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THE EXPERIMENTAL STUDY OF THE MUTAGENIC ACTION OF N-NITROSODIMETHYLAMINE IN MICE

The mutagenic activity of N-nitrosodimethylamine (NDMA) in the laboratory mice was studied using the chromosome aberration test. It was established that NDMA with intraperitoneal single administration (acute experience) in doses of 2.0; 4,0 and 8,0 mg/kg induced chromosomal aberrations in the mouse bone marrow cells with a frequency statistically significantly exceeding the control level. With an increase in the dose of xenobiotics, the frequency of aberrant cells increased by 2.23 ($p < 0.05$); 3.00 ($p < 0.05$) and 3.89 ($p < 0.001$) times, respectively. The dose dependence of the level of induced mutagenesis was revealed ($r = 0.97$, $p = 0.03$). A statistically significant increase in the level of aneuploid and polyploid cells was established, however, no dose dependence was found ($r = 0.85$, $p = 0.29$). Prolonged intoxication of NDMA (subacute experience, intoxication within 10 days) of experimental animals resulted in a statistically significant increase in the frequency of aberrant bone marrow cells and the number of chromosomal aberrations per 100 metaphase compared to intact animals and animals of acute experience. The dose of NDMA 8 mg/kg, equal to 1/5 LD_{50}, with repeated administration was lethal for all individuals. With repeated administration of NDMA at doses of 2.0 and 4.0 mg/kg, the frequency of aberrant cells increased statistically significantly in comparison with a single injection of 1.70 ($p < 0.001$) and 1.60 ($p < 0.01$), respectively, and the number of chromosomal aberrations per 100 metaphase is 1.73 ($p < 0.001$) and 1.51 ($p < 0.01$) times. With prolonged exposure to xenobiotic, the frequency of cells with genomic mutations also increased statistically. The increase in the overall frequency of chromosomal aberrations occurred mainly due to chromatin-type disorders. The mutagenic effect of N-nitrosodimethylamine on mice, established in our studies, may be due to an increase in the level of active forms of oxygen and the accumulation of lipid peroxidation products in the tissues of the body. Possible mechanisms of mutagenic and genotoxic action of NDMA can be the enhancement of free radical processes and DNA methylation.

Key words: N-nitrosodimethylamine, mutagenic effect, acute and subacute effects, chromosomal aberrations, genomic mutations.

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Тышқандарға нитрозодиметиламиннің мутагендік әсерін тәжірибелік зерттеу

НДМА-ны 2,0; 4,0 және 8,0 мг/кг мөлшерінде бір реттік ішастарішілік енгізгенде тышқандардың сүйек кемігінің клеткаларында хромосомалық аберрациялардың жиілігі бақылау

деңгейінен статистикалық маңыздылығы жоғары екендігі анықталды. Ксенобиотиктің мөлшері артқан сайын аберрантты клеткалардың жиілігі 2,23 ($p<0,05$); 3,00 ($p<0,05$) және 3,89 ($p<0,001$) есе сәйкес жоғарылады. Индукцияланған мутагенез деңгейінің мөлшерлік тәуелділігі анықталды, корреляция коэффициенті $r=0,97$, $p=0,03$ болғанда. Анеуплоидты және полиплоидты клеткалар деңгейінің статистикалық маңыздылығы жоғары болғаны анықталды, бірақ мөлшерлік тәуелділігі анықталмады (корреляция коэффициенті $r=0,85$, $p=0,29$ болғанда). Қалыпты және бір реттік уландырылған жануарлармен салыстырылғанда тәжірибелік жануарларды НДМА-мен ұзақ уландыру (10 күн бойы) сүйек кемігінің клеткаларында аберрантты клеткалар жиілігінің және 100 метафазалардағы хромосомалық аберрациялар жиілігінің статистикалық маңыздылығы жоғары болғаны анықталды. НДМА-ның 8 мг/кг мөлшері, 1/5 $ЛД_{50}$ тең, көп реттік енгізгенде барлық дарабастарға летальды болды. НДМА-ны 2,0 және 4,0 мг/кг мөлшерінде көп реттік енгізгенде бір реттікпен салыстырылғанда аберрантты клеткалар жиілігінің статистикалық маңыздылығы 1,70 ($p<0,001$) және 1,60 ($p<0,01$) есе сәйкес, ал 100 метафазалардағы хромосомалық аберрациялар жиілігінің статистикалық маңыздылығы 1,73 ($p<0,001$) және 1,51 ($p<0,01$) есе сәйкес жоғары болғаны анықталды. Ксенобиотиктің ұзақ әсерінде геномдық мутациялары бар клеткалар жиілігінің статистикалық маңыздылығы артты. Хромосомалық аберрациялардың жалпы жиілігінің артуы хроматидті типтердің бұзылыстарына байланысты. Тышқандарға нитрозодиметиламиннің мутагенді әсері организмнің ұлпаларында оттегінің белсенді формаларының деңгейінің жоғарылауына және майлардың асқынтотығу өнімдерінің жинақталуына байланысты болуы мүмкін. НДМА-ның мутагендік және генотоксиндік әсерінің мүмкіндік механизмдері бос радикалды үдерістердің және ДНҚ-ның метилденуінің күшеюіне байланысты болуы мүмкін.

Түйін сөздер: нитрозодиметиламин, мутагендік нәтиже, бір және көп реттік әсер, хромосомалық аберрациялар, геномдық мутациялар.

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Экспериментальное исследование мутагенного действия нитрозодиметиламина на мышах

Изучена мутагенная активность нитрозодиметиламина (НДМА) в организме лабораторных мышей с использованием теста по учету хромосомных аберраций. Установлено, что НДМА при внутрибрюшинном однократном введении (острый опыт) в дозах 2,0; 4,0 и 8,0 мг/кг индуцировал в клетках костного мозга мышей хромосомные аберрации с частотой, статистически значимо превышающей контрольный уровень. С увеличением дозы ксенобиотика возрастала и частота аберрантных клеток в 2,23 ($p<0,05$); 3,00 ($p<0,05$) и 3,89 ($p<0,001$) раза, соответственно. Выявлена дозовая зависимость уровня индуцированного мутагенеза, коэффициент корреляции $r=0,97$ при $p=0,03$). Установлено статистически значимое увеличение уровня анеуплоидных и полиплоидных клеток, однако, дозовой зависимости не выявлено (коэффициент корреляции $r=0,85$ при $p=0,29$). Длительная интоксикация НДМА (подострый опыт, интоксикация в течение 10 дней) экспериментальных животных привела к статистически значимому увеличению частоты аберрантных клеток костного мозга и числа хромосомных аберраций на 100 метафаз по сравнению с интактными животными и животными острого опыта. Доза НДМА 8 мг/кг, равная 1/5 $ЛД_{50}$, при многократном введении оказалась летальной для всех особей. При многократном введении НДМА в дозах 2,0 и 4,0 мг/кг частота аберрантных клеток статистически значимо возросла по сравнению с однократным введением соответственно в 1,70 ($p<0,001$) и 1,60 ($p<0,01$) раза, а число хромосомных аберраций на 100 метафаз – в 1,73 ($p<0,001$) и 1,51 ($p<0,01$) раза. При длительном воздействии ксенобиотика статистически значимо возросла и частота клеток с геномными мутациями. Увеличение общей частоты хромосомных аберраций происходило главным образом за счет нарушений хроматидного типа. Мутагенное действие нитрозодиметиламина на мышей, установленное в наших исследованиях, может быть обусловлено увеличением уровня активных форм кислорода и накоплением продуктов перекисного окисления липидов в тканях организма. Возможными механизмами мутагенного и генотоксического действия НДМА может быть усиление свободнорадикальных процессов и метилирование ДНК.

Ключевые слова: нитрозодиметиламин, мутагенный эффект, острое и подострое воздействие, хромосомные аберрации, геномные мутации.

Introduction

Pollution of the biosphere by different mutagenic factors attracts more and more attention of researchers. Every year, thousands of new artificially synthesized chemical compounds appear that are widely used by man in everyday life. According to the register Chemical Abstracts Service (CAS) of February, 2018, more than 140 million chemical compounds were registered. The daily CAS register replenishes about 15,000 new substances (CAS, 2018). However, not all of them are evaluated for toxic, mutagenic and carcinogenic activity (Abilev, 2015: 169-182). Increase in environmental pollution of xenobiotics can lead to an increase in the mutational background of populations, including humans. Unfortunately, to date unambiguous qualitative criteria for estimating the incidence of mutations in populations have not been developed (Abilev, 2015: 169-182; Geras'kin, 2010: 66-68).

As a result of the activities of the Baikonur Cosmodrome, significant areas of Kazakhstan are under the negative influence of rocket fuel components and its transformation products, which affect the environmental and public health status. The main component of rocket fuel used at the Baikonur Cosmodrome is unsymmetrical dimethylhydrazine (UDMH, heptyl) due to its high energy intensity. According to the monitoring complex studies, the content of the unsymmetrical dimethylhydrazine and its transformation products, in particular N-nitrosodimethylamine (NDMA), in places of carrier-rocket part fall, exceeds the maximum permissible concentration (MPC) in environmental objects (Adushkin, 2000: 10-15; Aidosova, 2005: 131-134; Bakaikina, 2018: 1-20; Batyrbekova, 2007: 12-17; Kalaev, 2004: 1-80; Kasimov, 2006: 668-670; Kenessov, 2012: 78–85; Musa, 2015: 26-29; Panin, 2006: 124-131; Shoikhet, 2005: 1-188). In the scientific literature, there are quite contradictory data on the genotoxicity of UDMH and its oxidation products, but their toxic effects are well known. Therefore, the study of genotoxicity of rocket fuel components and its transformation products does not lose its relevance.

NDMA is one of the oxidation products of unsymmetrical dimethylhydrazine. NDMA is more stable in soil and water, more toxic and mutagenic than UDMH (Bradley, 2005: 115-120). The natural synthesis of N-NDMA in the environment occurs with a high concentration of amines, nitrites and nitrates, which, upon entering into the nitrosation reaction, turn into NDMA (Liteplo, 2002: 1-45; Osipenko, 2005a: 5-9; Rodin, 2008: 1039-1044). NDMA is a carcinogenic nitrosamine and has a high toxic, mutagenic, teratogenic and embryotoxic effect. NDMA is widely used in the foundry industry, in the production of rubber, rocket fuel, pesticides, dyes, in tanning leather, in the food industry. NDMA can be formed in sewage as a result of biological and chemical transformations of alkylamines. Tobacco smoke is also a source of NDMA. Synthesis of NDMA occurs in the human stomach acids after eating a food rich in nitrites, secondary or tertiary amines, as well as certain medications (Guidelines for..., 2011: 1-39; N-nitrosodimethylamene..., 2008: 1-37; Osipenko, 2005a: 5-9).

NDMA led to the methylation of nucleic acids with the formation of mainly N^7-methylguanine, partially O^6-methylguanine and N^3-methyladenine. In a small volume, methylated derivatives of proteins and nucleic acids were found in the kidneys, spleen, pancreas, brain and other organs (Osipenko, 2005b: 20-23).

Tumor formation was observed in different animals with intoxicated NDMA (Madden, 2003: 672-676; Osipenko, 2005a: 5-9). NDMA increased the incidence of tumors of hepatocytes and Leydig cells in rats. An increase in malignant neoplasms was observed at a concentration of NDMA in drinking water from 0.01 to 5 mg/L (Guidelines for..., 2011: 1-39). With intraperitoneal and intragastric administration of NDMA to pregnant female of rats and mice, the incidence of liver and urinary tract tumors in offspring increased (Madden, 2003: 672-676; Osipenko, 2005a: 5-9). According to Agency for Research on Cancer (IARC), NDMA is classified in Group 2A (probable human carcinogen) (N-nitrosodimethylamene..., 2008: 1-37).

NDMA has high mutagenic activity under *in vitro* and *in vivo* conditions. It has been established that NDMA induces mutations detected in the Ames test, gene and chromosomal aberration assays, sister chromatid exchanges, unplanned DNA synthesis, mutations of transgenic rodents, on *mammalian in vitro micronucleus test*. In vitro Comet assay has shown the genotoxic effects of N-nitrosodimethylamine only at high concentrations in human hepatoma cell lines, primary hepatocyte culture, and TK6 lymphoblastoid cell line (Hobbs, 2015, 172-181; Liviac, 2011: 613-618; National Toxicology..., 2018; Ooka, 2016: 1901-1907; Wagner, 2012: 109-115; Watanabe, 2001: 57-63). In vivo Comet assay has shown the genotoxic effects of NDMA in different tissues, including liver of rats, as well as liver and stomach of mice (Hobbs, 2015, 172-181).

In connection with the biological effect of NDMA, low MPCs in the air of industrial premises (0.01 mg/m^3) and water in reservoirs (0.001 mg/L) were established. The biological essence of the influence of even these concentrations in humans and animals is still not entirely clear (Osipenko, 2005c: 5-12). Therefore, a comprehensive study of the toxic, genotoxic and mutagenic effects of NDMA on the somatic and sex cells of mammals, as well as the mechanisms of meiosis, leading to sterility and infertility, is extremely urgent. The obtained information will allow to conduct a purposeful search for means of protection of the organism.

Materials and methods

The objects were laboratory mice of the BALB/cYwal line, widely used in cytogenetic studies. N-Nitrozodimethylamine (NDMA, $(CH_3)_2N_2O$) was used as the test chemical compounds. In total, 35 laboratory male mice 2-3 months old with body weight of 25-30 g were used in the experiments. Intact and experimental animals were kept in a vivarium on a standard diet. Care for laboratory animals was carried out in accordance with international principles (Guide for the Care..., 2011: 1-246).

For the intoxication of animals, aqueous solutions of NDMA were used. The introduction of xenobiotic was performed intraperitoneally. Dosages were selected based on the available information on LD_{50} for mice with intraperitoneal administration of NDMA (40.0 mg/kg) (Lijinsky, 2011: 1-482). All animals were divided into 7 groups (I-VII) of 5 individuals in each: group I - intact animals; groups II-IV - animals that received NDMA in a single dose of 2.0; 4,0 and 8,0 mg/kg, respectively (acute effect); groups V-VII are animals that received NDMA doses of 2.0; 4.0 and 8.0 mg / kg, respectively, daily for 10 days (subacute effect). The animals were sacrificed under isoflurane anesthesia.

The Mammalian Bone Marrow Chromosome Aberration test was carried out according to the standard technique (Rukovodstvo..., 1989: 108-124). Before slaughtering, the weight of each mouse was determined and injected in mouse 0.04% colchicine solution intraperitoneally at a dose of 1 ml/100 mg body weight. 1.5-2 hours after the colchicine injection, the mice were sacrificed and the bone marrow was flushed out of the bone with a hypotonic solution of potassium chloride (0.56%) heated to 37 ° C. The washed bone marrow was carefully resuspended to homogenize the cell suspension. After hypotonic treatment, the cell suspension was centrifuged for 5 minutes at 1000 rpm. The precipitate was fixed in a mixture of methanol and glacial acetic acid (3: 1). The fixed cells were resuspended in a fixator and the suspension was applied to cooled wet slide glasses. To color the chromosome preparations, the Azure-Eosin dye was used according to Romanovsky-Giemsa. Cytological preparations were analysed and captured using light microscopes Axioskop-40 (CarlZeiss, Germany) and OlympusBX 43 (Olympus, Japan). Genomic and structural disorders of chromosomes were analysed using the metaphase method (Rukovodstvo..., 1989: 108-124; Nemtseva, 1970: 1-126).

Statistical data processing was performed using the Microsoft Excel add-in program "Analysis ToolPak". In all variants, the mean value and standard errors of the mean were determined. The significance of the mean differences was evaluated using the Student's parametric test. Differences were considered reliable with a confidence level of 95% or higher ($p < 0.05$-0.01). To determine the correlation dependence, the Pearson correlation coefficient (r) was calculated.

Results and discussion

The results of a cytogenetic study of experimental animals subjected to acute (single) and subacute (daily for 10 days) exposure to N-nitrosodimethylamine (NDMA) are presented in the table.

NDMA under the acute influence at all used doses induced chromosome aberrations in the mouse bone marrow cells with a frequency exceeding the control level. The level of structural rearrangements of chromosomes in animals of II-IV groups, intoxicated with NDMA in doses of 2.0; 4,0 and 8,0 mg/kg of body weight, statistically significantly increased in 2.23 ($p < 0,05$); 3.00 ($p < 0.05$) and 3.89 ($p < 0.001$) times as compared with the control. Along with the overall frequency of aberrant cells, the number of chromosomal aberrations per 100 metaphase, due to the lesion of more than one chromosome in one cell, also increased significantly. The number of chromosomal aberrations per 100 metaphase seen in animals of II-IV groups was statistically significantly higher than the control level of 2.27 ($p < 0.01$), 3.03 ($p < 0.001$) and 3.95 ($p < 0.001$) respectively.

Qualitative composition of structural mutations in control and experimental animals was represented by disorders of both chromosomal and chromatid types. The main disorders of the chromosome type were represented by paired

fragments, and the chromatid type by single breaks. As a result of acute exposure in animals of II-IV groups, which received respectively NDMA in doses of 2.0; 4.0 and 8.0 mg/kg, the number of chromosomal aberrations per 100 metaphase increased by 2.45; 2.00 and 2.95 ($p < 0.001$) times, and the number of chromatid type aberrations per 100 metaphase grown in 4.06 ($p < 0.001$); 6.65 ($p < 0.001$) and 8.94 ($p < 0.001$) times, respectively.

Table – Frequency and spectrum of structural chromosomal aberrations induced in the bone marrow cells of laboratory mice at **different doses and times of N-nitrosodimethylamine** exposure

Experiment type	Types of effect	Number of cells analyzed	Frequency of aberrant cells ($M \pm m$), %	Number of chromosomal aberrations per 100 metaphases				Frequency of genomic mutations, (M ± m),%	
				number of aberrations	chromosomal type	chromatide type	point fragments	aneuploid cells	polyploidy cells
Control		995	0.91±0.19	1.11±0.19	0.20±0.12	0.31±0.13	0.60±0.09	0.40±0.18	0.30±0.12
NDMA 2.0 mg/kg	acute effect	1030	2.03±0.23**	2.52±0.29**	0.49±0.22	1.26±0.12***	0.77±0.18	1.08±0.19**	1.83±0.34***
	subacute effect	1010	3.46±0.10***	4.35±0.14***	0.50±0.01*	2.57±0.17***	1.28±0.11**	2.09±0.21***	2.87±0.16***
NDMA 4.0 mg/kg	acute effect	1020	2.73±0.21**	3.34±0.24***	0.40±0.18	2.06±0.18***	0.88±0.18	1.00±0.24	1.76±0.17***
	subacute effect	1025	4.38±0.26***	5.06±0.52***	0.77±0.28	2.63±0.18***	1.65±0.18***	3.51±0.25***	4.48±0.35***
NDMA 8.0 mg/kg	acute effect	1015	3.54±0.11***	4.34±0.19***	0.59±0.08*	2.77±0.26***	0.98±0.15	1.70±0.29**	2.37±0.20***

* - $p<0.05$, ** - $p<0.01$; *** - $p<0.001$ as compared with control

A comparative analysis of the level of aberrant cells and the number of chromosomal aberrations per 100 metaphases in animals exposed to acute exposure revealed a dose dependence of the level of induced mutagenesis. An increase in the dose of xenobiotic to 8 mg/kg resulted in a statistically significant increase in all the studied indicators ($r = 0.97$, $p = 0.03$).

The level of polyploid cells under the influence of xenobiotic at all 3 doses used also increased statistically. However, an increase in metaphase with aneuploid sets of chromosomes was statistically significant only at exposure to doses of 2.0 and 8.0 mg/kg. Under the influence of NDMA, the level of polyploid cells increased in animals of II-IV groups, respectively, 6.10 ($p < 0.01$); 5.87 ($p < 0.001$) and 7.90 ($p < 0.001$) times in comparison with the animals of group I. There was no dose response in the induction of polyploid cells ($r = 0.85$, $p = 0.29$).

As a result of prolonged exposure to NDMA (subacute experience, intoxication within 10 days) in the experimental mice showed an increase in all the studied quantitative indicators compared with control and acute experience (table). However, a dose of 8 mg/kg of NDMA, equal to 1/5 LD50, was lethal to all animals.

The frequency of aberrant cells was statistically significantly increased in comparison with acute experience in animals of the V and VI groups in 1.70 ($p < 0.001$) and 1.60 ($p < 0.01$) times, and the number of chromosomal aberrations per 100 metaphase increased by 1, 73 ($p < 0.001$) and 1.51 ($p < 0.01$) times, respectively. Also, with prolonged exposure, the frequency of cells with genomic mutations increased significantly. The level of aneuploid and polyploid metaphases in animals of group V in comparison with animals of group II, respectively, increased in 1.94 ($p < 0.01$) and 1.57 ($p < 0.05$) times, and in group VI in comparison with animals of group III grown in 3.51 ($p < 0.001$) and 2.55 ($p < 0.001$) times, respectively.

The spectrum of structural chromosomal abnormalities in animals exposed to prolonged exposure to NDMA was represented by chromosome and chromatid rearrangements, dotted fragments. Disorders of the chromosome type were represented by

paired end fragments and centric rings, and the chromatid type by single fragments and acentric rings. In multi-aberrant cells, point fragments and single discontinuities of chromatids were simultaneously observed. The increase in the overall frequency of chromosomal aberrations occurred mainly due to chromatin-type disorders.

The revealed genotoxic effects of N-nitrosodimethylamine in mice are consistent with the results of a number of studies conducted *in vitro* and *in vivo*. It was found that NDMA induces mutations detected in the Ames test, tests on the inclusion of gene and chromosomal mutations, sister chromatid exchanges, unplanned DNA synthesis, mutations of transgenic rodents, micronucleus test on bone marrow cells and peripheral reticulocytes of mammals line Hobbs, 2015, 172-181; Liviac, 2011: 613-618; National Toxicology..., 2018; Ooka, 2016: 1901-1907; Wagner, 2012: 109-115; Watanabe, 2001: 57-63).

A number of studies have shown that NDMA is a promutagen and a pro-carcinogen, so it requires metabolic activation. Metabolism of NDMA suggests either α-hydroxylation or denitrogenation from nitrosamines. In both ways, as a result of cytochrome CYP2E1, the same intermediate $[CH_3(CH_2)NBN{=}O]$ is formed. Subsequently, when the metabolism passes through α-hydroxylation, hydroxymethylnitrosamine $[CH_3(CH_2OH)N{-}N{=}O]$ is formed, which decomposes into formaldehyde and monomethylnitrosamine ($CH_3NHN{=}O$). Monomethyl nitrosamine, due to its instability, undergoes transformation into a strongly methylated methyl diazonium ion ($CH_3H{+}{\equiv}N$), which can alkylate biological macromolecules such as DNA, RNA and proteins. It is believed that by the α-hydroxylation the active metabolites responsible for the genotoxicity and carcinogenicity of NDMA are formed. Metabolic transformations of the intermediate radical through denitrolylation lead to the formation of methylamine (CH_3NH_2) and formaldehyde (Guidelines for..., 2011: 1-39).

N-Nitrosodimethylamine is a simple methylating agent of the SN_1 type, which requires the activation of the metabolism in order to generate its DNA-active intermediate (probably the methyldiazonium ion). The main enzyme for this biotransformation is P450IIE1, which finds at the greatest activity in the liver. The main adduct of DNA formed after the action of N-nitrosodimethylamine is N^7-methylguanine (N^7-MEG), accounting for approximately 70% of the total amount of DNA methylation (Souliotis, 2002: 75-87). Given the high level of formation and relatively slow repair, N^7-MEG can accumulate in DNA upon repeated exposure to methylating carcinogens, including NDMA.

Another DNA adduct generated by NDMA is O^6-methylguanine, which is formed about 10 times less frequently than N^7-MEG (Ooka, 2016: 1901-1907; Souliotis, 2002: 75-87). This adduct plays an important role in mutagenesis, carcinogenesis and cytotoxicity of methylating agents of SN_1 type. Apparently, the cytotoxicity of the methylating agents is the result of the induction of disturbances in the repair of replication errors, which leads to multiple DNA ruptures and apoptosis. Other DNA-induced adducts induced by NDMA are N^3-methyladenine (3% of all induced adducts), O^4-methyltimine (<0.1%), and a number of other minor adducts (Souliotis, 2002: 75-87). N^7-methylguanine as a result of depurination can lead to the replacement of guanine by thymine, O^6-methylguanine to replace G: C by A: T pairs, O^4-methyltimine to replace A: T by G: C pairs (Abilev, 2015: 40-41).

Thus, N-nitrosodimethylamine at all doses and exposure periods to mice produced a pronounced mutagenic effect, manifested in a statistically significant increase in the frequency of structural and genomic mutations. With an increase in the duration of exposure to xenobiotics in laboratory mice, the level of induced mutagenesis increased. The mutagenic effect of N-nitrosodimethylamine on mice, established in our studies, may be due to an increase in the level of active forms of oxygen and the accumulation of lipid peroxidation products in the tissues of the body. This leads, ultimately, to methylation and/or oxidative degradation of DNA and nitrogenous bases. Metabolic activation of NDMA by CYP2E1, and hence further enhancement of lipid peroxidation, also leads to methylation and alkylation of DNA. Therefore, the possible mechanisms of mutagenic and genotoxic action of NDMA can be the enhancement of free-radical processes and DNA methylation.

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МАЗМҰНЫ – СОДЕРЖАНИЕ

Шолу мақалалары — Обзорные статьи

1-бөлім Қоршаған ортаны қорғау және қоршаған ортаға антропогендік факторлардың әсері — Раздел 1 Воздействие на окружающую среду антропогенных факторов и защита окружающей среды

2-бөлім Қоршаған орта ластаушыларының биотаға және тұрғындар деңсаулығына әсерін бағалау — Раздел 2 Оценка действия загрязнителей окружащей среды на биоту и здоровье населения

3-бөлім Биологиялық алуантүрлілікті сақтаудың өзекті мәселелері — Раздел 3 Актуальные проблемы сохранения биологического разнообразия