ENGLISH VERSION: INFLUENCE OF POLYOXYPROPYLENEPOLYOLS ON WATER OBJECTS*

Babienko V.V., Anishchenko L.V., Mykhaylenko V.L.

Odessa National Medical University

The article describes the results of toxicological and epidemiological characteristics of the new group and polyoxypropylene substantiated forecast of sanitary and epidemiological welfare of the water bodies. The study is based on research of biological action of polyols on the body of warm-blooded animals in the conditions of acute and subacute experiments, the effect of polyols on the organoleptic properties of water and sanitary water reservoirs regime. The study showed that the basis of the mechanism of biological action is polyoxypropylene stimulation of lipid peroxidation on the background of the depletion of the antioxidant system, violation of the structure of cell membranes, decrease of activity of membrane-bound enzymes, a violation of bioenergy, oxidative phosphorylation and redox processes in the body of warm-blooded animals. Leading pathogenetic link the formation of structural and metabolic disorders in the body are activated free radical lipid peroxidation, inhibition of antioxidant systems and energy processes that underlie the development of tissue hypoxia and reduced recovery processes.

Key words: hygiene, health, polyoxypropylenpolyols, water bodies.

Rapid industrial growth and changing of its structure significantly increase the amount of wastes going down into the water, changing their chemical composition. Protection of water from pollution is one of the important challenges and technological progress in public health [9].

The risk of water pollution exists almost everywhere. With the increasing pace of industrial development, there is a change of its structure and prevalence of slurry processes specific to the chemical industries, oil and coke, paper-pulp industry, production of artificial and synthetic organic materials [2].

The development of chemical industry, the use of chemicals and other industries of agriculture are accompanied not only by the rapid increase in the volume of waste water entering the reservoir, but more intense and diverse contamination of chemicals and ingredients, many of which are not indifferent to health. This applies to polyoxypropylenepolyols (POPP) [3, 5, 8, 11]. Insufficiently studied in relation to hygienic POPP that can pollute water objects are: polyoxypropyleneoxyetylenglicoluretane (POPP-100) polyoxypropilenamine (POPP-294), polyoxypropylated polyoxypropylentryol sucrose (POPP-504). It is known that these substances are widely used in various sectors of the economy as the basis for industrial production of synthetic leather, enamels, varnishes, hydraulic and brake fluids, plastics, polyurethane foams, surfactants, epoxy resins. At all stages of POPP production (synthesis, catalysis, oxidation, hydration, drying) wastewater is generated, which can cause water pollution and disturbance of natural self-cleaning [9].

At present, there is almost no information regarding the parameters of toxicity, biological activity, the impact of the conditions of polyols water and population's health and hygiene regulations results of water in water objects [1, 4, 7, 10, 12-15]. Therefore, the need to explore these questions determines the relevance of this study whose purpose is to obtain toxicological and hygienic characteristics of polyoxypropylenepolyols (POPP-100, POPP-294, POPP-504) and justification of the forecast for sanitary and epidemiological risk of water reservoirs.

Object of study: biological effects of POPP on the organism of experimental animals in acute and subacute experiments The impact of POPP on the organoleptic properties of water and sanitary water mode.

Subject of research: condition of experimental animals, condition of sanitary water mode.

Methods of research

The following methods of research were used: toxicological and hygienic (determining the average lethal doses, cumulative allergenic properties, skin-irritating and skin-resorptive action), health, immune spectrophotometric (determination of enzyme activity and concentrations of compounds) spectrofluorometric (determining the rate of oxidation compounds), chromatophotographic (separation into fractions, determination content metabolites), chemiluminescent (determining the intensity of chemiluminescence biological objects), standardized clinical methods using a standard set of reagents, morphological (definition of pathological changes in organs and tissues), histochemical (determination of enzyme activity), statistics.

Thus, the degree of danger in POPP study was based on a large range of research, including the definition of lethal effects, cumulative detection, skin-irritating, skin-resorptive, sensitizing properties, the study of chronic effects on the body to determine the thresholds of harmful effects. Of particular importance are the acquired toxycocinetic and metabolic criteria for assessing the toxicity of xenobiotics, study the long-term effects, impact on reproductive function of the body.

For this purpose, acute and subacute experiments on warm-blooded animals were conducted.

Results and discussion

A single oral administration of investigated polyols was performed using dose 5.0-20.0 g/kg of animal, who was elected so as to determine the dose mortality in the range LD_0-LD_{100} [6]. Observations of animals were carried out within 15 days. First day the administration of substances in animals led to excitement, which gradually turned into apathy. The reaction to sound stimulation and pain in animals significantly reduced. Heavy breathing, pale skin, loss of coordination of movements, weakness, lateral position, diarrhea, and coma were observed. The death of animals occurred during the first day of the experiment, depending on the dose. Average time of death

* *To cite this English version: Babienko V.V., Anishchenko L.V., Mykhaylenko V.L. Influence of polyoxypropylenepolyols on water objects // Problemy ekologii ta medytsyny. - 2016. - Vol 20, № 3-4. - P. 8–12.*

of animals in all groups was marked in the range of 16.4 to 24.3 hours from the start of acute action. Morphological examination of animals killed in the next day after the introduction of polyols showed plethora of internal organs, bloating, stomach, small and large intestines.

Internal organs were subjected to pathological investigation. They were identified as follows: in the brain - plethora of vessels and membranes of brain substance, stasis in the capillaries, perivascular and pericellular edema; heart - expressed hyperemia, perivascular edema of the heart muscle; in the lungs - moderate hyperemia; liver - acute hyperemia, focal degeneration, sometimes bleeding; kidney - acute hyperemia, focal and granular dystrophy protein in the lumen of the convoluted tubules, sometimes in the cortical hemorrhage and interstitial layer; stomach, small and large intestine - hyperemia, swelling of the submucosa, sometimes necrosis.

The clinical presentation included acute poisoning with prevailing symptoms of the central nervous, cardiovascular and respiratory systems. Various species and gender sensitivity has not been established.

Thus, polyols in the case of single ingestion into the body of warm-blooded animals were able to break hemodynamics mainly in the brain, liver, kidney, spleen, heart and cause of parenchymal degeneration.

It is known that most of the impact of xenobiotics in the body can lead to intensification of free radical reactions and reactions of lipid peroxidation (LPO), accompanied by increased formation of reactive oxygen, peroxides, hydroperoxides which can provide damaging effect on cell membranes. The criteria that indicate a change in the activity of LPO, used the registration of spontaneous and induced superweak light - chemiluminescence (CL) compared with the content in biological substrates of lipid peroxidation products - diene conjugates (DC) and malondialdehyde (MDA). Polyols investigated in a dose 1/100 DL_{50} led to a significant increase in GC content (average 78%) and MDA (average 126%) in the blood serum of the rats compared with the control on day 30 of the experiment. The study investigated the penetration of substances through intact skin using chemiluminescence method showed that the intensity of chemiluminescence serum of experimental animals increased from the first hour polyols application on the skin. This made it possible to conclude that the substances are able to penetrate intact skin of experimental animals. Such a high sensitivity makes it possible to use it in toxicological and hygienic studies for the rapid assessment of the penetration of substances through intact skin. Animal deaths in assessing skin-resorptive action polyols were observed.

Justification for characteristics of biological effects, setting thresholds and inactive doses of the compounds in rats conducted under conditions subacute experiment. All studied polyols reduced rate of increase in body weight, hemoglobin, red blood cells and white blood cells. The changes in the activity of catalase, peroxidase, glucose-6-phosphate dehydrogenase, lactate dehydrogenase, malate dehydrogenase, creatine, Ca^2 iMg^2 + + - dependent ATPase, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, α- hydroxybutyrate dehydrogenase, glutathione peroxidase and content of reduced glutathione, and vitamin C were observed.

The study of remote effects of polyols showed the presence of gonadotoxical action which is manifested in the reduction of the concentration of sperm in the epididymis suspension, time, mobility, osmotic resistance and increase the number of dead forms of acid resistance. Morphological assessment spermatogenic epithelium revealed a decrease spermatogenesis index, the number of tubules of the 12th stage of meiosis, normal form of spermatogones and growth in the number of desquamated tubular epithelium. Substances in doses 1/10 and 1/100 DL_{50} gave depressing effect on functional status and sperm spermatogenesis. Dose 1/1000 DL_{50} in subacute experiment was ineffective, that remained at general toxic action. At the same time polyols in 1/10 and 1/100 DL_{50} did not influence the number of live embryos resorption, corpora lutea of pregnancy, placenta weight, postimplantation death. POPP-294, and POPP-100 in 1/100 DL_{50} reduced the weight of the fetus, and overall increased preimplantation fetal death. In the study of embryonic differentiation of abnormalities in organs and tissues of white rats not found.

The study of mutagenic effect of POPP on red cells of cord of white rats showed that the substance in 1/10 and 1/100 DL_{50} significantly increased the percentage of cells with chromosomal disorders and decreased mitotic activity of cells. In a dose 1/1000 DL_{50} changes in the level of chromosomal aberrations and mitotic activity of red cells of bone marrow has not been established. The identified structural damage to the genetic apparatus was at the level of general toxic action.

Polyols do not give a positive reaction with intradermal, skin and conjunctival sensitization in guinea pigs. Specific lysis reactions of leukocytes, agglomeration of leukocytes, basophils damage posed in vitro after 24 hours after administration allowing doses were negative. This made it possible to suggest the absence of allergenic properties of this group of compounds. The symptoms of an allergic reaction of the skin, mucous membranes and the clinical picture were not observed, which allowed the group to exclude the presence of polyols and allergic sensitizing properties.

In the spleen and lymph nodes of experimental animals under the influence of polyols proliferative changes were identified, characterized by an increase in plasmocyte cell number. The increasing number of mature plasmocyte cells was also noted, plasmablasts as single cells, immature cells were observed slightly more often under the influence of 1/100 DL_{50} of polyols. In dose 1/1000 DL_{50} substance does not provide any significant effect on plasmocytic reaction of lymph nodes and spleen.

Thus, the studied group of polyols in certain exposure doses can alter the immunological reactivity of warm-blooded animals.

Study of polyols stability showed that the content in solution at 30^{th} day of the experiment was 50-96% of the original concentration. The rate of decay depended on the concentration of the substance. High polyols stability confirmed and indirect methods. POPP-294, POPP-100 and POPP-504 at the practical threshold for odor and taste retain odor and flavor within two weeks from the start of the experiment setting. Foam creating properties of substances are kept well in this period. All this has to indicate the high stability of polyols.

In aqueous solutions were identified qualitatively hydrocarbons (hexane, heptane, octane) acetaldehyde, acetone, methanol, ethanol, isobutanol, methyl ethyl ketone, ethyl acetate, dioxane and others. Availability of source products at the end of six months of exposure was also a direct confirmation of high studied the stability of xenobiotics. At the end of the experiment in aqueous

solutions of 60-80% of the original number of substances were stored.

For many products of transformation, hygienic standards were set in water reservoirs, the air of the working area and the soil. Most of the identified compounds are more toxic than the original material studied. Analysis and hygienic assessment of degradation products and polyols transformation allows us to talk about a wide range of biological effects. They can affect organs and systems of the body, being potentially dangerous in terms of the emergence of long-term effects. Some transformation products have neurotropic action. Others in certain concentrations influence the organoleptic properties of water and sanitary water mode.

Thus, studies of destruction and transformation are of great interest in the preparation of the forecast adverse for effects of xenobiotics on the sanitary condition of water and public health.

High stability of matters was confirmed by indirect methods. Foaming ability of agents, at the initial concentration of 20.0 mg/l, was kept throughout the observation period (15 days). At practical level, the threshold for bitter and astringent taste of aqueous solutions maintained for ten more days.

Both direct and indirect methods suggest that investigated polyols are highly stable and difficult for biological oxidation and hydrolytic degradation. This requires, in turn, the implementation of biological treatment of wastewater containing these chemicals, as well as justification release of sewage into the water. Chemical substances that enter the body of water with sewage, can change the organoleptic properties of water: odor, color, clarity, taste and foaming. The deterioration of organoleptic characteristics of drinking water can adversely affect the functional state of the cardiovascular, central nervous, respiratory and digestive systems. Polyols give the water an odor of petroleum products. The threshold of perception (intensity - 1 point) and practical threshold (intensity - 2 points) at 20^{o}C are at the following levels: 2.5; 51.04; 23.2; and 5.0; 105.8; 35.8 mg/l according to POPP-504, POPP-294, POPP-100.

Chlorination of water solutions of polyols with a starting concentration of 5.0; 10.0; 20.0; 40.0 and 80.0 mg/l is not accompanied by increased expression of existing and odors (chlorine dose was 0.5, 1.0, 2.0 mg/l). Heating water to 60^{o}C does not significant increase the odor. A more significant impact on odor is exerted by POPP-504. Threshold concentration of exposure to the smell is set at 5.6; 106.9 and 35.8 mg/l.

All compounds provide water solutions with bitter and astringent taste. The threshold of perception and practical threshold determination on these levels is 26.3; 30.5 and 24.26; 47.32 mg/l according to POPP-504 and POPP-100. POPP-294 at a concentration of up to 100.0 mg/l does not affect the taste of water solutions. Heating water solutions of substances to 60^{0}C does not lead to increased flavor or appearance of the water.

The substance does not affect the color and transparency of the water at concentrations up to 100,0 mg/l; opalescence and aqueous solutions are not detected. However, it should be noted that in shaking of aqueous solutions of polyols turbidity appears due to the formation of small and big grain foam. The nature of the foam and its stability is largely determined by the concentration of precursors. Threshold concentration of foaming is set at levels: 0.1; 0.3 and 2.0 mg/l, respectively for POPP-100, POPP-504 and POPP-294.

Thus, the studied group of polyols in certain conditions can give water the odor of oil, bitter, astringent flavor and cause foaming. At concentrations up to 100 mg/l, substances do not affect the color and clarity of aqueous solutions. Limiting organoleptic characteristics hazard is foaming.

In considering the question of the negative impact of harmful industrial waste water on water, special attention was paid to the impact on their health regime. Numerous studies have shown that these processes are based predominantly on biochemical conversion of organic matter connected with the life of saprophyte microflora. Indicators for the intensity of self-cleaning water are biochemical oxygen demand, the extent of mineralization and nitrification of organic compounds. For more complete disclosure of the POPP nature impact on water self-purification processes are additionally studied the dynamics of dissolved oxygen, the active reaction of water, developing water organisms (micro-algae, Daphnia, saprophyte microflora).

The most significant impact on the dynamics of biochemical oxygen demand in the investigated doses was exerted by POPP-294 and POPP-100, which are fully led to the disappearance of oxygen on the fifth day of the experiment at concentrations of 80.0 mg/l. Concentration thresholds set at 20.0 mg/l for POPP-294 and POPP-100 and 40.0 mg/l for POPP-504. In all cases, the concentrations of 10.0 mg/l of exposure were inactive.

Increased consumption of oxygen concentrations in 20.0; 40.0 and 80.0 mg/l began from the first day of the experiment and reached the maximum on the fifth day of observation. The substances did not reduce the rate of these processes, and in a dose-dependent effect, rather increased them, indicating the biochemical oxidation of organic compounds.

Investigated polyols in concentrations 5.0; 10.0; and 20.0 mg/l did not change the oxygen regime of water objects. In large doses dissolved oxygen decreased in the water compared to control by more than 20%. A clear influence on the content of dissolved oxygen in water was provided by POPP-294 and POPP-100. Threshold concentration appeared at 20.0 and 40.0 mg/l, respectively, for POPP-294 and POPP-504.

It is known that the transformation of chemicals in the aquatic environment can change the active reaction of water (pH), which in turn will contribute to the deterioration of the overall sanitary condition of water objects. At concentrations of polyols: 5.0; 10.0; 20.0; 40.0 and 80.0 mg/l, excess of pH: 6.5-8.5 was observed.

Investigated polyols inhibit the processes of mineralization of organic substances depending on the concentration in water reservoirs modeling. Polyols do not have an impact on the dynamics of accumulation of ammonia in all periods of observation in the studied concentrations. In studying the processes of mineralization second stage it appears that the dynamics of the formation of nitrite nitrogen is similar with that in the control ponds. All substances lead to increased accumulation of nitrate nitrogen. To a greater extent it is detected in model waters with concentrations of substances 40.0 and 80.0 mg/l.

Analysis of the results to determine which POPP-294 provides a somewhat more significant impact on the final stage of mineralization of organic substances.

The experimental results indicate that the observed increase in nitrogen as nitrate and inhibition of oxidation of organic compounds found in model waters. Maximum observed nitrate nitrogen by 18-20 days, and in the con-

trol ponds - 10-15 day follow-up. These results indicate mineralization inhibition processes of organic matter. The threshold concentration set at 10.0 mg/l for all compounds.

The influence of substances on aquatic organisms (Daphnia magna) showed that all compounds provided toxic effects of this type of protozoa. Concentration thresholds defined at these levels were 5.0; 10.0 and 20.0 mg/l for POPP-294, POPP-100 and POPP-504, respectively.

In solutions containing polyols studied at concentrations up to 20.0 mg/l, the growth of bacteria did not differ from controls. At the concentration of 40.0 mg /l more intensive growth of saprophyte microflora was observed, indicating that the stimulatory effect of substances on the growth of microorganisms. Threshold concentration for the whole group of substances was concentration of 20.0 mg/l.

Certain polyols concentration exert adverse effects on the different processes of self-purification of water, biochemical oxygen demand, dissolved oxygen, organic matter mineralization, growth and reproduction saprophyte microflora. Concentration thresholds are set at the following levels: biochemical oxygen demand - 10.0; 20.0 and 40.0 mg/l according to POPP-294, POPP-100 and POPP-504; dissolved oxygen in water - 20.0 mg/l; mineralization processes - 10.0 mg/l; saprophytic microflora - 20.0 mg/l for all substances.

Experimental study of influence on organoleptic properties of water and sanitary treatment of water allowed us to determine the potential danger of polyols for the conditions of water use. The coincidence of the results showed that limiting feature of harm in these studies is organoleptic, in particular, foaming.

Conclusions

Summary of hygienic rationing in the study group of POPP in water reservoirs shows that:

- All studied polyols include the category of high and in this regard highly desired degree of wastewater containing compound data;

- Polyols in certain concentrations can alter the organoleptic properties of water, giving it specific taste and smell of detergents, and some of them have an impact on the transparency and turbidity;

- The compounds have the ability to foam, by this indicator threshold concentration is 0.1; 0.3 and 2.0 mg/l respectively for POPP-100, POPP-504 and POPP-294;

- At concentrations of more than 10.0 mg/l substances are able to disrupt natural processes of self-purification of water objects, namely, the increase biochemical oxygen demand, reducing dissolved oxygen in the water, slow down the processes of mineralization of organic compounds. Threshold concentration of polyols in effect on Daphnia ranged from 5.0 to 10.0 mg/l. Depending on the concentration, they can stimulate or inhibit the growth and reproduction of microorganisms. Threshold concentration of exposure to medical treatment is 10.0 mg/l;

- Based on the parameters of acute toxicity of the substance, they are attributed to low-toxic (hazard class 4);

- The clinical picture is dominated by symptoms of poisoning polyols disorders of the central nervous, cardiovascular and respiratory systems. Differences species and gender sensitivity were found. Structural changes of internal organs are characterized by degenerative changes in the liver, kidneys, adrenal glands, spleen. All compounds in varying degrees, have skin-resorptive effect. Assessment of cumulative properties found that polyols relating to weakly cumulative compounds;

- The compounds provide significant impact on blood redox processes, activity oxidant-antioxidant system in the body of warm-blooded animals. Dormant dose in subacute experiment is 1/1000 DL_{50};

- Long-term effects of polyols appear at the same level with general toxic action. This substance inhibits the functional state of spermatogenesis and sperm. Embryotoxic effect is to increase pre- and postimplant death and total fetal death. Actions on the genetic apparatus polyols were not found. Sensitizing properties were not revealed;

- Polyols at general toxic doses exhibit inhibitory effect on cellular and humoral immunity;

- Limiting hazard rate for all connections - organoleptic (foaming);

- Maximum permissible concentrations are at levels: 0.1; 0.3 and 2.0 mg/l for POPP-100, POPP-504 and POPP-294, respectively.

Thus, polyoxypropylenpolyols which were studied, being biologically active compounds that stimulate the processes of free radical lipid peroxidation, cause the accumulation of peroxides, hydroperoxides, free radicals, diene conjugates malondialdehyde. However, as a result of microsomal oxidation of these substances are formed aldehydes, alcohols, ketones, i.e., substances that have radiomimetyc effects. The products of lipid peroxidation and metabolites biotransformation polyols reduce the activity of antioxidant systems, inactivate enzymes break the membrane structure and the state apparatus of the cell receptor blocking neurohumoral regulation of intracellular metabolism. These changes lead to disruption of bioenergetic and biosynthetic processes. Ridiomimetyc properties of polyols cause the development of free radical pathology in the body which is a conceptual model of the mechanism of biological effects.

References

1. Bagmut I. Yu. Izuchenie vliyaniya polioksipropilenpoliolov na immunologicheskuyu reaktivnost zhivotnyih v podostrom opyite i obosnovanie naibolee chuvstvitelnyih pokazateley diagnostiki immunologicheskih narusheniy / I. Yu. Bagmut // Visnyk problem biolohiyi i medytsyny. – 2010. – № 2. – P.24–25.
2. Barenboym G. M. Otsenka biologicheskoy opasnosti organicheskih ksenobiotikov / G. M. Barenboym, M. A. Chiganova, A. V. Aksenov // Metodyi otsenki sootvetstviya. – 2011. – № 7. – P. 28–33.
3. Bryantsev O. N. Toksikologo-gigienicheskaya harakteristika poliolov v svyazi s problemoy ohranyi vodnyih ob'ektov : avtoref. dis. na soiskanie uchen. step. kand. med. nauk / O. N. Bryantsev. – Rostov-na Donu, 2006. – 24 p.
4. Vliyanie polioksipropilenpoliolov na metabolicheskie protsessyi i funktsiyu detoksikatsii / A. V. Bondareva, L. I. Artyugina, I. Yu. Bagmut // Visnyk problem biolohiyi i medytsyny. – 2014. – Вип. 3, Т. 2 (111). – P. 110-113.
5. Vliyanie tehnogennyih himicheskih zagryazniteley okruzhayuschey sredyi na osnove poliproksipropilenpoliolov na generativnuyu funktsiyu i geneticheskiy apparat teplokrovnyih zhivotnyih / O. V. Zaytseva, V. A. Telegin, V. I. Zhukov [i dr.] // Problemy ekolohiyi ta medytsyny. – 2006. – T. 10, № 5-6. – P. 21-24.
6. Elizarova O. N. Opredelenie porogovyih doz promyishlennyih yadov pri peroralnom vvedenii / O. N. Elizarova. – M. : Meditsina, 1971. – 173 p.
7. Zhukov V. I. Vliyanie poliolov na okislitelnovosstanovitelnyie protsessyi u teplokrovnyih zhivotnyih v svyazi s problemoy ohranyi vodnyih ekosistem / V. I. Zhukov, O. V. Zaytseva, S. V. Pavlyicheva // Ekspery-

mental'na i klinichna medytsyna. - 2008. - № 2. - P. 107-112.
8. Mediko-toksikologicheskoe izuchenie poverhnostno-aktivnyih veschestv v svyazi s problemoy sanitarnoy ohranyi istochnikov pitevoy vodyi / N. G. Scherban, V. A. Kapustnik, V. V. Myasoedov [i dr.] // Mezhdunarodnyiy meditsinskiy zhurnal. – 2013. - № 2. – P. 116-120.
9. Mokienko A. V. Voda: k vzaimosvyazi gigienyi i ekologii / A. V. Mokienko // Voda: hihiyena ta ekolohiya. – 2013. - № 1, T. 1. – P. 20-34.
10. Rezunenko Yu. K. Osoblyvosti biolohichnoyi diyi polioliv na osnovi etylen i propilenhlikolyu za umov pidhostroho eksperymentu / Yu. K. Rezunenko // Dovkillya ta zdorov'ya. – 2012. - № 2. – P. 9-12.
11. Sirenko E. V. Vliyanie novyih grupp poliolov na sanitarnyiy rezhim vodoemov i esteticheskie pokazateli vodyi / E. V. Sirenko // Ekologiya i promyishlennost. - 2006. - № 1. - P. 39-43.
12. Antiirritant properties of polyols and aminoacids / C. Korponyai, R. K. Kovács, G. Erös [et al.] // Dermatitis. – 2011. - Vol. 22. - P. 141-146.
13. Effect of polyols P-5003-AC, P-373-2-20, P-294-2-35on the sanitary regime of water reservoirs and organoleptic properties of water in connection with the water reservoirs protection / V. Zhukov, O. Zaytseva, Y. K. Rezunenko // Am. J. Clin. Exp. Med. – 2013. – Vol. 1, № 1. – P. 16-19.
14. Kumar V. Effect of polyols on polyethylene glycol (PEG)-induced precipitation of proteins: Impact on solubility, stability and conformation / V. Kumar, V. K. Sharma, D. S. Kalonia // Int. J. Pharm. – 2009. – Vol. 366, № 1-2. – P. 38-43.
15. Politi R. The impact of polyols on water structure in solution: a computational study / R. Politi, L. Sapir, D. Harries // J. Phys. Chem. A. – 2009. – Vol. 113, № 26. – P. 7548-7555.

Матеріал надійшов до редакції 01.12.2016