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# IMPACT OF FEEDING MALE RATS $F_2$ WITH DIFFERENT DOSES OF GERMANIUM CITRATE ON THE CONTENT OF TRACE ELEMENTS IN THEIR TISSUES AND ORGANS

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**Aim.** To determine the impact of the dose of germanium citrate on the distribution and concentration of the trace elements Fe, Zn, Cu, Co, Mn in tissues and organs of male $F_2$ rats. **Methods**. Standard physiological, biochemical (including atomic absorption spectrometry), clinical and statistical methods were applied. **Results**. It was established that there were changes in the content of Fe, Zn, Cu, Co, Mn in soft tissues and their distribution in liver, kidneys and lungs of male $F_2$ rats. It was demonstrated that these were mostly changes in organ-tissue specific functioning of some physiological systems, for instance, hepatorenal and respiratory systems of the organism as induced with a few exceptions independent of the different doses of germanium (10, 20 and 200 μg/kg of bodyweight). The differences were most apparent in kidneys and less in liver and lungs. The doses of 10, 20 and 200 μg Ge, and those of Fe – 20 and 200 μg – caused higher concentrations of Cu, Co, Mn and Zn in muscle tissues. The differences in the weight of liver, kidneys and lungs of rats of experimental and control groups were determined in order to eliminate intergroup differences and to obtain the absolute content of the investigated trace elements in liver, kidneys and lungs. The mentioned differences were more expressed for the absolute content of Cu in liver and for Mn in kidneys and lungs. **Conclusions**. Long-term introduction of oral aqueous germanium citrate into the organism of a $F_2$ generation of rats at 10, 20 and 200 μg Ge kg-1 of the bodyweight is characterized by the changes in the content of Cu, Co, Mn, Fe, Zn both per one unit of soft tissue weight and their absolute content in the internal organs. The biological effect of germanium citrate is expressed more in the high dose of 200 μg Ge/kg of the bodyweight, conditioning the increase in the content of Cu (from 51 to 95 %) and Zn from 22 to 78 % in all the investigated tissues of rats of this group. There was a decreased level of Co in liver at the effect of 20 and 200 μg Ge, and at the effect of all the administered doses in kidneys and lungs. The level of Mn increased by 27.7; 74.0 and 23.4 % in groups II, III and IV respectively in the muscle tissues of male $F_2$ rats at the effect of all the administered doses of Ge, Co 20 and 200 μg, Fe 10 and 20 μg, and Zn 10 and 200 μg Ge, which testifies to the differences in the regulatory impact of NGeC on the level of investigated trace elements in the muscle tissues of rats.

**Keywords:** trace elements, soft tissues, muscle.

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## INTRODUCTION

It is known that the uptake and incorporation of trace elements in the organism of humans and animals is determined by a number of physiological mechanisms, including synergetic or antagonistic interactions. These interactions have been firmly established for most macro- and trace elements, and they are normalized in nutrition [1–3]. The regulatory impact of physiologically active, but insufficiently studied elements, among which germanium takes a prominent place, on organ-tissue distribution of other minerals, is presently actively studied in biology, medicine, and veterinary science [3, 4]. Organic formulations of macro- and trace elements (nanoaquachelates) as obtained by nanotechnology methods receive special attention [5, 6]. The

biological role of these organo-compounds and their interaction with other macro- and trace elements and their impact on their distribution in the organism and its organs are actively studied as well. In particular, our earlier research [7, 8] showed that the administration of germanium citrate, obtained via the erosive and explosive ablation with electro-impulse, caused a number of biological effects in the organism of rats. This may have found its cause in the fact that germanium (Ge) has an immuno-stimulating effect, enhances transport and transfer of $O_2$ and ensures the decrease of hypoxia at tissue level [3, 4]. Certain organic forms of Ge have negatively charged oxygen ions that can scavenge free damaging hydrogen ions and minimize their damage to cells and tissues [9]. A notable characteristic of organic forms of Ge is that they are removed fast with urine from the organism, which indicates its low accumulation in tissues [4, 10]. Different concentrations and duration of Ge intake affect physiological-biochemical processes in the organism differently, including their influence on the level of macro- and trace elements in tissues [3, 6, 7]. Recent experimental studies on physiological mechanisms of the effect of different doses of germanium citrate on organ-tissue and systemic level [6, 7, 9] and preparations, including Astrogerm, Germatranol, Germavit, elaborated on the basis of this chelate complex, stimulated a profound investigation of this compound on the intake of such vital elements as Cu, Co, Mn, Fe, Zn in the organism, the results of which are reported in this article.

## MATERIALS AND METHODS

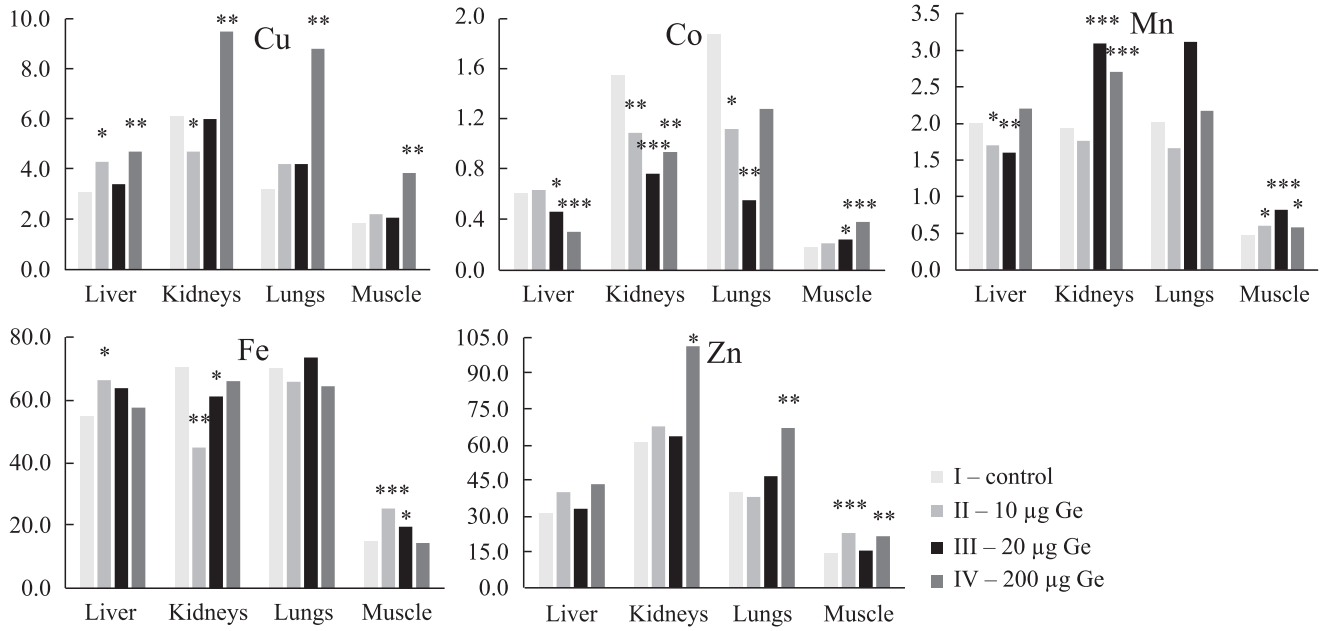
The studies were conducted using white laboratory male $F_2$ rats, divided into one control (I) and three experimental (II, III, IV) groups, 4 animals in each. Contrary to the control group, the rats of experimental groups daily received the addition of nanogermanium citrate (NGeC), manufactured by the nanotechnology method [11, 12], with drinking water, calculated as 10 (experimental group II ), 20 (III) and 200 (IV) µg Ge/kg of the bodyweight. Feeding female rats of generations $F_0$ and $F_1$ with germanium citrate in the mentioned doses during their ontogenesis and pregnancy, and feeding young rats of respective groups $F_1$ and $F_2$ with milk of the germanium-fed mothers was conducted. The effect of germanium citrate on the organism of young $F_2$ rats was revealed at the stages of embryonic, fetal and preweaning period of development via mothers' blood and milk as well as via absorption in the digestive tract after the start of independent consumption of feeds and water. At the age of 4–4.5 months, 4 male rats from each group were decapitated after narcosis to study their internal organs. The content of Fe, Zn, Cu, Mn, Co in homogenates of tissues of liver, kidneys, lungs and femoral muscle was determined after dry ashing in the muffle furnace at 450–500 °C and dissolving the mineral residue in 10 % HCl. The trace elements were detected during the period of burning their acid solutions in the acetylene flame, using an atomic absorption spectrophotometer SF-115 PC (Selmi, Ukraine) with the software for concentration calculation, as described in [13]. The obtained results were statistically processed using MS Excel and determining the mean values (M), and their deviations, where standard deviation = standard error of the mean (± m SD), and the probability degree by Student's coefficient ($P \leq 0.05$). The obtained mean results of the experimental groups were compared against those of the control group.

## RESULTS AND DISCUSSION

The analysis of the obtained results indicated unevenly directed changes in the content of the investigated trace elements in the tissues of internal organs and muscle tissue of $F_2$ males depending on the dose of NGeC. In particular, a higher content of Cu was 38.7 and 51.6 % detected in liver tissues of rats at 10 ($P < 0.05$) and 200 ($P < 0.01$) µg Ge/kg of the bodyweight, and the elevated Fe of 21.3 % at 10 µg ($P < 0.05$) with the preservation of this tendency for Fe also for males receiving 20 – 16.7 % and less so for those receiving 200 µg – 5.3 % (Figure).

The content of Co decreased by 23.3 ($P < 0.05$) and 50 % ($P < 0.001$) in liver tissues of males receiving 20 and 200 µg. The content of Mn decreased also by 15 and 20 % at the dose of 10 and 20 µg Ge. No significant differences in Mn content were detected in the tissues of liver, kidneys and lungs of $F_2$ rats with all dose rates applied, which was also noted by other researchers [2, 3]. It is known that Mn is found in all the tissues and liquids of the organism without considerable organ-, species- or age-related differences. The increase in Mn concentration in the liver of rats was noted at the effect of 5 pg Ge in the form of sodium germanate [3]. There was a confirmed impact of this compound on the mineral exchange via functioning of the main regulatory enzymes, activated by Mn – hydrolases, kinases, decarboxylases.

In the processes of absorption from the intestines, Mn competes with Co for the binding sites, whereas the mechanisms of absorption of Mn and Fe are similar and there is no competition [2]. The differences in Co




The content of trace elements in the tissues of male $F_2$. Note: Statistically significant differences from the control group I in Figure and Table are indicated as *– $p \leq 0.05$; ** – $p \leq 0.01$, *** – $p \leq 0.001$

content in the tissues of internal organs, noted for $F_2$ rats, were also established for male $F_1$ rats at the age of 2–2.5 months. In particular, the content of Co in liver tissues of male $F_1$ rats at the doses of 20 and 200 μg Ge was 40–50 % lower as compared to the control group [7]. The mentioned regularity of Co content in liver tissues of $F_1$ and $F_2$ rats at the effect of these doses of NGeC in male $F_1$ rats was also preserved for Co content in lung tissue of animals of generation $F_2$. In particular, the effect of germanium was revealed in the decrease by 40.3 and 70.4 % in the content of Co in lung tissues of rats of groups II ($P < 0.05$) and III ($P < 0.01$) and the decrease by 32 % – group IV.

A significantly lower content of Co (by 29.4; 50.3 and 39.2 %) was found in the tissues of kidneys of male $F_2$ rats of all the experimental groups, Cu and Fe – at the effect of 10 and 20 μg Ge at the background of a higher level of Mn ($P < 0.001$) in groups III and IV and Cu ($P < 0.01$) and Zn ($P < 0.05$) in male rats of group IV, which received 200 μg Ge. NGeC had a more visible inhibiting effect on the content of Fe and Co in the tissues of kidneys and on the content of Co in liver tissues at the effect of 20 and 200 μg Ge, and as for Mn – 10 and 20 μg Ge in liver, which may impact the hematopoietic ability of the organism of male $F_2$ rats as follows: it is known that Co enhances the intake of Fe and synthesis of hemoglobin, stimulating erythropoiesis. Co negatively affects the synthesis of proteins and repair of S-S group sulphur bridges, that operate in the processes of blocking and detoxification of poisonous elements in the organism [2, 3].

A less clear regulatory effect of NGeC compared to the liver tissue on the content of the investigated elements was noted for the tissues of lungs, but the content of Zn and Cu in lung tissue was also 66.9 and 175 % higher ($P < 0.05$; $P < 0.01$) for male rats of group IV. It is remarkable that the content of Cu in lung tissue of male rats of group IV was 27.5 % higher ($P < 0.01$) against the control compared to the tissues of liver, kidneys and muscles. It may indicate a stimulating effect of NGeC in the dose of 200 μg Ge on the intensity of Cu metabolism in the organism and as a result, the level of this microelement in the internal organs and muscles of rats.

The increase in the content of Cu in the tissues of liver, kidneys, lungs and muscles of rats may condition enhanced redox processes and supply of these tissues with $O_2$, which was also noted by other researchers [3, 14, 15, 16]. It is known that a high level of Cu in the tissues of the organism stimulates the processes of antioxidant protection with the participation of its incorporation into enzymes involved in these processes.

The content of trace elements in the tissues of femoral muscle of rats was found to be 2–10 times different from that of the tissues of internal organs. For instance, a higher content (by 27.7; 74.0 and 23.4 %) of Mn for males of all the experimental groups was noted in the

samples of muscle tissues at the effect of low (10 μg), medium (20 μg) and high (200 μg) doses of Ge, and Zn by 56.3 and 46.7 % – 10 ($P < 0.001$) and 200 μg ($P < 0.01$), see Table. The content of Fe was also considerably higher in the muscle tissues at the effect of 10 and 20 μg Ge, and as for Cu – 200 μg ($P < 0.01$).

The absolute content of the trace elements Cu, Co, Mn, Fe and Zn was also studied in the liver, kidneys and lungs in relation to the weight of these organs. The weight of the organs, except for kidneys in group IV, in males of all experimental groups showed a tendency to decrease in the range from 7.3 to 22.6 % which was statistically significant at least for liver in group II ($P < 0.01$) and III ($P < 0.05$), and for lungs in group III ($P < 0.05$) (Table). In particular, a lower content (from 35.7 to 56.7 %) of Co was found in the liver of rats in groups III ($P < 0.01$) and IV ($P < 0.001$) and for Mn in groups II and III ($P < 0.001$). To the contrary, a higher level of Zn was found in animals of group IV ($P < 0.05$). The absolute content of Cu in the liver of male rats of group IV increased from 34.9 % ($P < 0.05$).

The absolute content of the investigated trace elements in the kidneys of rats mainly preserved the direction of differences between the control and experimental groups relative to their level in mg/kg of the weight of the tissue (Figure). The absolute content of Mn in the kidneys of males of group II at the effect of a low (10 μg) dose of NGeC, however, was 15.5 % lower as compared to that of the control. It may be conditioned by the impact of lower indices of Mn content in these tissues and a smaller weight of this organ by 7.3 % in rats of group II. The absolute content of Mn in kidneys of males of groups III and IV was 47.8 and 54.8 % higher respectively ($P < 0.001$) at an insignificantly increased level (by 10.7 %) of the weight of this organ as compared to that of the control. A statistically significant higher absolute content of Mn in the kidneys of males of group III and IV was demonstrated at the expressed impact of 20 and 200 μg Ge of NGeC

The absolute content of trace elements in some internal organs of male $F_2$ rats at the age of 4 months, (mean, M and standard deviation, ± m; number of rats, $n = 4$)

| Groups | Organ weight, g | Content of the microelements, μg | | | | |
|---|---|---|---|---|---|---|
| | | Cu | Co | Mn | Fe | Zn |
| Liver | | | | | | |
| Control – I | 8.97 ± 0.46 | 27.5 ± 3.82 | 5.43 ± 0.27 | 17.9 ± 0.81 | 489.6 ± 27.7 | 489.6 ± 27.7 |
| Experimental/dose of Ge, μg | | | | | | |
| II – 10 | 6.94 ± 0.45** | 29.5 ± 3.03 | 4.39 ± 0.35 | 12.0 ± 0.52*** | 459.5 ± 23.1 | 278.4 ± 22.5 |
| III – 20 | 7.59 ± 0.39* | 25.6 ± 4.45 | 3.49 ± 0.18** | 11.9 ± 0.36*** | 483.6 ± 26.0 | 251.4 ± 33.5 |
| IV – 200 | 7.92 ± 0.26 | 37.1 ± 2.59 | 2.35 ± 0.12*** | 17.5 ± 0.75 | 455.1 ± 28.0 | 344.2 ± 63.2* |
| Kidneys | | | | | | |
| Control – I | 1.78 ± 0.08 | 10.8 ± 0.61 | 2.72 ± 0.14 | 3.43 ± 0.13 | 124.9 ± 5.1 | 109.2 ± 17.7 |
| Experimental/dose of Ge, μg | | | | | | |
| II – 10 | 1.65 ± 0.07 | 7.7 ± 0.46** | 1.77 ± 0.12** | 2.90 ± 0.04** | 73.9 ± 6.3*** | 111.7 ± 15.3 |
| III – 20 | 1.64 ± 0.04 | 9.8 ± 0.60 | 1.25 ± 0.06*** | 5.07 ± 0.09*** | 100.1 ± 3.4** | 104.4 ± 9.9 |
| IV – 200 | 1.97 ± 0.04 | 18.8 ± 0.97*** | 1.83 ± 0.13** | 5.31 ± 0.15*** | 129.9 ± 7.4 | 199.8 ± 10.1* |
| Lungs | | | | | | |
| Control – I | 1.55 ± 0.09 | 5.0 ± 0.33 | 2.88 ± 0.33 | 3.11 ± 0.11 | 108.4 ± 10.6 | 62.2 ± 3.69 |
| Experimental/dose of Ge, μg | | | | | | |
| II – 10 | 1.35 ± 0.09 | 5.6 ± 1.19 | 1.50 ± 0.01* | 2.24 ± 0.20* | 88.7 ± 7.8 | 51.4 ± 7.64 |
| III – 20 | 1.30 ± 0.06* | 5.4 ± 0.74 | 0.72 ± 0.22** | 4.04 ± 1.07 | 95.4 ± 7.5 | 60.8 ± 9.05 |
| IV – 200 | 1.36 ± 0.08 | 11.9 ± 1.19** | 1.72 ± 0.39 | 2.95 ± 0.14 | 87.5 ± 6.1 | 91.3 ± 7.29* |

on the increase in Mn content in kidneys. This effect is also confirmed by the increase ($P < 0.001$) in Mn content in the tissues of kidneys (in mg/kg) of males from groups III and IV (Figure).

Statistically significant differences in the absolute content of the investigated trace elements were preserved in the lungs of rats of experimental groups similarly to those as per one unit of tissue weight in mg/kg, presented in Figure. The detected changes demonstrated that the absolute content of Mn in the lungs of group II males showed a significant decrease similarly to the liver and kidneys. It was conditioned both by the lower level of this element in the lung tissue and by the tendency to the decrease in the weight of this organ (12.1 %) compared to the control. However, a lower index of the weight of lungs in animals of group IV had no considerable impact on the significant increase in the absolute content of Zn in this organ, as the content of Zn in the lung tissues of rats of this group was 46.9 % higher ($P < 0.01$). It should be noted that a high (200 μg) dose of Ge conditioned a significant increase in the absolute content of Zn in the liver, kidneys and lungs, Cu – in the kidneys and lungs, Mn – in the kidneys.

## CONCLUSIONS

Thus, the introduction of germanium citrate for 120–135 days, obtained via electric impulse ablation and its administration with drinking water in the amounts of 10, 20 and 200 μg Ge/kg bodyweight into $F_2$ rats is characterized by the changes in the content of Cu, Co, Mn, Fe, Zn both per unit of soft tissue weight and their absolute content in the entire internal organs. The biological effect of germanium citrate is more expressed in the high dose of 200 μg Ge/kg than in the lower doses conditioning the increase in the content of Cu from 51 to 95 % and Zn from 22 to 78 % in all the investigated tissues of rats. There is a decrease of Co by 40.3 % in the liver at 20 and by 70 % at 200 μg Ge, and at all the administered doses from 27 to 50 % in kidneys and 33–310 % in lungs. The level of Mn increased from 23.4 to 74 % respectively in the muscle tissues of male $F_2$ rats at all administered doses of Ge, for Fe it was respectively for the doses of 10 ($P < 0.001$) and 20 μg ($P < 0.05$), and finally for Zn respectively for the doses of 10 ($P < 0.001$) and 200 μg Ge ($P < 0.01$). There was a statistically significant increase in the content of Cu and Zn in all the investigated tissues and organs of $F_2$ rats at the effect of 200 μg Ge, which may indicate enhanced accumulation of Cu and Zn in the organism of rats at long-term ($F_0$-$F_1$-$F_2$) intake of germanium citrate with drinking water.

**Вплив випоювання різних доз германію цитрату на вміст мікроелементів у тканинах та органах самців щурів $F_2$**

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**Мета.** З'ясувати вплив дози германію цитрату на розподіл Fe, Zn, Cu, Co, Mn у тканинах та органах щурів-самців $F_2$. **Методи.** Фізіологічні, біохімічні, клінічні, статистичні. **Результати.** Встановлені зміни вмісту Fe, Zn, Cu, Co, Mn у м'яких тканинах та їх розподілу у печінці, нирках і легенях самців щурів $F_2$. Показано, що ці зміни зумовлюються в більшій мірі органо-тканинними особливостями функціонування окремих фізіологічних систем організму, зокрема гепато-ренальної і дихальної, а в меншій – дозою Германію (10, 20 і 200 мкг/кг м. т.). Більше виражені зміни вмісту цих елементів встановлені для нирок за дії всіх застосованих доз, а менше – печінки і легень. У тканинах м'яза відзначено позитивний вплив германію цитрату на вміст Cu, Co, Mn і Zn за дії 10, 20 і 200 мкг Ge, а Fe – 20 і 200 мкг. Встановлені різниці маси печінки нирок і легень щурів дослідних і контрольної груп, що нівелювало міжгрупові відмінності абсолютного вмісту досліджених мікроелементів у печінці, нирках і легенях. Вказані відмінності більше виражені для абсолютного вмісту Cu у печінці, Mn у нирках і легенях. **Висновки**. Тривале надходження в організм щурів $F_2$ з водою германію цитрату в кількості 10, 20 і 200 мкг Ge/кг м. т. характеризується змінами вмісту Cu, Co, Mn, Fe, Zn як на одиницю маси м'яких тканин, так і абсолютного вмісту їх у внутрішніх органах. Біологічна дія германію цитрату більше виражена у дозі 200 мкг Ge/кг м. т., що зумовлює підвищення вмісту Cu (від 51 до 95 %) і Zn (від 22 до 78 %) у всіх досліджених тканинах щурів цієї групи на тлі зниження рівня Co у печінці за дії 20 і 200 мкг Ge, а нирках і легенях – за дії всіх застосованих доз. У тканинах м'язів самців $F_2$ вірогідно зростав вміст Mn (на 27,7; 74,0 і 23,4 % в II, III і IV групах відповідно) за дії всіх застосованих доз Ge, Co – 20 і 200 мкг, Fe – 10 і 20 мкг, а Zn 10 і 200 мкг Ge, що свідчить про відмінності регуляторного впливу HGeЦ на рівень досліджених мікроелементів у тканинах м'язів щурів.

**Ключові слова:** наноматеріали, внутрішні органи, м'язи.

**Влияние выпаивания разных доз германия цитрата на содержание микроэлементов в тканях и органах самцов крыс $F_2$**

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**Цель.** Выяснить влияние дозы германия цитрата на распределение Fe, Zn, Cu, Co, Mn в тканях и органах крыс-самцов $F_2$. **Методы**. Физиологические, биохимические, клинические, статистические. **Результаты**. Установлены изменения содержания Fe, Zn, Cu, Co, Mn в мягких тканях и их распределения в печени, почках и легких самцов крыс $F_2$. Показано, что эти изменения обусловлены в большей степени органо-тканевыми особенностями функционирования отдельных физиологических систем организма, в частности гепато-ренальной и дыхательной, а в меньшей – дозой германия (10, 20 и 200 мкг/кг м. т.). Более выраженные изменения содержания этих элементов установлены для почек при действии всех примененных доз, а меньше – печени и легких. В тканях мышцы отмечено положительное влияние германия цитрата на содержание Cu, Co, Mn и Zn при действии 10, 20 и 200 мкг Ge, а Fe – 20 и 200 мкг. Установленные различия массы печени, почек и легких крыс опытных и контрольной групп сглаживали межгрупповые различия абсолютного содержания исследованных микроэлементов в печени, почках и легких. Указанные различия более выражены для абсолютного содержания Cu в печени, Mn – в почках и легких. Выводы. Длительное поступление в организм крыс $F_2$ с водой германия цитрата в количестве 10, 20 и 200 мкг Ge/кг м. т. характеризуется изменением содержания Cu, Co, Mn, Fe, Zn как на единицу массы мягких тканей, так и абсолютного содержания их во внутренних органах. Биологическое действие германия цитрата больше выражено в дозе 200 мкг Ge/кг м. т., и приводит к повышению содержания Cu (от 51 до 95 %) и Zn (от 22 до 78 %) во всех исследованных тканях крыс этой группы на фоне снижения уровня Co в печени при действии 20 и 200 мкг Ge, а почках и легких – при действии всех примененных доз. В тканях мышц самцов $F_2$ достоверно возрастало содержание Mn (на 27,7; 74,0 і 23,4 % во II, III и IV группах соответственно) при действии всех примененных доз Ge, а Co – 20 и 200 мкг, Fe – 10 и 20 мкг, Zn – 10 и 200 мкг Ge, что свидетельствует о различиях регуляторного влияния HGeЦ на уровень исследованных микроэлементов в тканях мышц крыс.

**Ключевые слова:** наноматериалы, внутренние органы, мышцы.

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