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THE EFFECT OF ROCKET FUEL ON THE MORPHOLOGICAL AND MORPHOMETRIC CHARACTERISTICS OF THE LUNGS OF RATS

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Abstract

It is important to study the impact of the Baikonur, Saryshagan, Azgyr space rocket test sites located on the territory of Kazakhstan, as well as Kapustin Yar, which is very close to the border, on the landscape, animal habitat and local health and determine the impact.

The areas in several areas where the detachable parts of the rocket launchers have fallen occupy a very large area [1]. The areas of collapse of the detachable parts of the rocket launchers belong to the category of "ecological disaster zone" according to their ecological status, and the areas affected by these parts belong to the "ecological crisis zone". The atmosphere, natural and anthropogenic landscapes are heavily polluted with all classes of harmful substances: asymmetric dimethylhydrazine (1,1-DMG), nitrosodymethylamine (NDMA), nitrogen tetraoxide, tetramethyltetrazen and other toxic substances [2-4].

Rocket complexes and rocket launches have a negative impact on all components of the environment and biological objects. There are reports that the number of animals living around the landfill is declining sharply, and some species are on the verge of extinction [1; 5]. Due to these circumstances, there is a need for regular environmental monitoring of these areas and morphological study of the structural components of the animals that inhabit these areas, arising from the current environmental situation in the country.

There are reports that heptyl or asymmetric dimethylhydrazine, one of the main components of rocket fuels and lubricants, causes various diseases when ingested by humans and animals due to an accident or other circumstances during a rocket launch [2-3; 5]. 1,1-DMG is converted into other compounds in the soil, plants, as well as in the body, which in turn appears to be toxic to the body in general or to a particular organ [4].

Keywords: effect of rocket fuel, morphological, morphometric, characteristics, the lungs, rats

However, the toxic effects of 1,1-DMG and nitrosodimethylamine (NDMA), one of its derivatives, are poorly understood. There is reason to believe that heptyl, which enters the body through respiration, primarily damages the respiratory and gas exchange (respiratory) parts of the lungs.

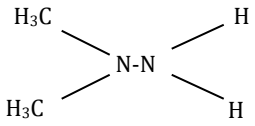
INTRODUCTION

Heptyl is a rocket fuel based on symmetric dimethylhydrazine (NDMG, 1,1-DMG), a highly toxic substance of class 1 in terms of risk. Heptyl is toxic to the human body and irritates the skin. It can enter the body through the respiratory tract, sweat glands, gastrointestinal tract. Heptyl, which enters the body through various routes, can spread throughout and damage the central nervous, cardiovascular, hematopoietic and other systems. In addition to the general toxic effects of asymmetric dimethylhydrazine, there are individual effects such as carcinogenic, mutagenic, gonadotoxic and embryotoxic. 1,1-DMG is a colorless liquid with an unpleasant odor (smelly herring). Not found in nature. Chemical formula: N2H2 (CH3) 2, relative molecular weight 32.05.

Specific gravity of 1.1-DMG - 0.78, boiling point - 630C, freezing point - minus 570C. For 1,1-DMG, the maximum allowable concentration in the air in the working area is 0.1 mg / m3, in atmospheric air: maximum single - 0.001 mg / m3, average daily - 0.001 mg / m3, in the reservoir water - 0.02 mg / l (sanitary -determines toxicological harm by this criterion) [8]. 1,1-DMG is involved in the redox reaction with organic bonds in carboxyl groups and in the complexing reaction. Easily oxidized by oxygen molecules and other oxidants (manganese acid in potassium, potassium iodide, mercury oxide, hydrogen peroxide, nitric and nitric acids, chlorine, hypochlorite). Dimethylamine (DMA), tetramethyl tetrazene (TMT), nitroso dimethylamine (NDMA), methylene dimethylhydrazine (MDMG), formaldehyde and other oxidation products are formed depending on environmental conditions (temperature, oxidation duration, presence of catalytic active metals).

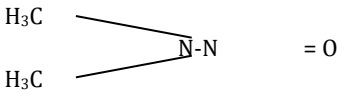
1,1-DMG is widely used as a combustible component of rocket fuel [literature] in aerospace industry, metallurgy, plastics and dyes in the chemical industry. Used in agriculture as a regulator of plant growth and herbicides. The degree of toxicity of asymmetric dimethylhydrazine for humans has not been determined. A person can feel a very faint odor of 1.1-DMG at the level of 0.01 mg / m3, perceive a concentration of 0.05-0.08 mg / m3 as a very strong ammonia odor, you can see the image with a concentration of 0.003 mg / m3. A person can get used to concentrations of 240 mg / m3 in 10 minutes, 120 mg / m3 in 30 minutes, 70 mg / m3 in 60 minutes. Concentrations of 10-20 mg / kg in the body lead to mild poisoning. Cases of mild poisoning in the presence of 1.1-DMG up to 2.6 mg / m3 in a polluted atmosphere for 1-2.5 hours have been described. Acute poisoning of people in the workplace due to the effects of nitroso dimethylamine (9%), nitric acid (42%) is common in the workplace (72%). possible. There is a latent period in the body of poisoned people, which can last from 30 minutes to 24 hours or more. About 85% of poisonings are mild, in which case the mortality rate reaches 2%, the result of moderate and severe poisoning is 15% [6].

There is little information on the level of 1,1-DMG in the environment. Despite the high rate of degradation of this substance, the concentration of 1,1-DMG in the soil in the areas where the remnants of rocket launchers crashed is



very high [7]. The pilot is highly soluble in water, can accumulate rapidly in the body and can form many malignant bonds, such as nitroso dimethylamine (NDMA) (literature). The molecular formula of N-nitrosodymethylamine (NDMA) is C2H6N2O and is a simple dialkyl nitrosamine with a specific molecular weight of 74.08 [8].

NDMA belongs to a class of chemical bonds, such as the



known N-nitro bond, which is characterized by the presence of the functional group N-N = O, as well as a specific amino activity (NR2, where R is a hydrogen atom or alkyl group). Also known as NDMA dimethyl nitrosamine, N, N-diethylenetriamines, N-methyl-N-nitro methylamine, N-nitroso- N, N-dimethylamine, DMN and DMNA [7]. NDMA is a volatile, yellow, ultraviolet absorbing, photolytically degradable, flammable, oily liquid [9].

NDMA is produced as a by-product of industrial processes, such as the use of nitrates, nitrites and amines. This occurs when alkylamines, mainly DMA and trimethylamine, react with nitric oxide, nitric acid, nitrites, or in the presence of trans-nitrosification bonds with nitro- and nitro-bonds. Therefore, NDMA can occur in the rubber, tanning, rocket and lubricant industries, food, foundry, pesticides, paints, and plant fertilizers. In addition, NDMA was detected in exhaust gases from diesel vehicles [10]. As a result of transport of biological and chemical alkylamines in the presence of nitrites and nitrates, NDMA can be formed directly in wastewater [11]. Toxic water rich in nitrites and nitrates can be released into the environment as a result of exposure to soil. 1,1-DMG and NDMA are xenobiotics that require metabolic activity to exhibit their toxic properties. As a result, highly reactive derivatives are formed, which determine their toxic potential. The metabolic activity of 1,1-DMG and NDMA carries out a monooxygenase system located in the smooth endoplasmic reticulum to the reactivity of the derivatives. The main role in this activity is played by the cytochrome P450 2E1 enzyme, which carries out the hydroxylation of 1,1-DMG and NDMA.

CYP2E1 is the main enzymatic component of microsomal oxidation of ethanol. In addition, it is involved in the metabolism of more than 80 low-molecular-weight hydrophobic toxic carcinogens. For example, it is involved in the activation of some drugs up to highly reactive metabolites and many procarcinogens' [12-15]. The liver

is the most damaged organ of these xenobiotics in the body, so many studies on the toxic mechanisms of 1,1-DMG and NDMA have been performed on the liver. However, despite studies of the toxic properties of 1,1-DMG and NDMA, the mechanisms that cause cell death are still unknown. However, studies have shown that 1,1-DMG is activated by various oxidative metabolic pathways to highly reactive derivatives [15]. It is known that 1,1-DMG is close to free radical derivatives in the role of derivatives. Rat liver microsomes and hepatocytes are able to metabolize 1,1-DMG to methyl radical radicals. These radicals are formed under the pressure of cytochrome P450 (SKF 525A, metyrapone and carbon monoxide) and flavin inhibitors in the monooxygenase system (methimazole). The source of free radicals in NDMA metabolism was the unstable diazene cation (Figure 1). It was observed that cytochrome P450 2E1 plays a role in the formation of these products. Diazene cations and other substances formed during the metabolism of methylhydrazines, DNA damage [16-19] and fat peroxidation [20-25], which play a role in the development of cytotoxicity of NDMG, may be the cause of various biological effects.

Figure 1. NDMG [89] oxidative exchange pathway NDMA metabolism can occur in two ways, such as hydroxylation or denitrification (Figure 2).

Both metabolic pathways begin with total intermediate radicals (CH3 (CH2) N-N = O) resulting from the action of cytochrome P450CYP2E1. During hydroxylation, hydroxymethyl nitrosamine (HOCH2CH3N-N = O) is formed into carbon dioxide and formaldehyde, which is converted to monomethyl nitrosamine (CH3NHN = O). These bonds are unstable and, as a result of their structural transformation, are converted to methylated methyl diazonium ions, which alkylate biological macromolecules such as DNA, RNA, and protein. Denitrification leads to the formation of methylamine and formaldehyde. The main factors of NDMA leading to cell death may be methylation of biological macromolecules [26-27]. In addition, the cytotoxic effect of NDMG and NDMA is based on the unique enzymes of NDMG and NDMA metabolism - CYP2E1 to highly reactive molecular oxygen: superoxide anion, singlet oxygen, hydrogen peroxide and hydroxyl without the presence of substrates. Intensive synthesis of the active form of oxygen leads to an increase in fat peroxide, protein oxidation, DNA damage and carcinogenesis [28-30]. Methylation of biological macromolecules or cell damage with the active form of oxygen may be the main factors causing cell death.

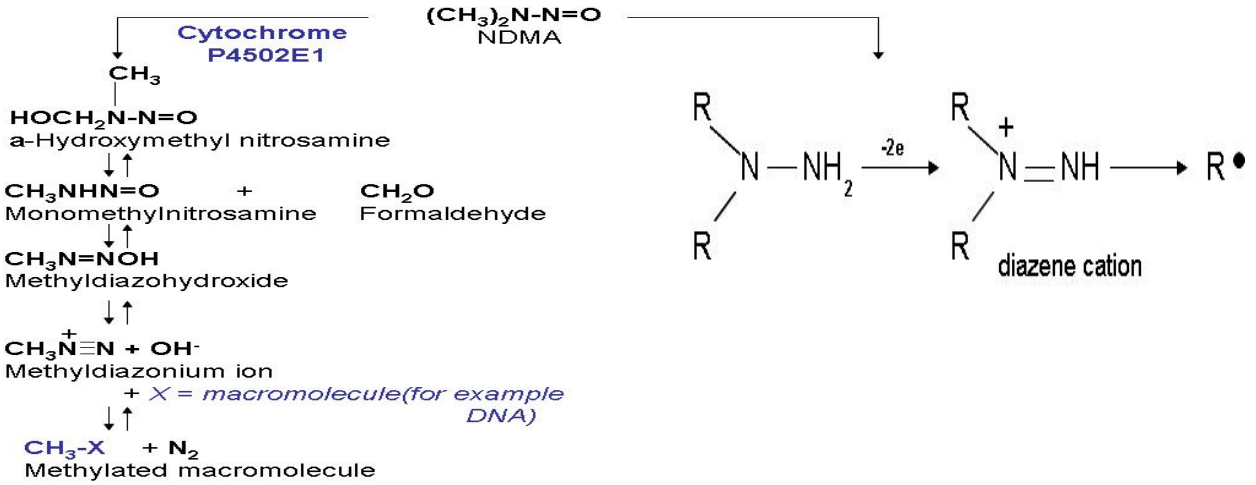


Figure 2. NDMA [26] exchange path Thus, according to the above literature, the high toxicity of NDMA depends not on how it enters the body, but on the duration and intensity of action.

Hepatotoxic and nephrotoxic effects are observed when a single dose of this substance in different doses. However, if the poisoning lasts for a long time, even in small amounts, this substance is very carcinogenic and stimulates the growth of tumors in various organs, including the lungs. However, in many studies on the effects of NDMA on human and animal lungs, the authors present the final results on cancer, and it is safe to say that there are no studies describing the morphological changes that lead to severe lung pathology. Experiments have been performed to study the pathomorphology of rocket fuel components with 1,1-DMG, the derivative of which has a chronic effect on the body of a growing rat by inhalation through NDMA.

RESEARCH METHODS

Materials and research methods Infertile white male rats with a body weight of 220-250 g were used in the experiment, the experimental animals were divided into 7 groups: Group I - animals of the control group; Groups II-IY - animals taken by inhalation of 1.1-DMG at concentrations of 205, 410, and 1028 mg / m3 (5.4; 10.8 and 26.8 mg / kg) for 1 hour for 10 days; Y-YII-groups - in this case the concentration is 2.4; 12.0 and 48.0 mg / m3 (0.06; 0.31 and 1.25 mg / kg) NDMA inhaled animals Data on the lethal doses of the xenobiotics studied in rats (RM50) and their ultimate concentrations (MPCs) in the air, which are very dangerous to human life, were obtained from the latest data in the scientific literature. 1.1-DMG is equivalent to 50 = 620 mg / m3 for rats and 1 μg / m3 for humans in the air (literature). NDMA for rats is equal to RM50 = 240 mg / m3, and for humans the maximum allowable concentration in the air is 50 ng / m3 / literature /. The effect of NDMA on rats with 1.1-DMG through the respiratory tract was carried out in a specially prepared airtight box with a volume of 59 liters. After exposure to the drug, the box was ventilated through a special filter. Animals in the control group and experimental animals were slaughtered simultaneously under nebutal anesthesia 10 days later.

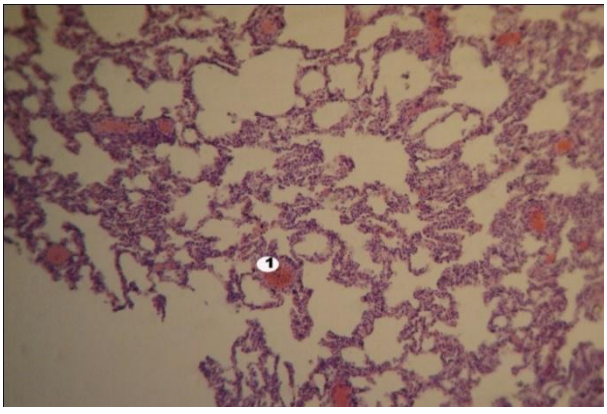
DISCUSSIONS

All experiments on animals were carried out in compliance with the international principles of the European Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes (ETS 123), Strasbourg, 1986), as well as in accordance with the "Rules for work using experimental animals. Keeping laboratory animals corresponded to the "Generally accepted ethical principles of experiments on animals of the Republic of Kazakhstan".

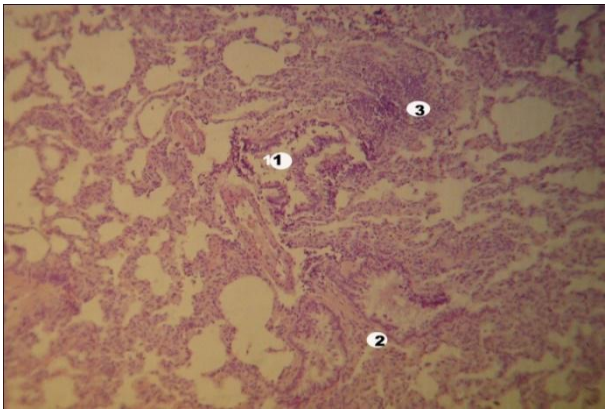
Cuts of rats' lungs were fixed in 10% neutral formalin at a rate of 5x5 cm for 10 days. After approval, the sections were washed under running water, dehydrated with ethyl alcohol, sealed with paraffin and obtained a section with a thickness of 5-7 microns [literature]. Histological sections were stained with hematoxylin-eosin, Masson and Van Gizon stains.

The stained drugs were examined under the microscopes MBI-15 and Leica DMLS (Jena, Germany). Microscopes were taken with the help of Mikmed-1 (LOMO, Russia) microscopes. The drugs were photographed using microscopes Leica DMLS (Jena, Germany) and Axiostar Plus Carl Zeiss Jena GmbH (Germany). Quantitative morphometric analysis of histological specimens from lung sections using Axiostar Plus Carl Zeiss Jena GmbH (Germany) microscopes, digital 3SDC Sony (Sony Corporation, Japan) video camera and AMD Athlon XP 2000+ CPU-based Leytron framerMB Made on a special computer type PC. The software part of the 4.0 version of the image was reviewed by the analyst "VideoTest-Master Morphology" (LLP "VideoTest", developed in St. Petersburg, Russia). The measurement was made with a magnifying glass x200. Length, width, diameter of the alveoli and area based on these data (μm2); The thickness of the alveolar wall, the width of the alveolar entrance was determined. When determining the area of the alveoli, the parameters of their shape (length and roundness of the alveoli) were also considered. Measurements of these parameters in each animal were taken from 10 randomly visible locations. Further processing and calculation of morphometric parameters were performed automatically and manually using the image analyzer "VideoTest-Master Morphology". Statistical processing of the obtained results was carried out automatically with the help of the program "SPSS Corporation" for versions 11.5 and 13.0.

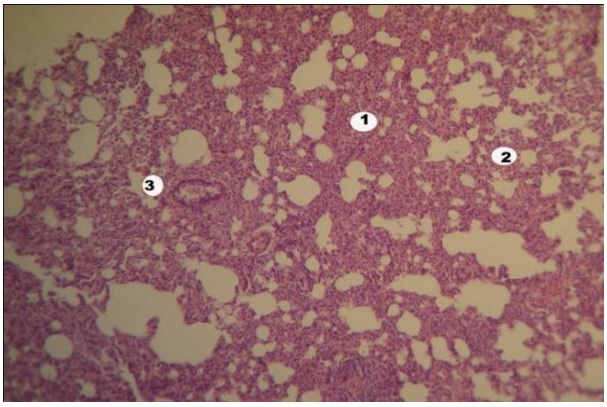
Research results Macroscopic examination of the lungs of rats exposed to multiple doses of 1,1-DMG showed significant changes in the consistency and color of the organ. The lungs of rats exposed to a dose of 5.4 mg / kg were light red, soft and full of air, and with high doses of the drug - 10.8 and 26.8 mg / kg, the affected organ was red, dense, with blood vessels, a slice of the limb. mucous-purulent fluid flowed from the surface. The rats, which received a maximum dose of 1.1-DMG of 26.8 mg / kg, had their air-enlarged lungs crispy. Examination of the lungs of animals under a microscope revealed various histological changes. In the lungs of rats receiving 1.1-DMG at a dose of 5.4 mg / kg, there was a violation of blood circulation - dilation of small vascular cavities, tension with blood, interstitial edema around the vessels (Fig. 1). We found that the ciliated epithelium, which resembles the middle and small bronchi, is torn in some places, and there is a protein fluid in the cavities of the bronchi and bronchioles (Figures 1-2). This indicates a violation of the air permeability of the bronchi and bronchioles. In the area of gas exchange in the lungs, the focus was on the concentrated enlargement of the bronchodilated lymphoid nodes (BLT) (Figure 3). That is, due to the prolonged exposure of the toxin through the respiratory tract, an increase in CKD leads to the activation of the local immune response. In some parts of the lungs there was a thickening of the interalveolar septum and weakening of the alveoli. Due to this, the alveoli lose their normal hexagonal polygonal shape and become round (Fig. 4). Examination with a large microscope revealed lymphocytes, leukocytes and histiocytes in the interalveolar septum, in addition to alveocytes, fibroblasts and endothelial cells, formed due to the inflammatory process (Fig. 5).



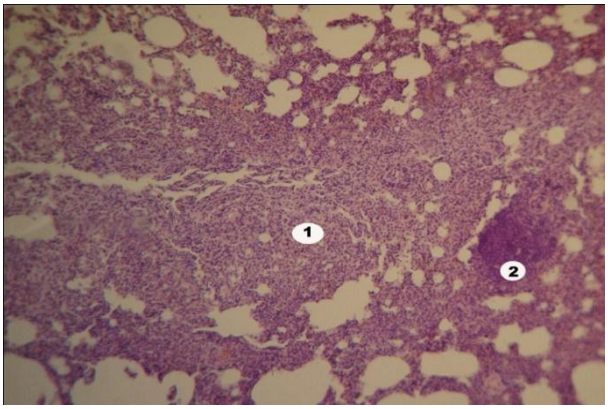
1 Some blood vessels are tense with blood Figure 1 - Histological structure of the lungs of rats exposed to 1,1-DMG (5.4 mg / kg). Magnification: about x 20, ok. 10; Hematoxylin-eosin staining



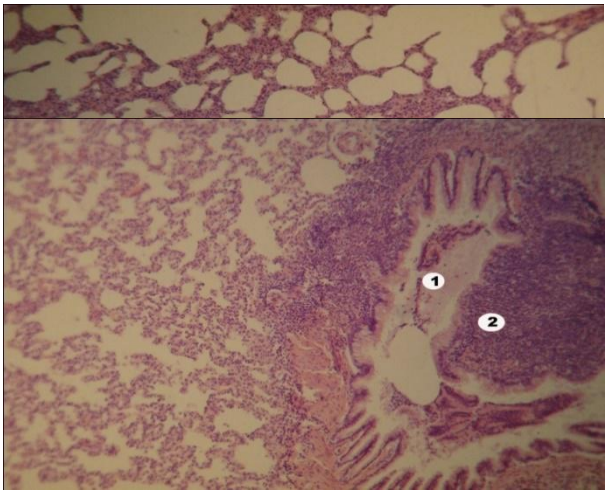
1 bronchial ciliated epithelium is torn and separated; 2-respiratory protein fluid in the bronchial cavity; Bronchial lymphoid nodule 3 Figure 3 - Histological structure of the lungs of rats exposed to 1.1-DMG (5.4 mg / kg). Magnification: about x 20, ok. 10; Hematoxylin-eosin staining



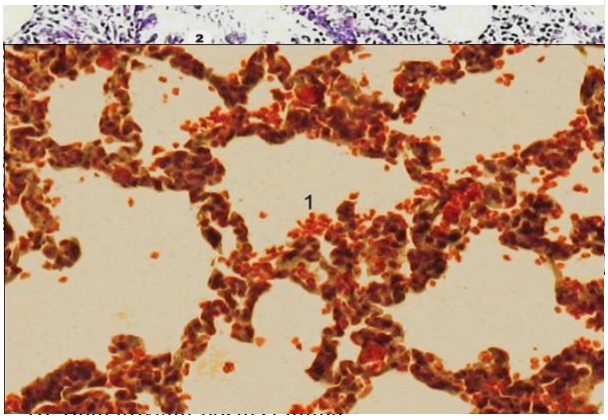
1-thickening of the interalveolar septum; 2-shrinkage of the alveolar cavity; Reduction of the width of the 3-alveolar entrances Figure 6 - Magnification: about x 20, ok. 10; Hematoxylin-eosin staining



1-thickening of the alveolar membranes due to lymphocytes, leukocytes, histiocytes, fibroblasts and macrophages; 2 lymphocyte nodes Figure 7 - Histological structure of the lungs of rats exposed to 1.1-DMG (10.8 mg / kg). Magnification: about x 20, ok. 10; Hemotoxylin-eosin staining



Filling of the bronchial cavity with catarrhal exudate, which is subject to the inflammatory process of the 1st row; Narrowing of the bronchial cavity from the node of the 2nd bronchial lymphocytes Figure 8 - Magnification: about x 20, ok. 10; Hematoxylin-eosin staining



1 - the outflow of blood cell elements into the interstitial and alveolar cavities Figure 9 - Histological structure of rat lungs exposed to 1.1-DMG (26.8 mg / kg). Magnification: about x 90, ok. 10; Masson paint

In rats who repeatedly inhaled 1.8-DMG at a dose of 10.8 mg / kg, we observed an increase (stagnation) in the lungs, as well as in the large and small blood vessels. Due to hypoxia, the histo-hematic barrier is damaged, tissue and vascular permeability is increased, serous exudate accumulates in the interstitial space of the lungs and alveolar cavities, blood cells appear outside the blood vessels. As a result, the interalveolar membranes thicken and the size of the alveolar entrances and alveoli decreases (Fig. 6). In addition to vascular lymphocytes and neutrophilic leukocytes, histiocytes, fibroblasts and macrophages were observed in the walls of the alveoli and intervertebral membranes (Figure 7). Repeated poisoning with 1,1-DMG disrupts the structure of the respiratory tract, in addition to the gas exchange part of the lungs. Bronchial lymphocyte nodules increase in size, compress and narrow the bronchial cavity, the cavities of the small bronchi are filled with exudate (Fig. 8).

When animals were exposed to a maximum dose of 1.1-DMG of 26.8 mg / kg, numerous diapedic (focal) hemorrhages in the lung parenchyma and edema around the large blood vessels were observed. In this case, we observed erythrocytes and other cell elements not only in the interstitial space, but also in the alveolar cavity (Fig. 9).

Under a large microscope, we saw that the hemocapillaries were blocked by erythrocytes, the damaged blood cells were separated from the alveocytes in the case of necrobiosis and necrosis. Cases of necrobiosis and necrosis of alveocytes are confirmed by the processes of cariorexis, pyknosis of their nuclei. We found that the volume of destroyed alveocytes increased due to water (in comparison with the cells in the control and necrobiotic conditions, it appeared swollen and empty), the cell did not contain any nuclear remnants. Attention was drawn to the thickening of the alveolar membranes in these areas due to inflammatory cells of the interventricular septum and swelling of the interstitium.

Table 1. Morphometric parameters of normal and asymmetric rat lungs poisoned with dimethylhydrazine (1,1-DMG)

Exp experimental situation		n	The area of the alveolar cavity, μm2 x 102	Thickness of the alveolar barrier, μm	Width of the alveolar entrance, μm
Concontrol (intact animals)		10	86 ± 3,4	25,8 ± 0,8	44,3 ± 1,1
Experience (Poisoning with 1,1-DMG)	5,4 мг/кг	10	72 ± 3,8 *	31,7 ± 1,2 ***	36,9 ± 1,8**
	10,8 мг/кг	10	67 ± 3,8 **	33,3 ± 0,7***	37,4 ± 1,9 **
	26,8 мг/кг	10	117 ± 4,5***	20,9 ± 0,8 ***	57,5 ±1,5***
Note: * -P≤0,05; ** - P≤0,01; *** - P≤0,001 was compared with the experimental control group. n is the number of animals.					

The results of morphometric studies suggest that our histological findings suggest that rats exposed to 1.1-DMG at 5.4 mg / kg and 10.8 mg / kg are exposed to interstitial inflammation of the lungs, and the interventricular septum is thickened by inflammatory cells. the area of air filled with alveoli decreases. In contrast, in the lungs of rats exposed to the highest levels of 1,1-DMG, the alveolar cavity area was higher than in the control group, and the thickness of the interveolar membranes was lower than in the control group. This was due to alveolar emphysema.

Table 2. Morphometric parameters of rat lungs in normal condition and nitrosodymethylamine (NDMA) poisoning

Exp experimental situation		n	The area of the alveolar cavity, μm2 x 102	Thickness of the alveolar barrier, μm	Width of the alveolar entrance, μm
Concontrol (intact animals)		10	86 ± 3,4	25,8 ± 0,8	44,3 ± 1,1
Experience (Poisoning with NDMA)	0,06 мг/кг	10	74 ± 3,7*	31,7 ± 1,2***	37,2 ± 1,9**
	0,31 мг/кг	10	66 ±3,9 **	33,8 ± 1,1***	33,9 ± 1,6***
	1,25 мг/кг	10	57 ± 2,5***	38,9 ± 1,5***	29,5 ± 1,1***
Note: * -P≤0,05; ** - P≤0,01; *** - P≤0,001 was compared with the experimental control group. n is the number of animals.					

Thus, in our experience, inflammatory processes in the lungs of rats exposed to NDMA (bronchitis, interstitial pneumonia) did not lead to obstructive emphysema observed in animals exposed to 1,1-DMG, regardless of the amount of xenobiotics used to treat animals. This situation and the results of morphometric studies show that the pneumotoxic effect of 1,1-DMG is stronger than that of NDMA. It is known that obstructive emphysema is associated with chronic bronchitis, bronchiolitis, and their consequent pneumosclerosis. Thus, bronchitis (bronchiolitis), which develops under the influence of high doses of 1,1-DMG, becomes acute, which leads to obstructive emphysema.

CONCLUSION

Based on the results of complex histological and morphometric studies, it was determined that 1,1-DMG and its derivatives are pneumatic substances due to the appearance of very strong structural changes in the lungs of laboratory rodents repeatedly exposed to NDMA. The level of structural changes in the lungs of rats depended on the amount of xenobiotics affected. The changes (pathological processes) caused by the amount of xenobiotics in the lungs under the influence of NDMA are similar to the changes caused by 1,1-DMG. Comparing the pneumococcal effects of the studied compounds, inflammatory processes in the lungs of NDMA-affected rats did not lead to obstructive emphysema and carnification in 1.1-DMG-affected animals, regardless of the amount of xenobiotics used to treat the animals. NDMA is heavier in molecular weight than 1.1-DMG and has a lower evaporation rate in the respiratory tract. There is reason to believe that prolonged exposure of animals to NDMA (more than 10 days) gradually leads to severe pathological processes in the lung parenchyma caused by 1,1-DMG. In addition, the pneumococcal effect of NDMA may occur during its metabolic process. NDMA metabolism is carried out by enzymes of the monooxygenase system of the cytochrome relative P450 through the formation of highly reactive radicals [literature]. Based on the results of the research, we came to the following conclusions: 1. 1,1-DMG and NDMA led to the development of bronchopneumonia in the lungs of rats, apparent morphological disorders of the blood, perivascular and interstitial edema, lesions of types I and II of alveocytes, inflammation of the alveoli and small bronchi, exudate exudate. This lung pathology observed in 1,1-DMG-affected rats was followed by the development of emphysema.

According to the results of morphometric studies at exposure to 5.4 and 10.8 mg / kg of 1.1-DMG, the width of the alveolar areas and alveolar entrances of the rat lungs was relatively reduced compared to control animals, and the thickness of the interventricular septum increased. Increasing the dose of 1.1-DMG to 26.8 mg / kg significantly increases the volume of the area of the alveoli and alveolar entrances, the thickness of the interventricular septum compared with control animals and previous experiments (1.1-DMG 5.4 and 10.8 mg / kg sizes), which indicates the development of emphysema. The width of the alveolar areas and alveolar entrances of the lungs of rats affected by NDMA decreased, and the thickness of the alveolar membranes thickened as the amount of xenobiotics increased (0.06; 0.31 and 1.25 mg / kg). 3. Based on the results of histological, electron microscopic and morphometric studies, it was observed that the pneumatic effect of 1,1-DMG is higher than that of NDMA. It can be assumed that the high pneumococcal effect of 1,1-DMG compared to NDMA is due to its volatile properties.

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