	0,21 [0,19; 0,25] p=0,009	0,8±0,23 p<0,001	1,2±0,27 p<0,001	1,3±0,47 p<0,001	1,7±0,44 p=0,002
$OENP_4$	0,14±0,055 p<0,001	0,34±0,042 p=0,039	1,2 [0,9; 1,6] p<0,001	2,5 [1,9; 2,7] p=0,002	1,5±0,52 p<0,001	2,6 [2,0; 3,0] p=0,21
CM-$OENP_4$	0,20±0,055 p=0,001	0,37±0,045 p=0,003	1,5 [1,1; 1,7] p=0,016	2,7 [1,9; 3,0] p=0,001	1,8 [1,4; 2,0] p=0,006	2,9±0,74 p=0,014
Control	0,29±0,083		1,8 [1,5; 2,2]		2,3±0,56	

Note: p – level of statistical significance comparatively with the control

An antibacterial enzyme lysozyme is an important factor of nonspecific immune resistance of an organism. Results of the study revealed statistically significant, comparatively with the control, decrease of its content on 45-day of the influence in a dose 1/10 DL_{50} CM-$OENP_5$ (by 1,8 times, p<0,001), CM-$OENP_6$ (by 1,6 times, p<0,001), CM-$OENP_4$ (by 1,5 times, p<0,001) and $OENP_4$ (by 1,3 times, p=0,01) (tabl. 6). Under the influence of chemical compounds in a dose 1/100 DL_{50} the content of this index was decreased only for CM-$OENP_5$, CM-$OENP_6$ and CM-$OENP_4$ at the average by 1,2 times. The decrease of lysozyme content testifies about the depression of the nonspecific immune resistance of the rats organism and the decrease of antibacterial defence.

Table 6 **The content of lysozyme in blood of rats on 45-day of the influence of oxyethylized nonylphenols and their derivatives in doses 1/10 and 1/100 DL_{50} (n=15; Me [25%; 75%] or M±s)**

Indices	Dose, DL_{50}	
	1/10	1/100
CM-$OENP_5$	3,9±1,27; p<0,001	5,8±1,26; p=0,03
CM-$OENP_6$	4,3±0,91; p<0,001	6,3 [5,0; 7,0]; p=0,05
$OENP_4$	5,4±1,67; p=0,01	6,6±1,29; p=0,65
CM-$OENP_4$	4,8±1,05; p<0,001	5,8±1,11; p=0,049
Control	7,0 [5,4; 8,2]	

Note: p – level of statistical significance comparatively with the control

Results of the study testify that the long-term influence of OENP and their derivatives, especially in a dose 1/10 DL_{50}, results in expressive exhaustion of basic factors of nonspecific immune resistance of the rats organism.

Conclusions.

1. The long-term intoxication of the rats organism by OENP and their derivatives in doses 1/10 and 1/100 DL_{50} causes the change of indexes of nonspecific immune resistance, that is confirmed by disturbance of leukogram, phagocytic activity of neutrophils due to the decrease to the percent of phagocytosis, phagocytic index, absorption index and digestion index of staphylococci, by reduction of haptoglobin, ceruloplasmin, fibrinogen, lysozyme in blood serum.

2. An increase of the indexes of phagocytic activity of neutrophils, content of haptoglobin, ceruloplasmin and fibrinogen in the conditions of the long-term influence of least toxic among all studied chemical compounds – $OENP_4$ and CM-$OENP_4$ in a dose 1/100 DL_{50} is the protectivly-compensatory reaction of the rats organism.

3. The long-term influence of OENP and their derivatives in doses 1/10 and 1/100 causes an immunotoxic effect, results in disturbances of protective function of the immune system. Cumulation of changes of separate compartments of an immune defence in the conditions of the long-term influence of studied chemical compounds, probably, is realized by violation of structural integrity and functional wholeness of the immune system.

4. Consideration of the mechanisms of immunotoxic action of OENP and their derivatives is necessary at the choice of method of prevention and treatment of intoxications in persons which contact by them in the conditions of production and environment, and development of methods of early diagnostics and prevention of the occupationally and ecologically conditioned pathology.

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