AGRICULTURAL BIOLOGY,
2023, V. 58, Iss. 6, pp. 1137-1147
[SEL'SKOKHOZYAISTVENNAYA BIOLOGIYA]

ISSN 2412-0324 (English ed. Online)

ISSN 0131-6397 (Russian ed. Print)
ISSN 2313-4836 (Russian ed. Online)

UDC 636.38:546.815

doi: 10.15389/agrobiology.2023.6.1137eng
doi: 10.15389/agrobiology.2023.6.1137rus

MATHEMATICAL MODEL OF THE TRANSFER OF LEAD FROM PERIPHERAL BLOOD INTO THE ORGANS AND MUSCLE TISSUE OF SHEEP (*Ovis aries*)

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The authors declare no conflict of interests
Acknowledgements:
The research was carried out within the framework of the terms of reference on the complex topic 5P.7.1 "Development of scientifically based technological methods of crop, feed production and livestock in conditions of technogenic pollution".
Final revision received June 05, 2023
Accepted July 10, 2023

Abstract

To obtain livestock products that meet sanitary and hygienic standards for lead, it is necessary to establish the permissible limits of its daily intake by animals from the ration. In this work, based on the model we have developed, the parameters of lead transport between peripheral blood, organs and muscle tissue were determined for the first time, depending on the daily concentration of the metal in the ration and the duration of its entry into the body. Our aim was to develop and parametrize a chamber model of the transfer of lead from peripheral blood to the organs and muscle tissue of sheep during chronic dietary intake. The experiments were carried out on 27 Romanov sheep. The age of the animals is 1-1.5 years, body weight is 33.5±0.7 kg. Sheep were kept in boxes of 4-5 heads in the vivarium of the All-Russian Research Institute of Physiology, Biochemistry and Nutrition (BIFIP, Kaluga region, Borovsk). Feeding was carried out twice a day with free access to water. The animals were divided into four groups: group I (control) — 4 sheep, group II — 5 sheep, groups III and IV — 9 sheep each. The concentration of lead in the ration for group II was 5 mg · kg^{-1} (1 MPL), for group III — 25 mg · kg^{-1} (5 MPL), for group IV — 150 mg · kg^{-1} (30 MPL). Lead nitrate $Pb(NO_3)_2$ was added to compound feed once a day. The daily intake of metal for group II was 10 mg/head, group III — 50 mg/head, group IV — 300 mg/head, or 0.3, 1.5 and 9 mg · kg^{-1} body weight. Blood samples were taken before feeding from the jugular vein before the experiment, on days 30, 60 and 90. During the study period, animals were slaughtered, 1 sheep before the experiment, on days 30 and 60 1 sheep from group II and 3 sheep from groups III and IV; on day 90 — 3 sheep from each group. The patterns of distribution and accumulation of lead in the organs and tissues of sheep were analyzed using a mathematical model in which the liver, kidneys, spleen, lungs, heart and muscle tissue are represented as separate chambers physiologically interconnected by transport communications. Changes in the constants of the rate of transfer of lead from peripheral blood into different organs and muscle tissue of sheep, depending on the metal content in the ration and the duration of its intake, were established. The parameters characterizing the ratio of the constants of the rate of transfer of lead from the blood into the organs and back (from the organs into the blood) are determined. It is shown that the values of the parameters for the liver and kidneys as compared to other organs and tissues (spleen, lungs, heart and muscle tissue) are 10 and 100 times lower, respectively. Comparative analysis of experimental data and calculations on the model is carried out. The degree of coincidence of the results shows that the chamber model satisfactorily describes the transfer of lead from the peripheral blood into the organs and muscle tissue of sheep. The developed mathematical model is recommended for assessing and predicting the safety of sheep products.

Keywords: lead, chamber model, sheep, blood, liver, kidneys, spleen, lungs, heart, muscle tissue

Contamination of agricultural land with lead compounds increases the likelihood of its transfer into food (meat, milk, offal) via the trophic chain soil—

plant—animal [1-3]. Lead is highly cumulative and, depending on the dose and duration of exposure in mammals, exhibits high general toxicity, embryotoxicity, carcinogenicity and genotoxicity [4-6]. The World Health Organization (WHO) has approved the maximum permissible level of lead for humans at 25 $\mu g \cdot kg^{-1}$ body weight per week, or 3.6 $\mu g \cdot kg^{-1}$ body weight per day. However, in 2011, this threshold was canceled because it did not ensure the health safety of children and adults [7]. In the Russian Federation, permissible daily doses of lead for humans have not been established, although in the USSR the recommended dose was 4 $\mu g \cdot kg^{-1}$ body weight per day [8]. In the United States, the Food and Drug Administration (USFDA) in 2020 issued a temporary permissible daily intake of lead for children and adults of 3 and 12.5 μg, respectively [9]. In 2021, the US Centers for Disease Control and Prevention (CDC) updated the standard for lead concentrations in peripheral blood, and the temporary permissible daily intake of lead was reduced to 2.2 μg for children and 8.8 μg for women of childbearing age [10).

The toxic effect of lead on mammals is more correctly assessed not by daily intake, but by peripheral blood concentration which plays an important role in the transport and redistribution of the metal to organs and tissues. Determination of lead concentrations in peripheral blood eliminates the uncertainties caused by gastrointestinal (GI) absorption of the metal [11]. In the USA, the standard for the lead concentration in human peripheral blood was 60 $\mu g \cdot dl^{-1}$ in 1960-1970, 30 $\mu g \cdot dl^{-1}$ in 1970-1985, 25 $\mu g \cdot dl^{-1}$ in 1985-1991, in 10 $\mu g \cdot dl^{-1}$1991-2012, 5 $\mu g \cdot dl^{-1}$ in 2012-2021, 3.5 $\mu g \cdot dl^{-1}$ from 2021 to the present [9, 10, 12]. Biokinetic models were used to calculate the permissible amount of lead entering the body [13-15]. It should be noted that mathematical models for predicting has primarily been used to assess the risk of human exposure to lead [16-18] through food intake [19].

Currently, mathematical models for predicting the risk of lead exposure in farm animals have not been developed. Existing conceptual and chamber models assess the accumulation of radionuclides in animal products (meat, milk) [20] or in the organs and tissues of laboratory animals [21]. In 2023, a simulation model was presented to assess the permissible levels of cadmium, lead, mercury and arsenic in the diets of cows and sheep for food production (meat and milk) that meet the requirements of SanPiN 2.3.2.1078-01 [22]. It must be emphasized that with chronic intake of lead, the kidneys and liver of farm animals are most severely affected. Producing meat and milk that meets sanitary and hygienic standards does not fully guarantee the safety of livestock products. The functional activity of the organs of the detoxification (liver) and excretory (kidney) systems can have a negative impact on the animal metabolism and healt. Therefore, when exposed to lead, the safety assessment of meat, milk and by-products must be carried out.

An analysis of scientific information on the lead effects in mammals suggests that research on farm animals is fragmented. The main attention was paid to livestock farming under lead contamination of territories and to obtaining food products (meat, milk) that meet sanitary and hygienic standards [23-25]. Animal model studies have assessed exposure to lead in food-producing animals at concentrations that significantly exceeded maximum permissible levels (MPLs) in feed [2, 26, 27].

Lifetime assessment of lead content in the organs and tissues of farm animals can predict the degree of contamination of livestock products. To predict the lead content in meat and milk, transition coefficients (CT) are mainly used. Thus, with chronic intake of lead in sheep, CTs from the diet were established for the peripheral blood, liver, kidneys and spleen [28, 29] and a method was proposed

for estimating the amount of metal in muscle tissue based on the concentration in wool and feces [30]. Note that the high variability of CTs does not allow us to correctly predict the lead content in organs and tissues. Therefore, the alternative methods for intravital assessment of the lead accumulation is still relevant.

Previously, a conceptual scheme of the lead distribution in ruminants [31] and a chamber model of the transition of the metal from different parts of the gastrointestinal tract into the peripheral blood of sheep [32] were reported.

In this work, based on the model we developed, we assessed for the first time the parameters of lead transport between peripheral blood, organs and muscle tissue depending on the daily dietary concentration of the metal and the duration of its entry into the body.

Our goal was to develop and parameterize a chamber model of the lead transition from peripheral blood to the organs and muscle tissue of sheep during chronic intake of the metal in the diet.

Materials and methods. The model used was developed based on our own experimental data [28-30]. The experiments were carried out on 27 Romanov sheep (*Ovis aries)* aged 1-1.5 years, live weight 33.5±0.7 kg. Animals were kept in boxes, 4-5 sheep per each (the vivarium of the All-Russian Research Institute of Physiology, Biochemistry and Nutrition, ARRIPB&N, Borovsk, Kaluga Province). Sheep were fed twice a day with free access to water. The animals were divided into four groups: group I was 4 control animals, group II contained 5 animals, groups III and IV 9 animals each. The dietary lead was fed at 1 MPL (5 mg · kg^{-1}) to group II, at 5 MPL (25 mg · kg^{-1}) to group III, and at 30 MPL (150 mg · kg^{-1}) to group IV. Lead nitrate Pb(NO3)2 was fed with mixed feed once a day, given on average 2 kg of feed entering the gastrointestinal tract. To do this, 100 g of feed was mixed with 50 ml of a Pb(NO3)2 solution of a certain concentration. The daily Pb intake in group II was 10 mg per sheep, in group III 50 mg per sheep, in group IV 300 mg per sheep, or 0.3, 1.5 and 9 mg kg^{-1} bodyweight.

To collect organs and muscle tissue, animals were slaughtered before priming (one sheep), on days 30 and 60 (at each term, one sheep of group II and three sheep of groups III and IV), and on day 90 (three sheep of each group). Blood was sampled from the jugular vein before feeding (at proming as the basal level, on days 30, 60 and 90). The lead content in samples (blood, liver, kidneys, spleen, lungs, heart, and muscle tissue) was measured by the atomic emission method on a Liberty AX Sequential ICP-AES spectrometer (Varian, Austria) after dissolving the ash sediment.

Given that changes of the lead concentrations in organs and tissues depend on the intensity of their blood supply and the peripheral blood concetration of the metal, the lead transition from peripheral blood to the liver, kidneys, spleen, lungs, heart, and muscle tissue of sheep was describrd as a system of differential equations:

$$\begin{aligned} dq_1/dt &= k_{bl1} \cdot q_{bl} - k_{1bl} \cdot q_1; \\ dq_2/dt &= k_{bl2} \cdot q_{bl} - k_{2bl} \cdot q_2; \\ dq_3/dt &= k_{bl3} \cdot q_{bl} - k_{3bl} \cdot q_3; \\ dq_4/dt &= k_{bl4} \cdot q_{bl} - k_{4bl} \cdot q_4; \\ dq_5/dt &= k_{bl5} \cdot q_{bl} - k_{5U} \cdot q_5 - k_{5bl} \cdot q_5; \\ dq_6/dt &= k_{bl6} \cdot q_{bl} - k_{6U} \cdot q_6 - k_{6bl} \cdot q_6, \end{aligned} \quad (1)$$

where q_1, q_2, q_3, q_4, q_5, q_6 and q_{bl} are the lead concentration (mg · kg^{-1}) in the heart, spleen, lungs, muscle tissue, liver, kidneys and peripheral blood, resprctively; k_{bl1}, k_{bl2}, k_{bl3}, k_{bl4}, k_{bl5}, k_{bl6} are rate constants (day^{-1}) for the transition of lead from peripheral blood to the heart, spleen, lungs, muscle tissue, liver, kidneys; k_{1bl}, k_{2bl}, k_{3bl}, k_{4bl}, k_{5bl}, k_{6bl} are rate constants (day^{-1}) for the transition of lead

from the heart, spleen, lungs, muscle tissue, liver and kidneys to peripheral blood; k_{5U} and k_{6U} are rate constants (day^{-1}) for lead excretion from the liver and kidneys; t — days of observation.

The lead concentration in the peripheral blood of sheep depended on the dietary metal content, the duration of its entry into the body [32] and was determined by the formula:

$$q_{\text{bl}} = \frac{\sum_{j=1}^{6} k_{j,bl} \cdot q_j - 0.00002 \cdot d}{k_{blU}}, \quad (2)$$

where q_{bl} is the lead concentration in peripheral blood, mg · kg^{-1}; d is daily intake of dietary lead, mg · kg^{-1} · day^{-1}; $k_{j,\text{bl}}$ is the rate constant of transition from the j-th section of the gastrointestinal tract to the blood, day^{-1}; q_j is the lead concentration in the j-th section of the gastrointestinal tract, mg · kg^{-1}; $k_{\text{bl}U}$ is the rate constant for the removal of lead from the blood, day^{-1}.

The elimination of lead from the sheep liver and kidneys was described by the equations

$$\begin{aligned} dU_1/dt &= k_{5U} \cdot q_5; \\ dU_2/dt &= k_{6U} \cdot q_6, \end{aligned} \quad (3)$$

where U_1 and U_2 are the lead concentration in feces and urine, mg · kg^{-1}; $q5$ and $q6$ are lead concentrations in the liver and kidneys, mg · kg^{-1}; k_{5U} and k_{6U} are the rate constants for lead excretion from the liver and kidneys, day^{-1}; t — days of observation.

Statistical processing of the data was carried out by the variation statistics method using the Excel 2013 and Mathcad application package. The article presents the mean values of the indicators (M) and standard errors of the means (±SEM).

Results. The patterns of lead distribution and accumulation in the organs and tissues of sheep during chronic dietary intake of lead were analyzed using a model in which organs and tissues are conidered as separate chambers [33, 34], physiologically interconnected by transport communications (Fig. 1).

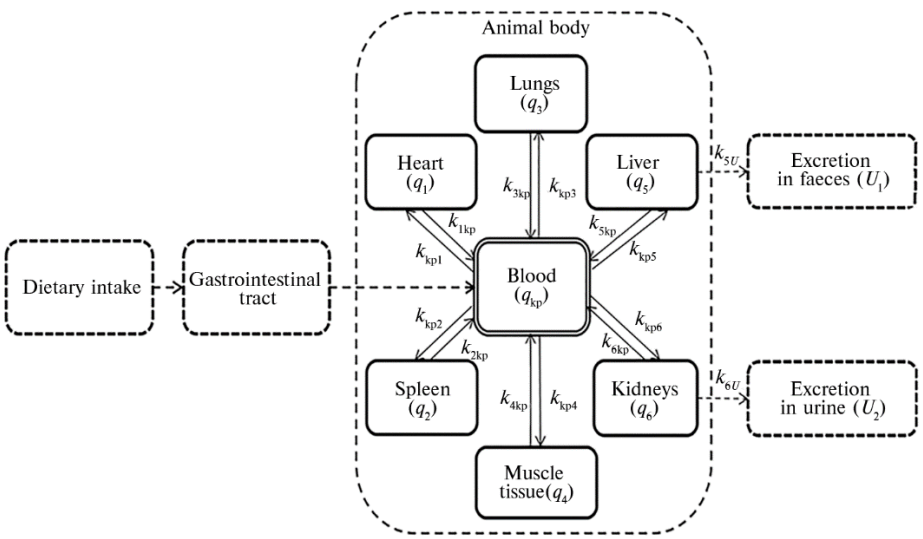

Fig. 1. Conceptual scheme of the lead transition from the diet into the sheep (*Ovis aries*) organs and tissues:: q_1, q_2, q_3, q_4, q_5, q_6 and q_{bl} — the concentration of lead in the heart, spleen, lungs, muscle tissue, liver, kidneys and peripheral blood, respectively, mg · kg^{-1}; $k_{\text{bl}1}$, $k_{\text{bl}2}$, $k_{\text{bl}3}$, $k_{\text{bl}4}$, $k_{\text{bl}5}$, $k_{\text{bl}6}$ — rate constants for the transition of lead from peripheral blood to the heart, spleen, lungs, muscle tissue, liver and kidneys, day^{-1}; $k_{1\text{bl}}$, $k_{2\text{bl}}$, $k_{3\text{bl}}$, $k_{4\text{bl}}$, $k_{5\text{bl}}$, $k_{6\text{bl}}$ — rate constants for the transition of lead from the heart, spleen, lungs, muscle tissue, liver and kidneys to peripheral blood, day^{-1}; k_{5U} and k_{6U} — rate constants for lead elimination from the liver and kidneys, day^{-1}.

Solving a system of differential equations (1) resulted in a formula that allows us to assess the change of the lead concentration in the liver, kidneys, spleen, lungs, heart and muscle tissue of sheep depending on the lead content in the peripheral blood and daily intake from feed:

$$q_i = \frac{1}{f_i} \cdot \left(q_{bl} - \frac{a_i \cdot d}{k_{bli}}\right), \quad (4)$$

where q_i is the lead concentration in the i-th organ or muscle tissue, mg · kg^{-1}; q_{bl} is the lead concentration in peripheral blood, mg · kg^{-1}; d is daily intake ofdietary lead, mg · kg^{-1} · day^{-1}; k_{bli} is the rate constant for the lead transition from peripheral blood to organs, day^{-1}; f_i (i = 1.6) stands for parameters characterizing the of the rate constant ratio for lead transition from organs and muscle tissue to peripheral blood k_{bli} and from peripheral blood to organs and muscle tissue k_{bli}; a_i (I = 1.6) are calculated constants (for kidneys $25.2 \cdot 10^{-3}$, for liver $18.4 \cdot 10^{-3}$, for spleen $8.0 \cdot 10^{-5}$, for lungs $2.0 \cdot 10^{-5}$, for the heart $16.0 \cdot 10^{-6}$, for muscle tissue $12.0 \cdot 10^{-6}$).

The lead transport from peripheral blood to organs and back depends on the physiological processes occurring in the animal's body. Based on experimental data, the rate constants for the lead transition from organs and muscle tissue to peripheral blood (k_{ibl}) and from peripheral blood to organs and muscle tissue (k_{bli}) were calculated. For the liver, kidneys, spleen, lungs, heart and muscle tissue of sheep, acceptable values of the parameters f_i were determined, characterizing the ratio of k_{ibl} to k_{bli}. Analysis of f_i parameters revealed the following descending order: heart (< 0.57) > muscle tissue (< 0.49) > lungs (< 0.34) > spleen (< 0.23) > liver (< 0.042) > kidneys (<0.0032).

Given the uncertainties in the lead transition from the blood to organs and tissues, f_i values were established that are most suitable for describing the accumulation of the toxicant in the sheep liver, kidneys, spleen, lungs, heart and muscle tissue. Below there are formulas for calculating the rate constants for the lead transition from peripheral blood to organs and tissues, depending on the daily dietary concentration and the duration of entry into the body:

heart (f_i = 0.1) — $k_{bl1} = \frac{d}{3380.625+1.15 \cdot d \cdot t}$;

spleen (f_i = 0.1) — $k_{bl2} = \frac{d}{632.75+0.15 \cdot d \cdot t}$;

lungs (f_i = 0.1) — $k_{bl3} = \frac{d}{2334.5+0.9 \cdot d \cdot t}$;

muscle tissue (f_i = 0.1) — $k_{bl4} = \frac{d}{4428.35+1.57 \cdot d \cdot t}$;

liver (f_i = 0.01) — $k_{bl5} = \frac{100 \cdot d}{320.842+0.08695 \cdot d \cdot t}$;

kidneys (f_i = 0.001) — $k_{bl6} = \frac{1000 \cdot d}{2488.467+0.587 \cdot d \cdot t}$.

The maximum rate constants for the lead transition from the blood to organs and muscle tissue, regardless of daily intake occurred on day 1 of intoxication (Table, Fig. 2). In next periods, there was a decrease in the values of indicators. On day 90 of intoxication, changes in the transition rate constants were weakly expressed.

Values of the rate constants for the lead transition from the blood into the organs and tissues of Romanov sheep (*Ovis aries*) depending on the metal content in the diet and duration of its intake (ARRIPBF, Kaluga Province, Borovsk)

Constant	Lead content in the diet, mg · kg^{-1}											
	5				25				150			
	Days											
	1	30	60	90	1	30	60	90	1	30	60	90
K_{bl1}	0.0015	0.0014	0.0013	0.0013	0.0073	0.0059	0.0049	0.0042	0.0422	0.0175	0.0109	0.0079
k_{kbl2}	0.0079	0.0076	0.0074	0.0071	0.0393	0.0335	0.0291	0.0258	0.2289	0.1147	0.0757	0.0564
K_{bl3}	0.0021	0.0020	0.0019	0.0018	0.0106	0.0083	0.0068	0.0057	0.0607	0.0235	0.0144	0.0104

Continued Table

K_{bl4}	0.0011	0.0011	0.0010	0.0010	0.0056	0.0045	0.0037	0.0031	0.0322	0.0131	0.0081	0.0059
K_{bl5}	1.5563	1.4975	1.4412	1.3890	7.7395	6.4758	5.5400	4.8405	44.9256	21.0639	13.5944	10.0357
k_{kbl6}	2.0069	1.9406	1.8765	1.8165	9.9874	8.5362	7.4207	6.5630	58.2181	29.2400	19.3014	14.4051

N o t e. k_{bl1}, k_{bl2}, k_{bl3}, k_{bl4}, k_{bl5}, k_{bl6} — rate constants for the transition of lead from peripheral blood to the heart, spleen, lungs, muscle tissue, liver and kidneys, day^{-1}.

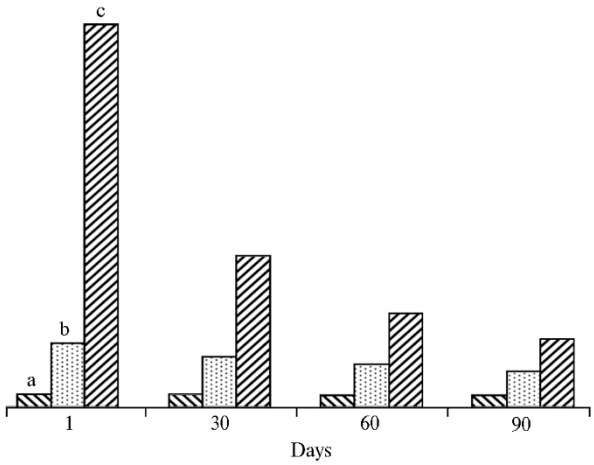

Fig. 2. Relative values of rate constants for the transition of lead from peripheral blood to the body of Romanov sheep (*Ovis aries*) depending on the metal content in the diet and duration of its intake: a — 5 mg · kg^{-1}, b — 25 mg · kg^{-1}, c — 150 mg · kg^{-1} feed (ARRIPBF, Kaluga Province, Borovsk). The diagram shows constant values in proportion to those at minimum lead level (5 mg · kg^{-1}, a). The patterns of constant changes are similar for all studied organs (heart, spleen, lungs, liver, kidneys) and muscle tissue.

We calculated the rate constants for the lead transition from the *i*-th organ and muscle tissue into the peripheral blood ($k_{i\text{bl}}$, $i = 1.6$):

$$k_{i\text{kbl}} = f_i \cdot k_{\text{bl}i}. \quad (5)$$

According to formula (5), changes in the rate constants for the lead transition to peripheral blood are of a similar nature.

The simulation quality was assessed by a comparative analysis of calculated and experimental data using the Theil test (discrepancy index). The discrepancy index shows the degree of similarity, the closer it is to zero, the closer the compared series are [35]. In our experiment, the Theil test value ranged from 0.058 to 0.186 (Fig. 3).

Mathematical models as a tool to assess the parameters of lead accumulation in mammals are of scientific and practical interest. Currently developed mathematical models are mainly aimed at assessing the lead transfer from the food into human peripheral blood [34, 36] or from the feed into livestock products (milk, meat) [22]. This approach does not take into account the fact that the critical organs for lead exposure are the liver and kidneys [29].

The construction of a logically sound and consistent conceptual scheme underlies the development of mathematical models of the transition of lead into the organs and tissues of productive animals. Previously, based on the analysis of lead metabolism in the body, we presented a conceptual scheme for the transition of the metal into the organs and tissues of ruminants [31]. Considering the complexity of the mathematical description of lead metabolism in sheep, we decided to develop two independent but interrelated models. One is a chamber model of the lead transition of from the rumen, mesh, book, abomasum, small and large intestines into the peripheral blood [32], another is a chamber model of the lead transition from peripheral blood to organs and muscle tissue.

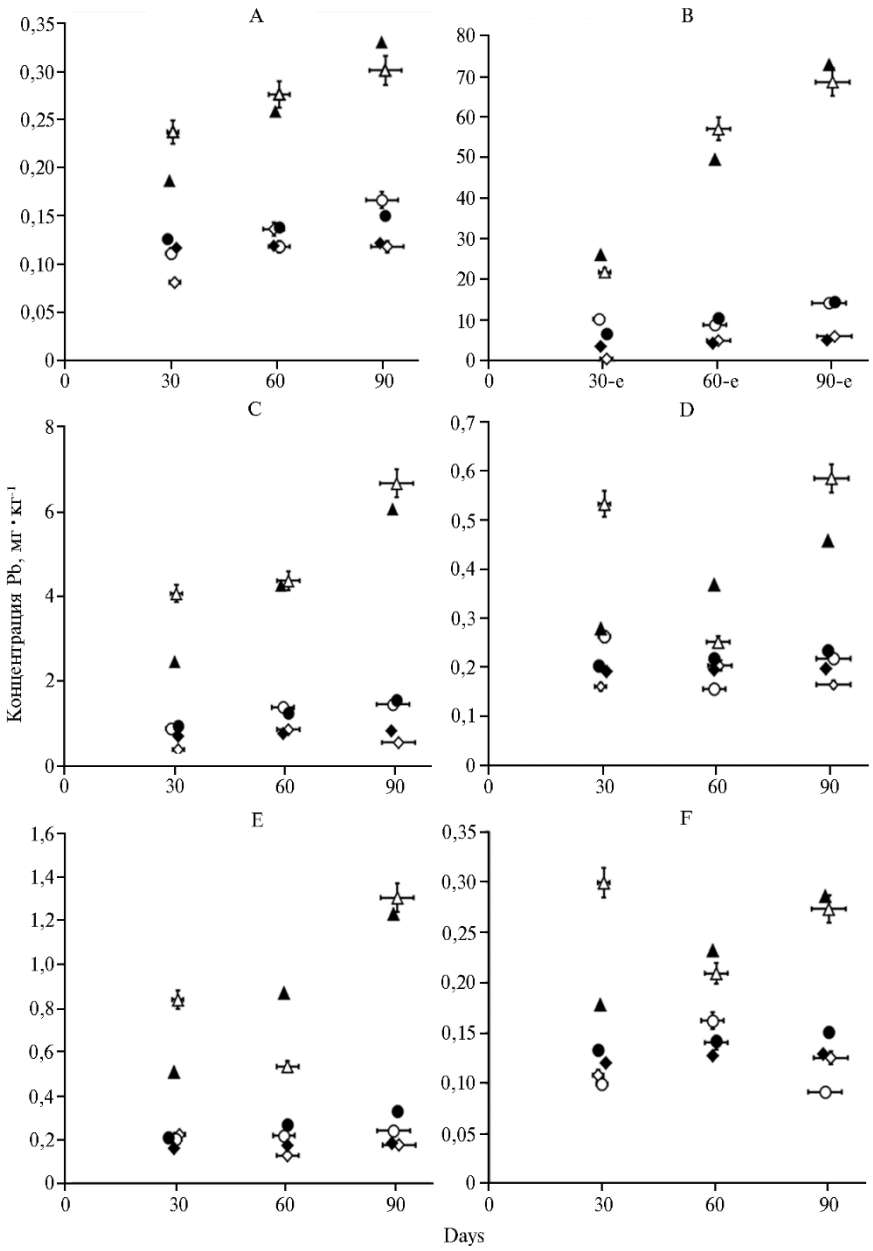

Fig. 3. Concentration of lead in organs and muscle tissue of Romanov sheep (*Ovis aries*) depending on the metal content in the diet and duration of its intake: A — heart, B — kidneys, C — liver, D — lungs, E — spleen, F — muscle tissue; ◊ and ♦ —observed and calculated data, respectively, for 5 mg · kg^{-1} dietary lead, ○ and ● — 25 mg · kg^{-1}, Δ and ▲ — 150 mg · kg^{-1} feed (M±SEM; ARRIPBF, Kaluga Province, Borovsk). For sample sizes depending on the dietary lead concentration for each observation period, see the Materials and methods section.

In the presented work, changes in the rate constants for the lead transition from peripheral blood to organs and muscle tissue and back, depending on the amount of lead in the diet and the duration of its entry into the body of sheep, were established for the first time. It was shown that on day 90 of intoxication, the transition rate constants practically do not change and reach a plateau, which suggests the onset of an equilibrium state. This can be supported by data that when a drug is administered orally to mammals, the time to reach its maximum concentration in the peripheral blood (approximately 97% of its steady-state level) is

approximately five half-lives [37]. Since the half-life of lead in soft tissues and peripheral blood is 24-40 days [38], the equilibrium state between the entry of the metal into the organs and its excretion should be expected on days 120-200 of intoxication.

It has been shown that the ratio of the rate constants for the lead transition from the blood to the liver and kidneys and back to the blood is 10 and 100 times lower, respectively, than for the spleen, lungs, heart and muscle tissue of sheep. It is likely that the lead content in the peripheral blood entering the liver and kidney tissues is significantly higher than in the outflowing blood. It is assumed that low parameters for the liver and kidneys characterize, on the one hand, the detoxification and excretory functions of the organs, and on the other hand, the level of lead accumulation. This is supported by data on the content of lead and metallothioneins in the liver and kidney tissues of sheep [29, 39]. It is not possible to experimentally confirm or refute the obtained research results because of the complexity of the blood supply system to organs and tissues.

A comparative analysis of experimental data and model calculations using the Theil test showed that the chamber model satisfactorily describes the lead transition from peripheral blood to organs and muscle tissue. The degree of agreement between the results allows us to recommend a mathematical model for determining the concentration of lead in the liver, kidneys, spleen, lungs, heart and muscle tissue of sheep during chronic dietary intake. The chamber model we developed can be used to estimate the permissible daily intake of dietary lead and forecast the safety of sheep products. This will optimize sheep feeding technologies through feed formulaying.

Thus, based on our own experimental data, a mathematical model of the lead transition from peripheral blood to different organs and muscle tissue of sheep has been developed. The model predicts the concentration of lead in the liver, kidneys, spleen, lungs, heart and muscle tissue of sheep, depending on the amount of metal in the diet and the duration of its intake. Changes in the rate constants for the lead transition from peripheral blood to various organs and muscle tissue of Romanov sheep have been established. The minimum transition rate constants were on day 90 of the examination. Parameters have been determined that characterize the ratio of the rate constants for the lead transition from the blood to the organs and back from the organs to the blood. It has been shown that the parameter values for the liver and kidneys are 10 and 100 times lower than for the spleen, lungs, heart and muscle tissue.

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