TOXICOLOGIC AND HYGIENIC CHARACTERISTICS OF P-373-2-20; P-5003-AC; P-294-2-35 POLYOLS AND PROGNOSIS OF THEIR POTENTIAL DANGER FOR ENVIRONMENT

Kharkiv National Medical University, Kharkiv, Ukraine

ZHUKOV V., Dr. Sci. (Biology, Medicine), Professor, Chief of Department of Biochemistry

TELEGIN V., PhD (Medicine), Associated Professor

ZAYTSEVA O., Dr. Sci. (Biology), Professor

KNIGAVKO V., Dr. Sci. (Biology),Professor, Chief of Department of Medical and Biology Physics

GRAMATIUK S., Associated Professor

GRANKINA S., Assistant

LEVSHENKO T., Assistant

Abstract. *Studied the toxic effects polyoxipropylenpolyols in acute and subacute experiments on warm-blooded animals. It is established that they are pertained to the IV hazard class; have polytropic general toxic effect; on the level of toxic doses they influence on the generative function and the genetic apparatus; inhibit and disrupt the interaction between the cellular and humoral immunity.*

Key words: *xenobiotics, general toxic effect, the specific types of biological effects.*

Now it is clear that human activity can lead to a profound transformation of the biosphere, which adversely will affect on the vital functions. This requires intensification and expansion of knowledge about the biological effects of chemicals and prognosis ground of their potential danger for flora and fauna. Our knowledge about the possible consequences of xenobiotics effects are limited and are inadequate for the compounds to which people in the process of evolution had

never met. Emerged a significant gap between the high capacity of modern civilization to create a new chemical potential of our planet and the disabled man and the biosphere as a whole to accept the action of this potential with reasonable efficiency and without serious adverse consequences [1-3]. Currently, it is created such situation when the influence of combinations of different chemical compounds on humans and wildlife in general is difficult to predict. The uncontrolled use of chemicals can have irreparable consequences. This fully applies to the products of organic synthesis, which in volume of output and range of goods occupy a leading position in the world. These products include polyols of grades P-373-2-20, P-5003-AC and P-294-2-35, which are widely used in various sectors of the economy to produce polyurethanes, foamrubbers, thermoplastics, lacquers, enamels, hydraulic, and brake fluids, epoxy resins, plastics, artificial leather, etc. [1]. In order to avoid the harmful effects of application of chemicals a system of preventive measures is created, among which one of the main is toxicological assessment of xenobiotics and compounds, including their pre-selection for the postblowing production and use, limiting the exposure levels on the production and the environment.

The aim of this work was to study toxicologic and hygienic characteristics and prognosis of the potential danger to humans of a new group of chemicals - polyols of grades P-373-2-20, P-5003- AC and P-294-2-35.

Materials and research methods. The research program included the study of the polyoxipropylenpolyols effect on the organoleptic properties of water, natural purification processes in reservoirs, and influence on the warm-blooded animals under conditions of acute and subacute exposure [1-3]. Experiments were performed on adult Wistar white rats, white mouses, guinea pigs, hybrid mouse lines BALB / C, (SBAc57BL) F_1, CBA / Lac, and rabbits of the chinchilla race [4-6]. The objects of the investigation were polyoxipropylenthriols with molecular masses 5000M (P-5003-AC), and 370M (P-373-2-20), and polyoxipropylated amine with molecular mass 290M (P-294-2-35). The first priority was to establish the parameters of the toxicity, species sensitivity, cumulative properties of

xenobiotics under oral entrance into organism. We used conventional sanitary-chemical, physiological, toxicological, morphological, cytological, biophysical and statistical research methods [4]. In order to obtain toxicologic characteristics of the compounds and to substantiate features of the mechanism of biological, action we used a set of techniques for estimation of the status of various organs, systems and organism functions. Jaking into account that given substances have a low toxicity, haven't high-cumulative properties, in the subacute experiment we selected doses of 1/10; 1/100; 1/1000 DL_{50}. DL_{50} for the P-373-2-20, P-5003-AC, and P-294-2-35, respectively, is 32,3 g/kg; 36,2 g/kg and 14,8 g/kg of animal weight.

Results of research and their discussion. Experiments have shown that the test substances are low-toxic compounds (IV class of danger), haven't specific sensitivity and skin-irritating properties it is coordinates with results of [5], all compounds have weak skin-resorptive properties. Based on the coefficients of cumulation (C_c), they are low and moderate-cumulative substances (Table 1). The mean effective time (ET_{50}) of the animals death was in the range of the first day of observation.

Table 1. Parameters of polyoxipropylenpolyols toxicity

Substance	Species	DL_0, g / kg	DL_{50}, g / kg	DL_{100}, g / kg	ET_{50}, h	C_c
P-373-2-20	white rats	70,0	32,3±1,4	45,0	17,3	6,12
	white mouses	20,0	33,5±1,7	45,0	15,8	-
	Guinea pigs	20,0	35,0	45,0	16,7	-
P-5003-AC	white rats	20,0	36,2±2,3	50,0	20,3	7,35
	white mouses	20,0	38,3±1,6	50,0	19,8	-
	Guinea pigs	20,0	35,0	50,0	20,6	-
P-294-2-35	white rats	10,0	14,8±1,2	20,0	14,7	3,74
	white mouses	10,0	15,5±1,3	20,0	15,2	-
	Guinea pigs	10,0	15,0	20,0	16,4	-

The clinical picture of acute poisoning symptoms of disorders in breathing, hemodynamics and central nervous system are dominated. Polyoxypropylenpolyols at a doses of 1/10 and 1/100 DL_{50} reduced the percentage of increase in body weight, contents of erythrocytes, leucocytes, hemoglobin. Changes in the leukocyte formula of blood are not detected. Dose of 1/1000 DL_{50} had no effect on the indices of white and red blood. At the end of subacute experiment (on the 45th day of observation) there were significantly altered activities of the creatin phosphokinase (CPK), lactate dehydrogenase (LDG), aspartate and alanine aminotransferases (AsAT and AlAT), alkaline phosphatase (AlP), α-hydroxybutyrate dehydrogenase (α- GBDG), γ-glutamattranspeptidaze (γ-GT). All compounds had a unidirectional effect on the dynamics of the enzyme activity. In serum they increased the activities of CPK, AsAT, AlAT, AlP, γ-GT, LDG and decreased the activity of α-GBDG that witnesses about disorders of the redox processes in the body and the liver, kidneys, heart fuctions, that is, organs that play a leading role in the detoxication of xenobiotics (Table 2). Dose of 1/1000 DL_{50} had no effect on the dynamics of enzyme activity, which allowed to consider this dose inoperative.

Table 2. The enzyme activity in the subacute experiment on the 45th day of observation under the influence of 1/100 DL_{50} dose (M ± m) mcat / l

The enzyme	P-5003-AC	P-373-2-20	P-294-2-35	Control
CPK	10,46±0,35*	9,62±0,48*	12,30±0,43*	5,20±0,30
LDG	11,63±1,20*	10,34±0,65*	10,72+0,80*	7,80±0,40
AsAT	1,52±0,08*	1,43±0,22*	1,60±0,04*	0,90±0,04
AlAT	0,32±0,04*	0,35±0,06*	0,27±0,01*	0,100±0,001
AlP	10,30±0,43*	11,25±0,56*	9,80±0,30*	6,30±0,20

α-GBDG	6,54±0,15*	5,72±0,28*	5,43±0,20*	9,30±0,08
γ-GT	0,620±0,015*	0,64+0,04*	0,56±0,02*	0,20±0,01

Note: * - difference from control is valid, p<0,05.

An important step in hygienic regulation of harmful chemicals in the environment is to study the effects of the genetic apparatus and the generative function. Gonadotoxic effect of xenobiotics is studied in adult albino rats (males). Experiments have shown that the substances in doses of 1/10 and 1/100 DL_{50} reduce sperm motility, their number in the suspension of the epididymis, osmotic stability and acid resistance of spermatozoons in the background of increasing number of dead forms of sexual cells.

Morphological evaluation of spermatogenic epithelium showed a reduction in the index of spermatogenesis, the number of tubules with the 12th stage of meiosis, the number of normal forms of spermatogonia and the increase in the number of tubules with desquamated epithelium (Table 3).

Table 3. Long-term sequences of polyoxipropylenpolyols effect in dose of 1/100 DL_{50} in white rats (M ± m)

Parameter	P-5003-AC	P-373-2-20	P-294-2-35	Control
The functional state of sperm: motility time, min	137,2±4,8*	141,5±6,2*	129,8±4,5*	168,4±7,3
The number of spermatozoon's, million / ml	14,60±1,05*	12,3±1,2*	11,8±1,3*	21,4±4,4
The number of dead forms,%	9,30±0,67*	10,20±0,93*	8,60±0,72*	4,7±0,5
Osmotic stability,% NaCL	1,86±017*	1,9±2,2*	2,10±0,18*	3,70±0,15

Acid resistance, pH	4,50±0,35*	4,20±0,27*	4,60±0,32*	2,50±0,18
Morphological indicators of testicles: the index of spermatogenesis	2,30±0,18*	2,80±0,22*	2,70±0,25*	4,20±0,16
The number of spermatogonia	47,20±2,65*	49,60±1,87*	53,40±1,54*	69,80±3,14
The number of tubules with the 12th stage of meiosis	1,90±0,23*	2,10±0,18*	2,20±0,26*	4,10±0,35
The number of tubules with desquamated epitheliumlium	6,20±0,33*	5,70±0,24*	6,8±0,3*	2,70±0,17
Embryotoxicity: the number of the living embryos	7,10±0,36*	7,60±0,25*	6,80±0,37*	10,20±0,45
The number of resorption	1,7±0,2*	1,40±0,18*	1,80±0,23*	0,60±0,12
The number of yellow bodies of pregnancy	10,5±0,8*	11,3±0,65*	10,90±0,60*	11,3±0,7
Weight of fetus, g	2,90±0,16*	3,1±0,2*	3,20±014*	3,90+0,15
Weight of placentas, g	0,77±0,08*	0,78±0,06*	0,74±0,05*	0,51±0,13
Fetal death:				
before implantation	12,4±0,6*	13,20±1,05*	10,4±0,8*	5,30±0,26
after implantation	8,60±0,73*	7,20±0,65*	9,3±0,6*	3,30±0,35
total	21,00±0,65*	20,40±0,83*	19,70±0,65*	8,60±0,29
Influence on gene mutation: the number of cells with chromosomic aberrations,%	6,30±0,42*	5,90±0,35*	6,60±0,28*	0,75±0,10
The mitotic index of cells of bone marrow	2,20±0,18*	3,10±0,22*	2,00±0,16*	6,8±0,4

Note: * - difference from control is valid, $p<0,05$.

Evaluation of embryonic material obtained at autopsy albino rats (females), showed that the compounds in doses of 1/10; 1/100 DL_{50} reduced fetal weight and increased the amount of resorptions, the weight of placenta, pre-implantatic, postimplantatic, and total fetal death, rate. Xenobiotics in these doses did not have teratogenic effects. Determination of mutagenic activity of polyoxipropylenpolyols detected that the test substances increased the number of bone marrow cells with chromosomic aberrations. Among of them the single and paired fragments, dicentrics, translocations, breaks, ring chromosomes were frequently. The increase of chromosomic aberrations under doses of 1/10 and 1/100 DL_{50} was accompanied by a significant decrease in mitotic activity of bone marrow cells (Table 3). In all cases, the dose of 1/1000 DL_{50} had no effect on the generative function and the genetic system of warm-blooded animals. Toxicologic and hygienic characteristics of xenobiotics require the study of their influence on the immune system. The results of this research showed that the polyoxipropylenes in the doses of 1/10 and 1/100 DL_{50} reduce the hemolysin-producing, antibody forming, antigen-binding abilities of immune cells and their homotransplantatic activity. In the animals of experimental groups it was observed inhibition of functional activity of T-and B-lymphocytes, and their cooperative interaction in the implementation of the immune response to T-dependent antigen. At these doses the substances violated the differentiation of immune cells, protein and nucleic acid metabolism in the limphomyelocytes, inhibited the intensification of these processes during antigenic stimulation and decreased endocolony formation in tissues of immune system. The test substances in doses of 1/10 and 1/100 DL_{50} raised in the organism the level of circulating immune complexes and disrupted the morphological, biochemical and cultural properties of the microbiota of the gastrointestinal tract. In all cases the dose of 1/10000 DL_{50} was inoperative.

Analysis of the results allowed us to obtain toxicological and hygienic characteristics and detect the potential risk of polyoxipropylenpolyols for warm-blooded animals and humans.

Findings

1. Polyoxipropylenpolyols of grades P-5003-AC, P-373-2-20 and P-294-2-35 are low-toxic compounds (IV class of danger), haven't the specific and sexual sensitivities, as well as skin-irritating properties, had the weak skin-resorptive properties. Based on the cumulative coefficients they are low and moderate-cumulative substances. The clinical picture of acute poisoning the symptoms of the disorders in breathing, hemodynamics, and central nervous system, are dominated.

2. Substances in the subacute experiment under the influence of 1/10, 1/100 DL_{50} doses violate the redox processes, lead to the development of hypochromic anemia and leukopenia, cause structural and metabolic desorders in liver, kidney, heart - organs that play a leading role in the detoxication of xenobiotics.

3. Polyoxipropylenpolyols P-5003-AC, P-373-2-20 and P-294-2-35 in doses of 1/10 and 1/100 DL_{50} have a toxic effect on the generatic function and the genetic apparatus, and in doses 1/10, 1 / 100 and 1/1000 DL_{50} inhibit and disrupt the cooperative interaction of cellular and humoral immunity. In all cases, the dose of 1/10000 DL_{50} was inoperative, it is equal to 3.23; 3.62 and 1.48 mg / kg of animal weight, respectively, for P-373-2-20, P-5003-AC and P-294-2- 35.

List of reference

1. Жуков В.И., Кратенко Р.И., Резуненко Ю.К. и др. Медико-биологические аспекты проблемы охраны водных объектов от загрязнения поверхностно-активными веществами. Харьков: Торнадо, 2000. 390 с.

2. Цыганенко А.Я., Щербанъ Н.Г. Пивень В.В. и др. Токсиколого-гигиеническая характеристика фосфорсодержащих детергентов применительно к проблеме санитарной охраны водоемов. Белгород, 2001. 194 с.

3. Цыганенко А.Я., Щербанъ Н.Г., Бондаренко ЛЛ. и др. Методические основы регламентации сложных смесей: триэтаноловых солей алкилфосфатов и алкилполифосфатов в воде водоемов. Белгород, 2001. 178 с.
4. Каспаров А.А., Саноцкий И.В. Токсикометрия химических веществ, загрязняющих окружающую среду. М.: Центр междунар. проектов ГКНТ, 1986. 426 с.
5. Korponyai, C.,Kovács, R.K., Erös, G., Dikstein, S. & Kemény, L. (2011). Antiirritant properties of polyols and amino acids. Dermatitis, Vol. 22, pp.