ASSESSING TOXICITY AND HAZARD OF AGIDOL-1, THE VITAMIN E SYNTHETIC ANALOGUE

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Agidol-1 belongs to non-enzymatic antioxidants and represents a synthetic vitamin E analogue, it is widely used in chemical and food industries, livestock production, cosmetology, perfumery and pharmaceutical production. The increase in its production is a prerequisite for creating optimal working conditions for employees and developing the currently not existing hygienic standard of the tentative safe exposure level (OBUV) in workplace air. The study aimed to develop and substantiate agidol-1 OBUV in workplace air through experimental study of toxicity and hazard. We studied toxicity, irritant, skin-resorptive effects and hazard of agidol-1 concentrations of 24.7 and 67.8 mg/m^3 after a single inhalation. Integrated indicators and functional indicators of some organs and systems were assessed in rats after inhalation. It has been shown that based on toxicometry data (DL_{50}) after a single intragastric injection to mice agidol-1 is a moderately dangerous substance (hazard class 3), while when administered to rats it is a slightly dangerous substance (hazard class 4). The substance has no irritant effect on the rabbit ocular mucosa and skin, it does not possess skin-resorptive or cumulative activity. Inhalation of agidol-1 concentrations of 24.7 and 67.8 mg/m^3 has no toxic effect on the nervous, carviovascular, and respiratory systems, it does not alter peripheral blood composition and biochemical parameters of blood serum and urine. The lack of agidol-1 harmful effects in the study, availability of MPC levels in ambient air for the Agidol brand substances with the chemical composition similar to that of agidol-1 and hygienic standards for agidol-1 in different countries have made it possible to substantiate OBUV for production facilities of 10 mg/m^3, aerosol, hazard class 4.

Keywords: agidol-1, toxicity, hazard, hygienic standardization

Author contribution: Golubeva MI — describing the results, literature review, manuscript writing; Sheina NI — literature review, describing the results, manuscript writing and formatting; Bidevkina MV — describing the results, manuscript w, processing and describing the study results; Bobrineva IA — testing, processing and describing the study results; Fedorova EA — experimental procedure, processing the study results.

Compliance with ethical standards: the experimental study was compliant with the necessary legal acts (Declaration of Helsinki 2013, GOST 33044-2014 “Principles of Good Laboratory Practice”; Order of the Ministry of Health of the RF No. 188n of 01.04.2016 “Rules of Good Laboratory Practice”). The study was approved by the Ethics Committee of the Pirogov Russian National Research Medical University (protocol No. 10/23 dated 15 May 2023).

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Received: 01.09.2024 **Accepted:** 16.02.2025 **Published online:** 30.03.2025

DOI: 10.24075/rbh.2025.125

ИЗУЧЕНИЕ ТОКСИЧНОСТИ И ОПАСНОСТИ АГИДОЛА-1 — СИНТЕТИЧЕСКОГО АНАЛОГА ВИТАМИНА Е

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Агидол-1 относится к неферментным антиоксидантам и является синтетическим аналогом витамина Е, он широко используется в химической и пищевой промышленности, животноводстве, косметологии, парфюмерной промышленности и фармацевтике. Увеличение объемов его производства является предпосылкой для создания оптимальных условий труда работников и разработки отсутствующего в настоящее время гигиенического норматива — ориентировочный безопасный уровень воздействия (ОБУВ) в воздухе рабочей зоны. Целью работы было разработать и обосновать ОБУВ агидола-1 в воздухе рабочей зоны посредством экспериментального изучения токсичности и опасности. Изучены токсичность, раздражающее, кожно-резорбтивное действие и опасность агидола-1 в концентрациях 24,7 и 67,8 мг/м^3 после однократной ингаляции. После ингаляции у крыс оценивали интегральные показатели и функциональные показатели отдельных органов и систем. Установлено, что по показателям токсикометрии (DL_{50}) при однократном внутрижелудочном введении мышам агидол-1 относится к умеренно опасным веществам (3-й класс опасности), а при введении крысам — к малоопасным веществам (4-й класс опасности). Вещество не оказывает раздражающего эффекта на слизистую оболочку глаза и кожу кролика, не обладает кожно-резорбтивным действием и кумулятивной активностью. Ингаляция агидола-1 в концентрациях 24,7 мг/м^3 и 67,8 мг/м^3 не оказывает токсического действия на нервную, сердечно-сосудистую и дыхательную системы, не изменяет состав периферической крови и биохимические параметры сыворотки крови и мочи. Отсутствие вредных эффектов агидола-1 в проведенном исследовании, наличие ПДК в атмосферном воздухе для веществ марки «Агидол», близких по химическому строению к агидолу-1, а также гигиенических нормативов агидола-1 в разных странах позволили обосновать ОБУВ для производственных помещений 10 мг/м3, аэрозоль, 4-й класс опасности.

Ключевые слова: агидол-1, токсичность, опасность, гигиеническое нормирование

Вклад авторов: М. И. Голубева — описание результатов, работа с литературой, написание рукописи; Н. И. Шеина — работа с литературой, описание результатов, написание и оформление статьи; М. В. Бидевкина — описание результатов, написание статьи, обработка и описание результатов исследования; И. А. Бобринева — проведение исследований, обработка и описание результатов исследования; Э. А. Федорова — проведение эксперимента, обработка результатов исследования.

Соблюдение этических стандартов: экспериментальное исследование проводили с соблюдением необходимых нормативных актов (Хельсинкской декларации 2013 г., ГОСТ 33044-2014 «Принципы надлежащей лабораторной практики»; приказа МЗ РФ № 188н от 01.04.2016 «Правила надлежащей лабораторной практики»). Исследование одобрено этическим комитетом ФГАОУ ВО «Российский национальный исследовательский медицинский университет имени Н. И. Пирогова» Минздрава России (протокол № 10/23 от 15 мая 2023 г.).

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Статья получена: 01.09.2024 **Статья принята к печати:** 16.02.2025 **Опубликована онлайн:** 30.03.2025

DOI: 10.24075/rbh.2025.125

Synthetic non-enzymatic antioxidants are widely used in almost all areas of human life and activity, and the importance of those is constantly growing. Their effects aim to inhibit oxidative activity of free radicals and other substances, since oxidative processes can impair the properties of polymeric materials, oils used in industry, reduce the quality of food products, etc. [1–3]. Antioxidants play an important role in comprehensive approaches to disease treatment and prevention allowing one to adjust the diet and prevent a number of disease processes in the body [4].

Antioxidants are extensively used as food additives to improve stability of food products. These ensure extended shelf life of food products, preservation of nutritional value, natural color and flavor. Antioxidants are contained in pharmaceutical and cosmetic preparations, these are used in livestock production when producing animal feed and to increase productivity [5–9].

In addition to natural antioxidants, an example of which is vitamin E in foods, there are antioxidants obtained through organic synthesis, i. e. synthetic ones, such as propyl gallate (PG, E310), tert-butylhydroquinone (TBHQ, E319), butylated hydroxyanisole (BHA, E320), and butylated hydroxytoluene (BHT, E321). The latter, BHT or agidol-1 represents one of widely demanded synthetic antioxidants.

It is used to produce petroleum products, synthetic rubbers, plastics, elastomers, oils, waxes, soap, paints, and ink [1, 2]. Agidol-1 is a synthetic vitamin E analogue registered and licensed for cosmetics and packaging materials, food products and animal feed. Thus, in cosmetology, it is used as an additive when producting suppositories, creams, gels, and skin care products [10–12]. Manufacture of cosmetics, perfumes and pharmaceuticals, food products (food additive E321) require the use of agidol-1 having a Vulkanox BHT GMP Grade specification, which ensures microbiological purity of the product and the quality compliant with the HACCP (Hazard Analysis and Critical Control Points), GMP standards.

Agidol-1 as a food additive E321 is widely used to produce various confectionery, dairy products, soft drinks, alcoholic beverages, etc. The E321 food additive content standards have been established for food products, which are 100–200 mg/kg of the final product, and permissible daily intake of E321 with food products of 0.125–0.3 mg/kg/day [13–15].

Taking into account the widespread use of agidol-1 as a synthetic antioxidant and the increase in its production, it is necessary to develop a hygienic standard (tentative safe exposure level, OBUV) in workplace air, which is currently unavailable. In turn, OBUV substantiation is an essential requirement for creating optimal working conditions for workers in chemical, food and chemical-pharmaceutical industries.

The study aimed to perform experimental assessment of agidol-1 toxicity and hazard in order to estimate its workplace safety.

METHODS

Butylated hydroxytoluene (Butylhydroxytoluenum, BHT), the aromatic hydrocarbon, phenol derivative ($C_{15}H_{24}O$), was the study object. Its chemical names are as follows: 2,6-bis(1,1-dimethylethyl)-4-methylphenol; 2,6-Di-tert-butyl-4-methylphenol; 2,6- Di-tert-butyl-4-hydroxytoluene; 2,6- Di-tert-butyl-p-cresol. Synonims: Dibunol, Ionol. CAS: 128-37-0, molecular weight 220.35 g/mol. Tradenames: agidol-1 crystal mark A; food additive E321. This is a white crystalline substance, odorless or with a characteristic faint odor. T_m = 69–73 °C. It is almost insoluble in water, soluble in 96% alcohol, acetone, organic solvents, esters, fats [16–19].

Determination of the dispersion of agidol-1 dust particles has shown that the sample of the test substance is homogeneous, it consists mainly of large particles (1000 μm and more), the presence of a small number of medium size particles (about 20–100 μm) has been reported; the ratio of the first and the latter is 9 : 1. The mixture of substance particles after mechanical grinding was used for inhalation: particles sized 50–200 μm (70%), 10–50 μm (20%), and less than 10 μm (10%).

Experimental studies of toxicometry parameters and prediction of safe industrial exposure levels were conducted in accordance with the current legislation [20–23]. The experiments involved laboratory animals: outbred white mice and white rats, albino guinea pigs, chinchilla rabbits (Andreevka branch of the Scientific Center for Biomedical Technologies of FMBA of Russia). The animals quarantined for 10 days were kept under standard vivarium conditions with ad libitum access to water and food.

The agidol-1 toxicometry parameters (DL_{50}) were determined when performing intragastric administration of the substance to both male and female mice (24 males, 18 females) and male rats (18 animals), as well as when performing intraperitoneal administration to male mice (24 animals). The DL_{50} determination groups consisted of 6 animals each. The average lethal doses were calculated by probit analysis modified by V.B. Prozorovsky.

The irritant effect was assessed through a single injection of 50 mg of the substance into the conjunctival sac of the rabbit eye (3 animals), while the skin irritant effect was assessed through a single or repeated application of 500 mg of the substance in the form of suspension in starch gel (1 : 1) to the depilated skin of the rabbit back (3 animals) for 4 h. The skin-resorptive activity of the substance was assessed in male mice by dipping 2/3 of the tail length in the test substance suspension in starch gel, i.e. by the test-tube method. Tails of the control mice were dipped in the starch gel. The control and experimental groups consisted of 6 animals each. The 2-h applications were made daily throughout 4 weeks (5 days a week). The agidol-1 cumulative activity was assessed in male mice with intragastric administration of the increasing doses of the test substance in starch gel throughout 24 days by the method by Lim et al. [24]. Initial dose was 150 mg/kg (0.1 DL_{50}). The control animals were subjected to intragastric administration of starch gel. Experimental groups consisted of 10 animals each.

Taking into account low melting point (69–73 °C) of the studied agidol-1, we studied inhalation hazard of the substance under conditions of static inhalation. Single inhalations of outbred male rats were performed in the specialized sealed 200 L chambers for 4 h. Each group consisted of 8 animals. To record manifestations of poisoning in rats, integral parameters (body weight, body temperature), indicators of functional state of certain organs and systems (nervous, cardiovascular and respiratory systems), peripheral blood composition, liver and kidney function were estimated.

To assess the nervous system functional state, the summation threshold index (STI) estimation by the method by S.V. Speransky was used [22], along with the complex of behavioral responses in the open field test and the test in the dark chamber with holes [23]. Respiratory rate (RR), heart rate (HR) were recorded; blood pressure (BP) was measured, and rectal body temperature was determined. The BC-2800 Vet hematology analyzer (Mindray; China) was used to record red blood cell, white blood cell, and platelet counts, hematocrit and the white blood cell differential components: relative lymphocyte, neutrophil, eosinophil, monocyte, and basophil counts.

To assess functional state of the liver in experimental animals, serum glucose, total protein, albumin, and cholesterol levels were determined, as well as enzyme activity (alanine

Table 1. Agidol-1 acute toxicity parameter, intragastric and intraperitoneal administration

Вид, пол животных	Administration route	DL_{16}, mg/kg	DL_{50}, mg/kg	DL_{84}, mg/kg
Male mice	intragastric	715	1550	2400
Female mice	intragastric	1550	2290	3020
Male rats	intragastric	–	> 5000	–
Male mice	intraperitoneal	200	480	757

aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (AP)). Functional state of kidneys was assessed based on the 17 h urine output following the 4% water load, as well as based on the urinary protein and chloride levels; urinary pH and the levels of urea and electrolytes (Na, K, and Ca) in blood serum and urine were determined. Electrolyte concentration was determined using the PFM flame photometer (ZOMZ; USSR). Urinary pH was determined using the Kelilong automated pH meter (Kelilong; China) for small amounts of urine.

Statistical processing of the results was performed using the StatTech software package (StatTech; Russia) in order to determine significant differences in the reported responses of experimental and control animals under exposure to the drug using Student's *t*-test in accordance with the 95% ($p > 0.05$) confidence level taking into account the number of animals used in each experiment.

RESULTS

Determination of acute toxicity parameters after intragastric administration revealed species differences in susceptibility of rats and mice to agidol-1. DL_{50} for rats exceeded 5000 mg/kg (hazard class 4, slightly dangerous substances, GOST 12.1.007-76), in male mice it was 1550 mg/kg, and in female mice it was 2290 mg/kg (hazard class 3, moderately dangerous substances, GOST 12.1.007-76) (Table 1). Death of mice was reported on days 5–8 after intragastric administration of the substance. There were no clinical manifestations of poisoning, only weight loss (up to 10–15%) was reported. In case of intraperitoneal administration to male mice, DL_{50} is 480 mg/kg (according to classification by K.K. Sidorov, the substance belongs to class 4 of slightly toxic substances) [25] (Table 1).

Agidol-1 had no irritant effect on the eye mucosa and the skin (after the single and repeated application). No signs of the skin-resorptive or cumulative activity was reported, a single exposure to the agidol-1 saturated vapor caused no changes in the overall state, animals' behavior, and body's functional indicators (RR, STI, body temperature).

To determine the minimal effective concentrations (Lim_{ac}), two concentrations of the agidol-1 aerosol were tested: 24.7 ± 5.6 mg/m^3 and the maximum achievable concentration of 67.8 ± 12.5 mg/m^3. No deaths of laboratory animals were reported during the experiments. There were no differences in appearance and overall state between the experimental and control rats. No effects of the substance on the rectal body temperature and the studied physiological indicators (RR, STI, BP, HR) or behavioral responses were reported.

Biochemical testing of the animals' blood serum components revealed no increase in hepatic enzyme activity, as well as in the levels of protein, albumin, cholesterol, glucose, metabolism and synthesis of which involve the liver (Table 2). There was also no renal function impairment when inhaling agidol-1 in both concentrations: no significant differences in urine biochemistry parameters between experimental groups and the controls were reported (Table 3).

There were no differences in peripheral blood hemoglobin levels, red blood cell counts, hematocrit, platelet and white blood cell counts between experimental groups of rats and the controls (Table 4). The experimental rats' leucogram shows no differences from controls.

Thus, inhalation of agidol-1 concentrations of 24.7 mg/m^3 and 67.8 mg/m^3 (maximum achievable) had no harmful effect on the animals' overall state, functional state of the nervous, cardiovascular, and respiratory systems, as well as on peripheral blood composition and biochemistry parameters of blood serum and urea. No acute inhalation effect threshold was determined during the experiment, therefore the acute effect threshold Lim_{ac} of agidol-1 > 67.8 mg/m^3.

DISCUSSION

Agidol-1 being a representative of synthetic non-enzymatic antioxidants is widely used in various various industries, including chemical, pharmaceutical, food, medicine, and livestock production [15–17]. In this regard, a goal was set for the study to develop the agidol-1 safe exposure level in workplace air for industries involving synthesis and its use. Based on the mechanism

Table 2. Blood serum biochemistry parameters in male rats following a single agidol-1 inhalation, M ± *m* (*n* = 8)

Indicators	Units	Control	Concentration, mg/m^3	
			24.7 ± 5.6	67.8 ± 12.5
Glucose	mM/L	5.11 ± 0.12	5.08 ± 0.13	4.89 ± 0.11
Cholesterol	mM/h·L	2.23 ± 0.07	2.21 ± 0.06	2.18 ± 0.09
Urea	mM/L	8.48 ± 0.13	8.35 ± 0.16	8.21 ± 0.18
Total proteins	g/L	63.35 ± 1.13	63.03 ± 0.83	62.77 ± 1.03
Albumins	g/L	33.28 ± 0.73	33.09 ± 0.55	32.85 ± 0.93
ALT	mM/h·L	1.08 ± 0.03	1.11 ± 0.04	1.07 ± 0.02
ASP	mM/h·L	3.62 ± 0.05	3.68 ± 0.08	3.71 ± 0.09
AP	mM/h·L	7.14 ± 0.16	7.26 ± 0.12	7.37 ± 0.14
Sodium	mM/L	128.3 ± 0.75	128.2 ± 1.06	128.6 ± 0.93
Potassium	mM/L	6.59 ± 0.12	6.55 ± 0.09	6.43 ± 0.11
Calcium	mM/L	2.03 ± 0.02	2.04 ± 0.01	2.02 ± 0.03

Table 3. Urine biochemistry parameters in male rats following a single agidol-1 aerosol inhalation, M ± *m* (*n* = 8)

Indicators	Units	Control	Concentration, mg/m³	
			24.7 ± 5.6	67.8 ± 12.5
Urinary output	mL	5.42 ± 0.67	5.63 ± 0.46	6.01 ± 0.58
Urinary pH	U	7.02 ± 0.11	6.83 ± 0.13	6.92 ± 0.17
Protein	mg/L	31.23 ± 1.74	32.48 ± 1.53	32.85 ± 2.18
Chlorides	mM/L	45.12 ± 2.15	47.03 ± 1.68	50.05 ± 2.17
Urea	mM/L	473.5 ± 17.38	468.8 ± 14.21	482.9 ± 18.25
Urea clearance	mL/min	0.30 ± 0.03	0.32 ± 0.02	0.35 ± 0.03
Sodium	mM/L	45.08 ± 1.56	46.13 ± 1.72	48.52 ± 1.51
Potassium	mM/L	32.23 ± 1.67	32.82 ± 1.26	34.69 ± 1.53
Calcium	mM/L	0.38 ± 0.03	0.39 ± 0.02	0.41 ± 0.03

of action agidol-1 is like natural vitamin E, it is also a hydrogen atom donor and converts peroxide radicals into hydroperoxides, and the agidol-1 molecule deactivates two peroxide radical molecules. Being a synthetic analogue of vitamin E, it nevertheless effectively suppresses autocatalytic processes of radical oxidation of various materials and products.

Agidol-1 is easily absorbed through the gastrointestinal tract. After the long-term consumption of foods containing the antioxidant it accumulates in the adipose tissue and the liver with the half-life of 7–10 days. Agidol-1 is excreted mainly in urine and to a lesser extent in feces [13]. The study of the dispersion of the agidol-1 sample presented has shown that it is almost homogenous based on the particle size and is represented mainly by very large particles (about 1000 μm and more). The ratio of large and medium particles is 9 : 1, which can indicate the lack of the ability to penetrate into the lower respiratory tract and elimination of agidol-1 in the upper respiratory tract. The substance is almost insoluble in water, which also makes it difficult for it to enter the lung tissue. The findings on dispersion suggest the lack of negative agidol-1 aerosol effects when inhaled.

Experimental data on toxicometry and the substance hazard assessment confirm the above. It has been shown that based on the acute toxicity (DL_{50}) reported following intragastric administration to mice and rats agidol-1 belongs to moderately dangerous and slightly dangerous substances (hazard classes 3 and 4, GOST 12.1.007-76) respectively, which is fully in line with the literature data [18, 26–28]. Agidol-1 had no irritant effect on the rabbit skin and eye mucosa, the experiment revealed no skin-resorptive or cumulative activity.

According to the literature data, agidol-1 and agidol-0 (2,6-di-tert-butylphenol, the basic raw material for obtaining agidol-1 and other effective phenolic antioxidants) do not possess skin-resorptive or cumulative activity. The available literature data on the irritant effects of agidol-1 are slightly different. Most of authors note a weak irritant effect on the rabbit eye mucosa and skin [13, 16, 28, 29], however, a number of researchers report the lack of such effect [26, 30]. A single exposure to agidol-1 saturated vapor causes no changes in behavior or functional indicators of the animal's body (RR, STI, body temperature).

The literature data analysis shows that the prolonged or repeated use of high-dose BHT (agidol-1) can affect the function and structure of the lung, liver, kidney, result in hyperfunction of the thyroid gland, adrenal glands, cause alteration of peripheral blood composition (red blood cell counts), blood serum composition, as well as lead to weight. The authors believe that liver is the main target organ for agidol-1 due to its lipophilicity. In cases of chronic oral exposure to the BHT doses exceeding 25 mg/kg of body weight/days, liver enlargement and induction of a number of liver enzymes were observed [31]. In this regard, when performing inhalations we relied on biochemical indicators of the liver and kidney functional state, not avoiding assessment of other body's vital organs and systems.

The tests have shown that the dynamic inhalation exposure to the agidol-1 aerosol concentrations of 24.7 mg/m³ and 67.8 mg/m³ (maximum achievable concentration) for 4 h had no general toxic effect: no deviations in the state of the nervous, cardiovascular and respiratory systems, as well as changes in the function of the liver, kidneys and the composition of the rat peripheral blood were noted.

Multiple experimental and clinical data unequivocally confirm that agidol-1 has no sensitizing effect. The substance is not classified as a mutagen or carcinogen. Agidol-1 shows no selective effect on the reproductive system, since minimal embryotoxic activity (decreased fetal weight) was reported in chronic experiments involving exposure to the doses toxic for maternal body [13, 16, 18, 26, 28, 30, 31].

When substantiating the agidol-1 OBUV, if no acute inhalation effect threshold is established even for maximum achievable concentration, it is necessary to refer to the standardized analogues of the substance or to the approved standards for the substance in atmospheric air of urban and rural settlements. In domestic literature, there are data on toxicity

Table 4. Peripheral blood indicators of rats following a single agidol-1 aerosol inhalation, M ± *m* (*n* = 8)

Indicators	Units	Control	Concentration, mg/m³	
			24.7 ± 5.6	67.8 ± 12.5
Hemoglobin	g/L	144.8 ± 5.9	139.6 ± 4.5	138.1 ± 4.4
Red blood cells	10^{12}/L	7.9 ± 0.3	7.5 ± 0.9	7.4 ± 0.6
Hematocrit	U	44.5 ± 1.2	43.2 ± 1.3	42.4 ± 1.5
Platelets	10^9/L	765.2 ± 35.4	740.5 ± 25.9	738.9 ± 23.7
White blood cells	10^9/L	7.7 ± 0.4	7.5 ± 0.5	7.6 ± 0.8

and hazard of three alkylphenol antioxidants of the Agidol brand (agidol-0, agidol-1, agidol-10), comparative toxicological characteristics of these are also reported. These studies have yielded estimates of safety of these substances and recommended safe exposure levels in atmospheric air of populated areas [30]. The evidence-based MPC for three compounds of the Agidol brand (MPC, daily average — 0.6 mg/m^3, MPC, maximum single — 2.0 mg/m^3, hazard class 4) were approved by the Chief State Sanitary Physician of the Russian Federation [32]. At the same time in different countries (USA, Germany, UK, Denmark) the maximum permissible levels of occupational exposure (TLV, ACGIH, PEL — NIOSH, MAK — Europe) have been established for BHT (butylated hydroxytoluene). These are within the concentration range between 2 mg/m^3 and 10 mg/m^3, however, the hygienic standard of 10 mg/m^3 is valid in most countries [28].

CONCLUSIONS

The testing conducted has shown that agidol-1 belongs to slightly toxic and slightly dangerous substances and shows no irritant effect in cases of single injection in the eye or repeated application to the skin. Based on the lack of general toxic effects of the agidol-1 inhalation in the study conducted, considering the established MPC for three Agidol brand compounds in atmospheric air and hygienic standards of occupational exposure for agidol-1 in different countries, the tentative safe exposure level (OBUV) in workplace air of 10 mg/m^3, aerosol, hazard class 4 has been proposed. The recommended value has been considered and approved by the Chief State Sanitary Physician of the Russian Federation. Agidol-1 in workplace air is controlled by spectrophotometry within the concentration range of 5.0–40.0 mg/m^3 at the wavelength of 278 nm.

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