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PECULIARITIES OF EXPERIMENTAL ANIMALS' BEHAVIORAL REACTIONS UNDER THE CONDITIONS OF LONG-TERM ORAL ADMISSION OF INDUSTRIAL URANIUM ORE DUST TO THE BODY

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ABSTRACT

The dynamics of animals' higher nervous activity disturbances and bioaccumulation of uranium in tissues under the conditions of prolonged oral admission of industrial uranium ore dust (UOD) at doses of 25 and 50 maximum exposure concentrations (MPC) to the body were studied. In the early periods after the admission of UOD into the animals' body, the maximum concentrations of uranium are determined in the kidneys, in the late period – in the bone tissue, while the content of uranium in organs and tissues correlated with the dose of UOD. On the background of an increased concentration of uranium in the rats' brain with chronic admission of UOD in the body, a steady alarm state is formed and terms of retention of acquired passive avoidance skills are reduced. The data obtained in this work indicate the presence of long-term effects of radiotoxic exposure of UOD, which dictates the expediency of long-term observation of the behavioral reactions of animals.

Key words: ionizing radiation, uranium, nervous system, alarm, conditioned reflex activity.

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1. INTRODUCTION

1. Relevance: Recently, data indicating the high sensitivity of nervous system's individual elements to the damaging effects of ionizing radiation has been accumulating. [1-3]. The relevance of the study of neuroradiobiological effects is determined by a number of scientific and practical objectives Related to security of the radiation safety of industrial enterprises workers which activities are associated with contact with sources of ionizing radiation.

Republic of Kazakhstan has one of the world's largest uranium raw materials bases. The professional exposure of uranium on a person is carried out during the mining of uranium ore, its processing and obtaining enriched uranium. At the same time, uranium industry worker is exposed to both external exposure and internal radiation exposure of radionuclides which are mainly which mainly incorporated as a result of inhalation and oral admission in the body [4]. According to the research According to the research According to the research data, uranium compounds are able to cross the blood-brain barrier and cause local cellular damage of various structures of the nervous system [5,7]. In addition to the direct damaging effect, other mechanisms of ionizing radiation exposure on the nervous system are possible, such as disturbance of regulatory processes in connection with afferentation into the nervous system due to damages of other organs, as well as reactions to radiation as an irritant within the physiological reactivity of the respective structures [8]. According to a number of authors, regardless of the mechanism of radiation exposure, shifts in the nervous system are predominantly functional [5, 6, 9]. Thus, materials of epidemiological researches in recent years have shown that among people who have been in contact with sources of ionizing radiation, diseases of the neuropsychic sphere are most frequently recorded out of the main diseases of the nervous system [1,11]. At present, experimental data has been accumulated in which the functional state of the nervous system has been studied during chronic radiation exposures. Disorders of motor activity, cognitive, emotional activity are noticed among the main uranium-induced behavioral effects [10-12]. In this research work, we studied the behavior of animals for a long time after the oral admission of uranium, including the study of emotional-behavioral reactivity and conditioned-reflex activity of rats.

The purpose: to study the dynamics of behavioral reactions and bioaccumulation of uranium under conditions of prolonged oral admission of industrial uranium ore dust to the animals' body during the experiment.

2. MATERIALS AND METHODS

2.1. Modeling of incorporated admission of uranium ore dust to the animals' body

Experiments were carried out on adult white outbred male rats. The experiment selected healthy adult animals weighing 160–200 g kept in identical conditions. 45 animals were used in the experiments. Male rats were divided into 3 groups: Group I was intact individuals, Group II and Group III were laboratory rats exposed to incorporated uranium ore dust (UOD) at doses of25 and 50 MPC, respectively. The experiment was used UOD, obtained at the enterprise of the Step nogorsk city of the Republic of Kazakhstan.

Prolonged internal irradiation of animals was modeled by daily feeding with food mixed with uranium ore dust (UOD) for 7 days. The period after incorporation of animals in 7 days was equal to the year of human life [13]. The composition of the uranium ore dust is presented in table 1.

Table 1 The chemical composition of the uranium ore dust,%

UO_3	MoO	ZnO_2	Fe_2O_3	SiO_2	Al_2O	As_2O	Sulfur
0,398	0,123	0,027	6,1	40,6	4,61	0,008	1,5
MgO	CO	P_2O_5	Na_2O+KO	FeO_2	MnO	CaO	Carbon/ Moisture
3,5	10,0	2,0	10,0	4,0	0,22	7,0	2/7,9

UOD was added to the Nestle milk-free porridge and mixed to a homogeneous mass. In this case, UOD was ingested by animals under conditions of natural food consumption as the sole source of nutrition. It should be noted that this model does not require the use of complex technical structures.

To control the eaten portions of animals of the experimental and control groups, they were seated in individual cells, in the corner of which fixed containers with food and water were placed. After feeding, an account was taken of the food eaten and residues, the volumes of which were insignificant (less than 1% of the total volume of the mixture).

The dosimetric studies used in the UOD experiment showed that the total activity of its α-emitting radionuclides was 98.8 Bq/g, and the ß-emitting activity was 30.4 Bq/g. The calculations of the parameters of the seed for the experimental study were carried out taking into account the possible ways of the intake of UOD into the human body under the conditions of professional activity: inhalation, oral, percutaneous.

To calculate the mass and dose of UOD after incorporation of rat in the testing laboratory of the Institute of Radiobiology and Radiation Protection (IRRP) of Astana Medical University, the activity of the following uranium isotopes in the uranium ore dust was determined: 238U, 235U, 234U. At the first stage, the value of the activity of uranium entering the personnel for 1 year of production activity[Bq] and the effective dose E, [Sv] formed by α- radiation of uranium that entered the body during the same time were calculated. Then, the dose coefficient $\varepsilon = E / \Pi_A$ was calculated and, according to the found value of the coefficient ε and according to the effective dose norms E_{max} = 20 mSv / year, the limiting permissible values of physical quantities characterizing environmental pollution in production were estimated : the maximum allowable uranium intake by activity $MAI_{Amax} = E_{max} / \varepsilon \cdot ($ year); maximum allowable uranium intake by mass $MAI_{m_{max}} = MAI_{Amax} / A_{specific}$, where $A_{specific} = A / m$ is the specific activity of uranium by weight, $MAI_{mmax} = E_{max} \cdot m / (\varepsilon A) \cdot$ year. For the calculation, the following formulas were taken to determine the maximum annual uranium intake by activity and mass:

$MAI_{Amax} = E_{max} /$ (1)

where E_{max} is the normalized effective dose for personnel which is equal to 20 mSv / year;

ε dose rate given in table values

And the formula for calculating the maximum annual receipts by weight:

$MAI_{m_{max}} = MAI_{Amax} / A_{specific},$ (2)

where is $E_{max} = A / m_U$.

Taking into account the obtained values of the dose coefficient and the limiting dose E,we get the following values:

$MAI_{Amax} = 0.02 / 7.3 * 10^6 = 0.0027x10^6 = 2.7kBq$;

$MAI_{mmax} = 2.7x10^3 x0.014 / 0.033 * 10^3 = 0.115g = 115mg$

Thus, the mass of uranium ore dust for a single feeding of animals of the experimental group in doses of 25 and 50 MPC was 2.8 and 5.8 g, respectively.

2.2. Study of the distribution of uranium in the organs and tissues of laboratory animals after oral administration of UOD

The concentration of uranium in the organs and tissues of laboratory animals was measured during the experiment 24 hours and 7 weeks after the last UOD feeding. Using inhalation anesthesia, Experimental animals were decapitated and the organs and tissues necessary for analysis were removed after inhalation anesthesia. The concentration of uranium in the organs and tissues of laboratory animals was determined on the basis of IRRP on the mass spectrometer with inductively coupled plasma "Agilent-7800". At the first stage, the microwave decomposition of the samples of the organs of rats was carried out according to the decomposition program in Multiwave PRO 3000 for biomaterials recommended by the manufacturer of the furnace. Acid decomposition of samples Conducted with concentrated nitric acid in an amount of not less than 6 ml and 1 ml of concentrated hydrochloric acid for each sample weighing 0.3 g till complete transparency and decomposed for 50 minutes. At the second stage, the content of uranium isotopes in the solution was determined on a mass spectrometer in the blood, kidneys, liver, intestines, and rat brain.

2.3. Study of the integrative activity of the nervous system

The level of anxiety in rats was assessed using a multivariate scale of alarming-phobic states (further - APS) By RodinaV.I. (1993), the use of which makes it possible to characterize an animal's reactions to the presentation of a series of test stimuli provoking states of anxiety and fear. During the experiment, 9 tests were used, which are part of the ranked scale (Table 2). The assessment of APS is based on 2 situations: 1) getting into an unfamiliar environment (tests I-V) and 2) the action of the experimenter's hand (tests VI-IX). In tests I-III, the rat from the experimental situation was returned to the cage no earlier than 20 seconds after the execution of the corresponding action or after the test time expired in case of non-execution of the action. The intervals between these tests were 15-20 minutes. The baseline level of anxiety was assessed in all experimental animals, then the study was conducted on the 1st, 7th, and 14th, 21st, and 30th days after priming with uranium ore dust.

The conditioned passive avoidance reflex (further - PAR) was developed on the basis of a single electric skin reinforcement according to the method of Bures G. and Buresova O. (1963) in an experimental setup consisting of two compartments connected by an opening: a large illuminated and a small dark with electrified floor. To produce the reflex, the rat was placed in the light compartment. Investigating the installation, the animal penetrated into the dark chamber. After three minutes of observation (180 s) a training session was conducted: the window between the compartments was closed with an organic glass curtain and on the floor of the dark compartment in which the animal was at the end of the study, an alternating pulse current was applied for one minute (20 pulses per minute, pulse duration - 10 ms) on the floor of the dark compartment in which the animal was located at the end of the study. The power of electro-punishment was 1 mA, the frequency was 50 Hz, the voltage was 40 V. Before the last pulse was applied, the window was opened and another rat followed the rat into the light chamber, and another 180 s were observed. We registered the first indicator — the time the animal stayed in the light compartment and the second indicator — the number of rats who spent all 180 of the experience in the safety chamber, that is, the percentage of animals with complete preservation of the memory trace. If the animal was in the light chamber 80% (144 s) or more of the total observation time, then the engram was considered formed. The safety of long-term memory was determined within 2 weeks of the study.

2.4. Statistical Processing of Research Results

Statistical processing of the results was performed using the IBM SPSS Statistics 20 software package and Microsoft Excel. The statistical significance of the results of the anxiety-phobic status study was calculated using the unpaired Student's t-test, conditioned reflex activity using the non-parametric Mann-Whitney test to identify intergroup differences. The hypothesis about the normal distribution of the experimental values of the considered parameters using the Kolmogorov-Smirnov criterion was pre-tested. Differences were considered statistically significant at $p < 0.05$.

3. RESULTS AND DISCUSSION

Uranium is absorbed in the gastrointestinal tract, mainly in the small intestine after oral intake into the body. By circulating in the body in a dissolved form, uranium enters the parenchymal organs through the blood stream, but its delay occurs in insignificant amounts. According to experimental data, the main organs of uranium deposition are bones and kidneys. Although in the early stages, uranium in the kidneys can be contained significantly in greater quantities than in the bones. Therefore, during this period, the kidneys can be a critical organ [4,14]. We determined the content of uranium in the blood, kidneys, small intestine and liver, brain, bones of experimental animals in the early and long-term periods after receipt of dust from uranium ore. Despite the fact that the natural content of uranium in the body is extremely low (0.01–0.2 μg/g of tissue) [4], in our work we measured its content in the group of control individuals.

The results showed that in the early stages after the intake of UOD, the highest concentration of uranium was observed in the organs and tissues of rats treated with UOD at a dose of 50 MPC and differed significantly from the content of uranium in irradiated rats at a dose of 25 MPC and intact individuals (Figure 1). The maximum concentration of uranium was recorded in the kidneys of experimental animals of group II and III. Thus, the average uranium content in the kidneys of irradiated rats at a dose of 50 MPC was 18623.8±4326.4 ng/l, which was significantly different from the concentration of uranium in groups II and I of rats (10103.12±3201.8 and 18.13±13.9 ng /l, respectively, $p < 0.05$).

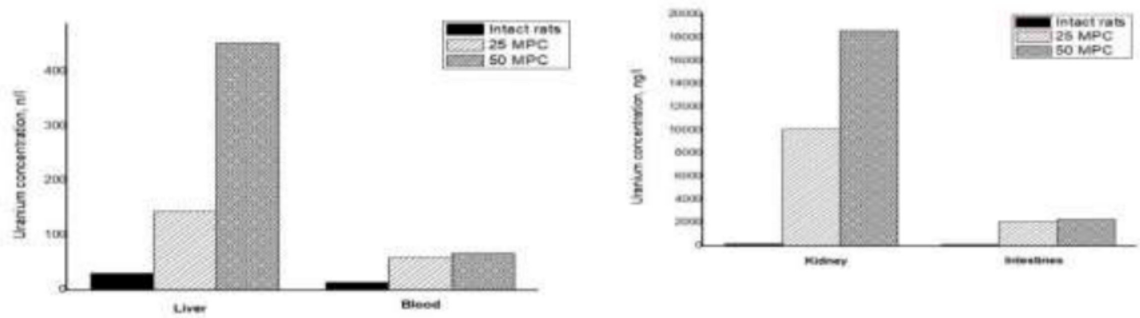

Figure 1 The content of uranium in the blood and organs of male rats in the early period after the intake of UOD, ng/l

As is well known, an intestinal tract in the acute period after oral intake of radionuclides into the body is a critical organ, and its damage greatly aggravates the severity of damage to all systems of the body. The concentration of uranium in biological samples of small intestine tissue was high and also made 2137.9±370.9in animals treated with a dose of UOD 25 and MPC 2306.21±366.6rats reported dose UOD 50 MPCs. The results obtained in the experimental groups animals differed significantly from the uranium concentration in the small intestine in intact animals (35,7±10,03 ng/l). In the liver of rats of III group uranium concentration was 452±315,9 ng /l, and significantly higher than the values in II (253.9±103.5 ng/l) and I groups of animals. In the blood and brain tissues of rats exposed to UOD, the concentration of uranium also exceeded control values.

As mentioned earlier in the Long-term period after uranium intake of critical organ becomes a skeleton. Experimental data established that the deposition of uranium in different parts of the skeleton occurs unequally: the greatest amount is deposited in the spine, the minimum is in the skull [4]. In our experimental work, the uranium content was measured in the bone tissue of the spine of experimental and control groups of animals in the long-term period after the intake of UOD. The concentration of uranium in animals of II and III groups was 1486.2 and 1051.2±186.4ng/l, respectively . Indicators of the content of uranium in bone tissue of animals exposed to ESD greater than the values in the control group at 3 times (327.8±111.8 ng/l), and the uranium concentration indicators in other organs and tissues of the corresponding groups.

Thus, in the early periods after the intake of UOD into the organism of animals, the maximum concentrations of uranium are determined in the kidneys, small intestine and liver, and the content of uranium in the organs correlated with the dose of UOD. In the late period after exposure to the dust of uranium ore, the highest concentration of uranium was recorded in the bone tissue of laboratory animals.

The next stage of our study was the study of the anxiety-phobic status (APS) of rats after the modeling of uranium intoxication. There is a dozen of literature on the increase in anxiety in persons exposed to radiation. [15,16].As you know, anxiety belongs to the category of concepts covering the most complex problems of the existence of organisms. Anxiety as a psychological phenomenon is an emotional state that arises in situations of danger and manifests itself in anticipation of unfavorable developments [17]. Functionally, anxiety not only warns the subject of a possible danger, but also induces them to search for and specify this danger, to actively explore the surrounding reality with the aim to determine a threatening object. In this case, anxiety is a response to an objective external threat, but this phenomenon may become pathological and underlie mental pathology [18].

Study of anxiety among intact males preceded the analysis of the dynamics of the level of APS in rats after prolonged intoxication of UOD. Then, there was a gradual reduction in the anxiety rates with significant differences in the last days of the study - 21 th and 30 th day, when the total score of anxiety was 6.04±2.7 and 6.11±2.5 , respectively (versus 9.87± 2.98 in the initial state, $t = 3.65$, $p <0.05$). The data obtained in the control group with a steady decrease in anxiety, according to some authors, contribute to the adaptation, training and reinforcement of new skills, and therefore increase the likelihood of survival of an individual in nature [19].

In rats, after seeding at a dose of 25 MPC, the level of anxiety throughout the study was approximately the same throughout the study days. When comparing the results of TPS II experimental animals with individuals of the control group were found significant differences on the 21st and 30th day of the study. At this time of observation, the integral indicator of anxiety in rats after seeding at a dose of 25 MPC was significantly higher than that in the control group and was 8.29±1.8 and 8.25 ±2.2 points, respectively (t = −2.42, t =−2.29, p <0.05).

The level of anxiety of rats exposed to UOD at a dose of 50 MPC was significantly higher than that of intact animals during whole studystudy days with the highest values on day 1, then the total number of anxiety scores was 12.1±3.3. Significant differences between the III and I groups of animals were recorded throughout the entire series of experiments; in addition, the TPS was at a fairly high level up to the 30th day of observation.

Such results may indicate the formation of a stable anxiety in animals of the experimental group, which persists until the end of the experiment. When comparing the results obtained in groups II and III of animals exposed to UOD in different doses, a significant increase in the integral indicator of anxiety in animals was found, with a higher dose of UOD intake all experimental days. Investigation of the state of situational anxiety in male rats led to the conclusion that during the admission admission of UOD at 25 MPC anxiety changes were observed in the last days of the study, indicating the formation of chronic psych emotional stress.

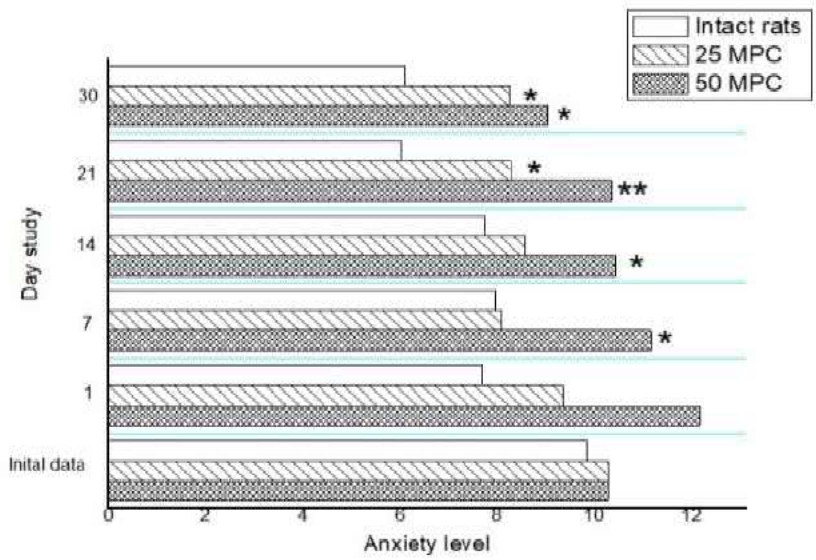

Figure 2 Average values of the level of anxiety of male rats in the experimental and control groups. The asterisk indicates the statistically significant differences in the anxiety- phobic status of the experimental animals with the control group (* p <0.05, ** p <0.01).

Upon receipt of UOD in a dose of 50 MPC, the level of anxiety was high all study days with maximum DPS values at the beginning of the experiment.

It is known that such fundamental emotions as anxiety and fear prepare the body for an adequate response in case of danger. However, the pathological enhancement of these emotions, expressed in anxious phobic states, is one of the main features of a number of neuropsychiatric diseases, such as depression, manic-depressive psychosis, panic disorders, various types of neuroses [20].

For a more complete psychophysiological characteristics of individuals exposed to UOD, we carried out the experiments about studying their conditioned reflex activity (CRA). Acquired memory, the experimental model of which are different conditioned reflexes, "responds" to various adverse factors earlier than other forms and their pathological changes stay longer after various pathogenic influences. By now, the data about more persistent and longstanding changes of experimental animals' CRA after exposure of ionizing radiation were obtained [21]. Therefore, the conditioned passive avoidance reflex was formed in the late period after intoxication with UOD. The full period of the research of the nervous system's functional state was more than two months after incorporation of animals. In the long-term period after the admission of UOD, in different doses, the uranium content in the brain of rats was more than 3 times higher than this indicator in the control group.

The research of conditioned reflex activity of intact animals has allowed us to establish that in the first day of observation (24 hours after electrodermal irritation) the residence time in the lighted compartment of the camera was 179.5±1.7 sec. Average values of the residence time in the light compartment of the camera were more than 144-second criterion of reflex performance [22], which testify about successful formation of conditioned passive avoidance reflex (CPAR) of animals. Animal observation in the next few days Revealed exceed criterion exceed criterion performance of the reflex during whole series of experimental research. In addition, the largest number of rats with a maximum residence time (180 sec) in the light compartment of the camera were recorded in this group of animals. Practically on all observation days, 91.7% of the animals completely reproduced conditioned passive avoidance reflex.

In group II of animals exposed to UOD at a dose of 25 MPC, a decrease in the residence time in the safe compartment of the camera during all days of observation after electrical irritation was detected . The average values of this indicator were recorded below the 144-second reflex performance criterion , however, significant differences in comparison with a group of intact rats were detected on the 2nd and 14th day of the research and were 98.9±85.4 ($U=39$, $p<0.05$) and 81.8±70.4 ($U=15$, $p<0.01$), respectively. In the research group a low percentage of animals that fully reproduced the acquired skill of CPAR was also noted : an average of 40% during all days of experience

In the group of male rats receiving UOD at a dose of 50 MPC, the following picture was observed: a significant decrease in the residence time in the safe compartment of the camera on the 7th and 14th day after electrical irritation. On the presented days of the study, the duration of the time when male rats located in the light part of the setup was 116.3±68.7 ($U=32$, $p<0.05$) and 114.2±78.9 ($U=40$, $p<0.05$) seconds respectively . In addition, in the experimental group of animals, the number of rats completely reproducing the skill of passive avoidance significantly decreased: on average, only 62% animals that received UOD at a dose of 50 MPC were able to stay in the safe part of the experimental setup for 180 seconds.

When comparing the performance of conditionally reflex activity between experimental groups of animals admitted with various doses of UOD , differences were identified. In the second group of male rats, which received UOD in a dose of 25 MPC, the time spent in the safe compartment of the camera was less than the third group of animals all research days . Statistically significant differences were recorded on the first day of observation, when the duration of the residence time in the light compartment of the camera for II group was 118.5±62.6sec versus 168.7±39.3 ($U=31$, $p<0.01$) for group III . At the same time, the number of rats staying all 180 s in the safe compartment of the camera in the group with the lower dose of UOD were less on average by 20%. However, statistically significant differences were detected only on the first day after electro-irritation: 33.3% versus 91.7% ($\chi2=8.7$, $p<0.05$). The differences between the experimental groups obtained in our research work can be explained by the high level of excitation of animals receiving UOD at a dose of 50 MPC, which possibly contributed to the activation of compensatory processes in the central nervous system, ensuring its activities on the new functional level. Furthermore, there are data that ionizing radiation causes focal damages in higher parts of CNS that create preconditions for sufficiently effective compensation functions of affected sections [23]. It should be emphasized that, in general, the influence of uranium ore dust reduced the frequency of choosing a safe compartment in both experimental groups, which indicates its negative effect on the spatial component of memory. Thus, the results of researches show that in the long term after radiotoxic effects of UOD decreased ability to perform the conditional passive avoidance reaction (CPAR) and reduced terms of retention of acquired passive avoidance skills were observed.

4. CONCLUSIONS

According to the results of the study, after the oral intake of dust of uranium ore into the animal organism, the kidney was a critical organ for uranium, and bone tissue in the later periods. In this work, it was shown that oral intake of UOD in the body causes behavioral changes such as increased anxiety disorders of conditioned reflex activity, cognitive disorders.

The study of the dynamics of behavioral abnormalities indicates the long-term preservation of violations of the higher nervous activity of animals. The remoteness of the effects of UOD demonstrates the need for long-term observation of changes in the behavior of animals exposed to UOD under experimental conditions. The nature of the data we obtained confirms both the presence of a clear difference between animals that received oral UOD in various doses and rats of the control group, and the lack of a direct connection between the studied causes and the consequences of behavioral deviations in rats. Eventually, the results of the study showed that intoxication with dust of uranium ore has a negative impact on the behavior and emotional status of animals.

It should be noted that these changes in anxiety-phobic status and conditioned-reflex activity can reduce the efficiency, reliability and safety of professional activities among workers in the uranium industry. The data obtained in laboratory animals can be useful in radiobiological assessment of the health status of persons chronically exposed to the uranium ore dust.

CONFLICT OF INTEREST

None.

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