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ORIGINAL ARTICLE

Hygiyenic Assessment of The Toxicological Propertiyes of The Biological Active Additive "Nutromix"

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ABSTRACT

This article incorporates information from India's «Hexagon Nutrition (Exports) Pvt. Ltd», the results of an experimental assessment of the toxicological safety of the biologically active additive «NUTROMIX™ vitamin & mineral food supplement» for children. The presence of 16 types of vitamins and minerals in the composition of the selected biologically active supplement «NUTROMIX» has been assessed for toxicological safety. Experimental studies were carried out on experimental animals (non-breeding white rats and mice, guinea pigs and rabbits) in accordance with the current normative-methodological base. The biologically active additive «NUTROMIX» has been evaluated for average death value (LD_{50}) when peroral is administered, cumulative effect (subchronic) of biologically active additive «NUTROMIX», mucosal irritating property of biologically active additive, sensitizing effect of biologically active additive. While experimental animals received the same amount of the inspection object corresponding to mg/kg of body weight at the 16-20 hours observation limit, animals in the control group received a suitable amount of distilled water. During the observation, the body weight of rats changed, but it turned out, no sharp difference in body weight changes was detected in the animals in the experimental group and in the animals in the control group. When assessing the toxicity indicators of the product, the animals in the experiment were monitored for 28 days (4 weeks) in accordance with the methodological manual. In the study of the acute toxicity of the biologically active additive «NUTROMIX» in experimental conditions, 2 types of laboratory animals (non-breeding white rats and mice) were administered orally with a gastric tube at the same time using Working Solutions, the amount of the drug in 2000, 4000 and 6000 mg/kg per kilogram of animal weight. The maximum dose of the biologically active additive sent to the stomach by experimental animals for study is calculated 12 times more than the daily physiological need of a person. In the following days, it was observed that the body weight of experimental animals increased, the survival of normal reactions to external influences, their general condition improved. The lack of records of deaths among experimental animals made it impossible to calculate LD50 (average death dose) for a sample of the biologically active additive «NUTROMIX» being studied. A 0.05 ml solution (2 drops) of «NUTROMIX» biologically active additive was dripped into the conjunctival space of the right eye of the guinea pig, while the Left Eye performed a control function. During the observation, no cases of hyperemia, irritation of the mucous membrane or blepharospasm were detected in animals under the experiment. Differences between the experimental and control groups were not detected on the results of macro - and microscopic examination of the studied organs. When all the animals in the experimental group were ruptured, no fluids were detected in the chest and abdomen. No changes were detected in the thyroid gland, the inner intima floor of the aorta, the pericardium, the shape and size of the heart, the left and right ventricles, trachea and large bronchi, the lining of the esophagus and stomach, the inner layers of the small and large intestines, the shape and size of the liver, pancreas, spleen, size and shape of the kidneys, adrenal glands, bladder, biologically active additive «NUTROMIX» - no negative changes were observed in the health cases of laboratory animals in which the experiment was carried out, non–toxic in acute experiments (Class 4 -

less toxic), cumulation was not detected, did not have an irritating and sensitizing effect, dystrophic, necrotic and inflammatory processes were not detected in internal limbs.
Keywords: *Nutromix, toxicological safety, experiment, LD_{50}*

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INTRODUCTION

The problem of maintaining and strengthening the health of different layers of the population, as well as children and adolescents, is one of the priority tasks for all developed countries of the world. The role of healthy, safe nutrition in the normal growth and development of the growing body is incomparable.

Biologically active additives and food additives, which are safe in world experience, are widely used today to prevent macro and micronutrient deficiencies of the growing organism (15,16,17,18,26,27). Today, their widespread use is considered one of the leading conditions affecting the processes of lack of macro and micronutrients in different seasons of the year and their active development. The development of these conditions is followed by the failure of a healthy lifestyle and healthy diet.

The main attention of child and adolescent hygiene specialists should be focused on issues related to ensuring favorable conditions for the harmonious development of the children's contingent and the harmonious formation of health status, namely: they, sanitary-hygienic and epidemiological procedures, organization of treatment-sanitization and educational processes, consists in improving the order and efficiency of medical services (5,6,9,10,15). The relevance of these specified hygienic requirements in the modern socio-economic and medical-demographic situations, in the implementation, the role of preschool education organizations is increasing.

Social and hygienic tasks aimed at strengthening the health of the next generation are carried out in pre-school educational organizations, the main thing is to adapt their daily routine to hygienic requirements, by increasing physical activity, ensuring healthy nutrition, through the education of each state and nation, and by protecting the health and prevention of diseases of the growing organism. is one of the main criteria for the implementation of genuine care [4,5,6,10,15,18].

In the decision of the President of the Republic of Uzbekistan dated November 10, 2020 No. 4887 "On additional measures to ensure healthy nutrition of the population", further strengthening of the state policy in ensuring healthy nutrition and physical activity of the population, further increasing the effectiveness of the work carried out in the prevention of non-communicable diseases, each in order to form a culture of healthy eating and physical activity of the citizen, it is established to provide children aged 6-23 months with micronutrient powder and vitamin "A" for children aged 6 months to 5 years at the expense of budget funds (6,9,10,15 , 16,17, 26,27).

The adoption of laws and decisions by our government (1, 2,3) has been assigned a number of tasks aimed at strengthening and protecting the health status of the population, including children of preschool age who are often ill, and providing food rations with micronutrients that are toxicologically safe and do not have a harmful effect on the body. enrichment consists in increasing the resistance of the children's organism to the influence of various factors of the external environment (7,8,11,24,26,27), reducing the level of morbidity of children is one of the urgent problems today.

The purpose of the study. It consists in evaluating the effect of biologically active supplement "NUTROMIX" on the growing organism from the point of view of toxicological safety in experimental conditions.

MATERIAL AND METHODS

In the study, for use by us in scientific research work, India's Hexagon Nutrition (Exports) Pvt. The biologically active additive "NUTROMIXTM vitamin & mineral food supplement" produced for children by the company Ltd. was selected and its toxicological effect on the organism of animals and its safety were evaluated under experimental conditions. The composition of the selected "NUTROMIX" biologically active supplement is a mixture of vitamins and minerals, 1 gram is issued based on special requirements, it contains 16 types of vitamins and minerals, and we will dwell on their classification during research.

In order to assess the toxicological safety of the biologically active supplement "NUTROMIX" in experimental conditions, it was conducted in the Department of Sanitary and Epidemiological Control of the General Directorate of Medicine under the Administration of the President of the Republic of Uzbekistan. We evaluated the average lethal value (LD_{50}) of the biologically active additive "NUTROMIX"

when administered orally, the cumulative effect (subchronic) of the biologically active additive "NUTROMIX", the effect of the biologically active additive on mucous membranes, the sensitizing effect of the biologically active additive.
GOST 32641 "Methods for checking the effects of chemical products on the human body. Determination of toxicity in rodents by repeated/multiple oral administration of a substance. The multi-dose toxicity level of the substances in the biologically active supplement was evaluated by the international standard "28-day test" (12).
The level of acute toxicity of biologically active substances was assessed based on the requirements of methodological recommendation No. 012-3/0244 "Acute oral toxicity - method of dividing acute toxicity into classes" (23);
The toxicological indicators of the biologically active additive "NUTROMIX" were evaluated on the basis of the methodological recommendation No. 012-3/0312 "Instructions for toxicological testing of food and biologically active additives" (24).
The amount of ingredients in the biologically active additive "NUTROMIX" SanQvaN No. 0366-19 "Hygienic requirements for the safety of food products" (21), No. 0338-16 "Hygienic requirements for the production and circulation of biologically active additives" (19), No. 0347-17 "Physiological norms of nutrition and energy requirements for gender, age and professional groups of the population of the Republic of Uzbekistan to ensure healthy nutrition"(20), SanPiN Standards No. 0016-21 "Organizing safe and quality nutrition of children raised in preschool educational institutions of the Republic of Uzbekistan Hygienic requirements" (22) were assessed for compliance with the requirements of sanitary rules and norms.
UzDST 8.072:2018. According to the requirements of the state standard, taking into account the number of animals participating in each experiment (25), relying on the 5% level of confidence ($P>0.05$), it was evaluated by the Student's t-test.
Experimental studies were carried out in experimental animals (white rats and mice, guinea pigs and rabbits) in accordance with the current regulatory and methodological framework. The manual "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" was used.
Statistical analysis was carried out using the Microsoft Excel computer program in accordance with the methodological recommendations "Use of evidence-based medical principles in the organization and conduct of hygiene research". Comparisons of samples were performed using Student's test (t), with differences considered significant at $R<0.05$.

RESULTS AND DISCUSSION

Vitamins and minerals contained in the biologically active supplement "NUTROMIX" play an important role in the normal growth and development of the child's body, and in the normal course of the metabolism of substances and energy in the body.
In order to eliminate the deficiency of micronutrients in the body of children of preschool age and to additionally use it as a preventive ration to enrich the content of the food products consumed daily, we found it permissible to analyze the composition and the amount of ingredients of the biologically active supplement "NUTROMIX" in order to fulfill the purpose of the research, and the composition and its the results are presented in Table 1.
As can be seen from the analysis of the data presented in Table 1, the biologically active supplement "NUTROMIX" is produced in the form of powder in a sachet.
The analysis of the amount of vitamins in the biologically active supplement shows that the amount of vitamin A is 88.88% of the daily norm, the amount of V1, V2 and V6 is 83.33%, and the amount of vitamins C and E and iron microelements is marked.
The amount of iodine is 81.81% of the norm, and when added with the amount of iodine contained in the salt consumed in general, it becomes the basis for ensuring the daily intake of children. The fact that this biologically active supplement is enriched with zinc and selenium is the basis for strengthening the immune system of children and increasing their resistance to unfavorable factors of the external environment.

Table 1: The amount of vitamins and minerals contained in the "NUTROMIX" biologically active supplement (compared to the product in 1 gram sachet)

Ingredients	Quantity	SanPiN Standards (016-2021)
Vitamin A (Vitamin A Acetate), µg	400 µg	450 µg
Vitamin V1 (Thiamine Mononitrate), mg	0,5 µg	0,6 µg
Vitamin B2 (Riboflavin), mg	0,5 µg	0,6 µg
Vitamin V6 (Pyridoxine), mg	0,5 µg	0,6 µg
Vitamin V12 (Cyanocobalamin), µg	0,9 µg	1,2 µg
Vitamin C (Accorbic Acid), mg	30 µg	30 µg
Vitamin D (Cholecalciferol), µg	5,0 µg	10,0 µg
Vitamin E (Vitamin E Acetate), mg	5,0 µg	5,0 µg
Folic acid, µg	90 µg	200 µg
Niacin (Niacinamide), mg	6,0 µg	8,0 µg
Copper (Copper Gluconate), mg	0,56 µg	0,8 µg
Iodine (Potassium Iodide), µg	90,0 µg	110,0 µg
Iron (Ferrous Fumarate), mg	10,0 µg	10,0 µg
Zinc (Zinc Gluconate), mg	4,1 µg	8 µg
Selenium (Sodium Selenite), µg	17,0 µg	22,0 µg
Maltodextrin, silicon dioxide	-	-

When the organoleptic and biological value indicators of the product were studied, the following was revealed: appearance - powder; color – white-yellowish; taste and smell - most of the raw materials used in production correspond to the taste and smell of the product.

As a result of the toxicological laboratory examination, administration of biologically active additive "NUTROMIX" into the stomach of laboratory animals and toxicological assessment of clinical signs of intoxication during experimental observation, risk classification was evaluated based on the data obtained as a result of observations.

An aqueous suspension of the powder in a sachet (solubility in water is 100%) was used in accordance with the requirements of normative and methodological documents to evaluate the toxicological parameters of the biologically active additive "NUTROMIX". Distilled water was used as solvent.

Experimental animals received the same dose of the test substance in mg/kg of body weight within 16-20 hours of observation, while animals in the control group received the same amount of distilled water. Feeding of the animals was done 3 hours after administration of the amount of the product.

Mortality/paralysis indicators of experimental animals - body weight, hematological and biochemical indicators of blood were evaluated daily from the first day to the last day of the experiment during acclimatization, before receiving biologically active supplements and after the end of the experiment.

Daily during the acclimatization period and 4 times (1, 2, 3 hours, and 4 hours) on the first day after dosing, and then once daily for the duration of the study depending on the appearance of clinical signs of toxicity.

After the end of the experiment, all experimental animals were put into deep sleep by ether anesthesia and euthanized. Macro- and microscopic preparations were prepared to study the morphological changes. Materials from each organ or tissue were not used for other purposes. Used biomaterials were destroyed in the established order.

Acute poisoning in the assessment of toxicological indicators.

In experimental conditions, the maximum amount of biologically active supplement sent to the stomach of animals was 12 times more than the daily physiological need of a person, and in the following days, it was observed that the body weight of the experimental animals increased, normal reactions to external influences were preserved, and their general condition improved.

During the study, the experimental animals were active, orderly, ate food with appetite, their fur was smooth and shiny, and it was found that the animals reacted well enough to external influences.

The results of the evaluation of the LD_{50} mg/kg mortality rate of the biologically active additive "NUTROMIX" are presented in Table 2.

Table 2: Results of evaluating the mortality rate of biologically active supplement "NUTROMIX"

Name of the drug	value, mg/kg	Number of experimental animals/number of animals killed	Clinical presentation of poisoning	LD_{50}, mg/kg
«NUTROMIX»	2000	6/0	not identified	>6000 мг/кг
	4000	6/0		
	6000	6/0		

As can be seen from the results presented in Table 2, it was not possible to calculate the LD50 (median lethal amount) for the sample of biologically active additive "NUTROMIX" under study due to the fact that there were no deaths among the experimental animals.
Observations after acute poisoning of experimental animals revealed that this biologically active supplement falls into class IV (low risk) according to the requirements of the international standard GOST 12.1.007 (14).

Results of evaluating the effect of "NUTROMIX" on the mucous membrane of the eye

0.05 ml solution (2 drops) of biologically active supplement "NUTROMIX" was instilled into the conjunctival space of the right eye of a guinea pig, and the left eye served as a control. The effect of this active ingredient on the mucous membrane of the eye was studied in 3 experimental animals, and the results obtained are presented in Table 3.
No cases of hyperemia, mucosal involvement, or blepharospasm were detected in the experimental animals during the follow-up.
The mucosal exposure (Iir) after eye contact of the biologically active additive resulted in a mean group summary score of 0 (see Table 3).

Table 3: Results of evaluating the effect of biologically active additive "NUTROMIX" on the mucous membrane of the eye (in points)

The name of the biologically active additive	Conjunctival hyperemia	Edema formation	Ptosis or blepharospasm	The formation of fistulas in the eyes	Iir, score
«NUTROMIX»	0/3	0/3	0/3	0/3	0

As can be seen from the data presented in Table 3, the biologically active supplement "NUTROMIX" does not affect the mucous membrane of the eye (Iir = 0 points).

Cumulative effect of "NUTROMIX" biologically active supplement (subchronic experience).

Cumulative properties of the biologically active supplement "NUTROMIX" were studied in white rats weighing 140-160 grams using the method developed by Lim A et al.
In order to study the cumulative nature of the tested biologically active supplement, it was injected into the stomach of rats for 28 days.
The initial dose was 1⁄10 of the maximal tolerance determined by increasing it by 1.5 times every 4 days, which was 4.5 times higher than the initial amount.
Control animals received an equivalent dose of distilled water. The following parameters were observed on the experimental animals during all periods of the tests: survival during the experiment, general condition, animal activity, food consumption, water consumption, body weight dynamics, morphological composition of blood, biochemical indicators of blood.
No changes in behavior were observed in the animals of the experimental group. Just like the control group animals, they became active, tidy, ate well and reacted well to external stimuli. Cases of poisoning and death were not recorded.
As can be seen from the tables presented below, the animals were allocated based on the same results in initial body weight. Observations on changes in body weight showed that body weight increased uniformly, with no difference in the rate of body weight increase in the experimental group when compared to the control group (see Table 4).

Table 4: Dynamics of body weight change of experimental animals rats (in %)

Follow-up period	Group of animals	
	Control group, distilled water was sent	"NUTROMIX" is biologically active
Before sending	100,0	100,0
After sending	145,0	145,3

When examining the hematological indicators in the peripheral blood of experimental animals, no reliable changes were detected in any of the studied parameters.
Hematocrit indicators, hemoglobin content, thrombocrit, leukocyte and erythrocyte content in all experimental animals did not have a statistical difference from the indicators of the control group (see Table 5).
It is known that multiple ingestion of any foreign substance in a short period of time can lead to its accumulation in the body or a cumulative effect in the form of a violation of biochemical processes, in which changes in biochemical indicators are noted much earlier than changes in the structure and histogram of internal organs.

Clarification of the extent and nature of such exposures may inform the likelihood of developing chronic toxicity.

Table 5: Average morphological indicators of blood of rats in the study of the subchronic effect of biologically active supplement "NUTROMIX"

Groups	Follow-up period	Hematological parameters				
		Hematocrit, %	Hemoglobin concentration g/l	Thrombocrit, %	Leukocytes, 10^9/l	Erythrocytes, 10^{12}/l
Control group (dist.water)	before sending	36,6±1,1	136,8±2,3	0,438±0,05	14,61±0,39	6,80±0,18
	after sending	37,5±1,6	137,6±5,3	0,467±0,04	14,57±0,60	6,67±0,15
Experimental group	before sending	33,8±1,2	131,8±4,2	0,459±0,04	14,65±0,53	6,67±0,13
	after sending	34,9±0,5	142,4±2,4	0,450±0,02	14,58±0,59	6,62±0,25

The amount of hemoglobin increased by 7.14% after the administration of the biologically active supplement NUTROMIX, which was carried out under experimental conditions, and the results show that the regurgitated protein among children is the basis for preventing energy deficiency. It shows that the amount of erythrocytes has increased by 1.16%.

The results of biochemical indicators in blood are presented in Table 6.

Table 6: Biochemical parameters of the blood of rats in the study of the subchronic effect of the biologically active supplement "NUTROMIX"

Groups	A statistician. indicators	Follow-up period, in weeks *	Biochemical indicators			
			ALT, IU/l	ACT, IU/l	ALP, E/l	TP, g/l
Control group (distilled water)	M±м	0	54,2±2,8	118,5±11,6	34,1±2,3	68,3±5,6
	M±м	4	55,3±5,2	113,5±8,9	32,4±2,9	65,5±2,6
Experimental group	M±м	0	53,2±3,7	116,4±5,17	32,6±5,6	62,0±0,5
	M±м	4	55,2±2,5	112,0±5,26	36,2,±7,5	66,2±0,7

The tests revealed that the activity of transaminase enzymes (AST and ALT) and alkaline phosphatases (ALP) in the experimental animals did not have a reliable difference from the control group.

Also, the total protein (TP) content of the control and experimental groups was statistically the same (see Table 6).

Pathomorphological examinations were carried out the day after the introduction of poled. No differences were found between the experimental and control groups on the results of macro- and microscopic examination of the studied organs.

No fluid was detected in the thoracic cavity and abdominal cavity when the animals of all experimental groups were dissected.

Thyroid gland, intima layer of the aorta, pericardial plate, shape and size of the heart, left and right ventricles, trachea and large bronchi, esophagus, mucous membrane of the stomach, inner layers of the small and large intestines, shape and size of the liver, pancreas, spleen, no changes were detected in the size and shape of kidneys, adrenal glands, urinary bladder, uterine body of females, testicles of males.

Pathologoanatomical examinations, determination of relative weight coefficients of internal organs and microscopic examinations of some organs showed that the biologically active supplement "NUTROMIX" did not cause toxic degenerative changes in lymphoid and internal organs, which are extremely important, no differences between the experimental and control groups were detected.

The summarized results of the cumulative effect of the biologically active supplement "NUTROMIX" are presented in Table 7.

Table 7: Results of evaluation of the cumulative effect of "NUTROMIX" biologically active supplement

Research indicators	"NUTROMIX" biologically active additive
General condition	Fits
Hematological parameters	Fits
Biochemical indicators	Fits
Organ and tissue examination	Fits

Thus, when the NUTROMIX biologically active supplement was injected into the stomach of experimental animals in high amounts for 28 days, no deaths were observed, no changes in their physiological parameters were detected, no dystrophic or destructive changes in their parenchymatous cells, and no signs of exposure to the mucous membranes of the gastrointestinal tract.
According to the integrated indicators of subchronic toxicity: "NUTROMIX" biologically active additive does not have toxicity and does not have cumulative properties.
Results of evaluation of sensitizing effect of "NUTROMIX" biologically active additive.
The sensitizing effect of biologically active additive "NUTROMIX" was evaluated by scarification test method.
The study of the effect of the tested biologically active additive on sensitivity was carried out by using the working solution of the test sample of the biologically active additive "NUTROMIX".
The method of studying the effect of local irritation on the skin was carried out in a 4-hour period on purebred white laboratory rats.
The animals were treated with the working solution of the test sample on the cut of the skin.
Wipes moistened with the sample solution were applied to the skin under an occlusive dressing and left for 4 hours, after which the bandage was removed and the skin surface was examined.
Response evaluation results of a single application test. No signs of intoxication or death were observed in animals during this method of inspection.
In order to determine repeated toxicological poisoning in white rats, it was studied by applying each sample to 20 skins for 4 hours a day for a week.
Results of evaluation of samples of repeated use. During the experiment, animal death and clinical signs such as intoxication were not observed.
Special equipment was allocated to determine the skin resorptive effect of white rats.
The tails of the experimental animals were immersed in special containers with working solutions of the sample for 4 hours.
Conditions and changes that violate the integrity of the skin were not observed in animals.
Results of evaluation of the skin resorptive effect of biologically active supplement "NUTROMIX".
No cases of toxic poisoning and death were detected during observation of experimental animals, it has no sensitizing properties (Iir, equal to 0 points), allergies did not develop.

CONCLUSION

In conclusion, it should be noted that India's "Hexagon Nutrition (Exports) Pvt. Biologically active additive "NUTROMIX" produced by Ltd. company - no negative changes were observed in the health conditions of experimental animals, it is not toxic in acute experiments (class 4 - low toxicity), accumulation was not detected, it has no impacting and sensitizing effect, dystrophic in internal organs, necrotic and inflammatory processes were not detected.

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