STUDY IN THE EXPERIMENT OF THE NATURE OF THE BIOLOGICAL RESPONSE OF THE ORGANISM AT SIMULTANEOUS AEROGENIC AND ORAL INTAKE OF LEAD AND DEVELOPMENT OF ITS PERMISSIBLE VALUES IN THE AIR, WATER AND FOOD PRODUCTS

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Abstract

Lead and its compounds are continuously detected in environmental objects at various concentrations and doses. Lead is a general plasma poison that affects the nervous, bone, endocrine system, blood and blood vessels, parenchymatous organs, gastrointestinal tract, metabolism, reproductive function, immune status and resistance. In this regard, there is an acute need to study in the experiment features of the response of the body of rats at the same time aerogenic and oral intake of lead and the development of its permissible values in the air, water and food products, taking into account the complex effects.

Objective: to determine experimentally the peculiarities of biological response of experimental animals at simultaneous aerogenic complex intake of lead and development of its permissible values in air, water and food products.

Methods: Concentration (dose) - time-effect relationship was used. For inhalation, 200-liter chambers were used in the experiment, proposed by B.A. Kurlyandsky. Modern highly sensitive biochemical, physiological, gonad and embryotoxic indicators were used to assess the resorptive toxic effect of lead.

Findings: Results of study of complex resorptive action of iso effective concentrations and doses of lead in small doses (0.029 mg/kg) and concentration (0.008 mg/m3) are estimated as the effect close to summation. At the simultaneous intake of lead into the body by inhalation and oral, its content in the air, water, food products should not exceed 0.33 maximum permissible concentrations (MPC) in each medium with isolated action.

Conclusions: The nature of the biological response of the organism of experimental animals at simultaneous aerogenic and oral intake depends on the amount of concentration and dose of lead. At the level of small concentrations and doses, maximum permissible hygienic norms in the air, water, and food products negatively impact the experimental animals and the functional state of several sensitive indicators (PPS, SH-group, erythrocytes, sperm motility time).

Keywords: Lead; experimental studies; atmospheric air; water; food products; coefficient of complex action; inhalation and oral pathway; maximum permissible concentration; toxicological assessment.

Introduction:

Among the multifaceted hygienic problems of large industrial cities around the world, one of the most important remains the protection of the environment from lead contamination and lead content. In recent decades, the level of lead concentration in nature has been increasing due to anthropogenic pressures. Development of various industries (metallurgical industry, fuel and energy complex, chemical complex, glass enterprises, woodworking and pulp and paper industry, defence industry, mechanical engineering, thermal power plant and motor transport) in the cities is associated with emissions into the atmosphere of a bouquet of toxic substances containing various compounds of lead. (2, 24p. 3, p. 26-29; 4,p. 21-21; 7. P.74; 9,P.120-127; 14,P.1171-1178; 15,P.31-36; 16,P.507-512). Lead is a common plasma poison that affects the nervous, bone, endocrine system, blood and blood vessels, parenchymatous organs. the gastrointestinal tract, metabolism, reproductive function (17.43 c.), as well as indicators of immune status and natural resistance of the body. (3, pp.26-29; 4, p.20-21.) Lead actively influences protein synthesis, cell energy balance and its genetic apparatus. Lead violates porphyrins and hem synthesis by inhibiting some enzymes involved in the exchange of porphyrins. Lead also

inhibits SH's activity - containing enzymes, cholinesterases in the membranes of red blood cells. Lead causes a marked abnormality in lipoid metabolism - increases the content of total and non-protein bound cholesterol. (20, www.chelpogoda.ru 20.09.2020) Lead is a poisonous substance, the issues of lead poisoning and health have been covered in many of the literature in recent years. (19;20 www.news.un.org; www.who.int 23.08.2019; www.news.un.org 30.07.2020 .) In the mechanism of lead toxic action , the effect of blocking SH-groups of proteins and enzymes comes to the fore. The blockade of sulfhydrilic groups disturbs the functional state of vital processes such as cell respiration, muscle contraction, and cell membrane permeability, particularly mitochondria, where important metabolic processes occur. As a result, there are serious disorders, primarily on the nervous system, blood, protein metabolism enzymes. In real life, a person can be exposed to lead simultaneously aerogenically and gastrointestinally when it enters the body with air, water and food (7, p.74; 15, p.31-36.) However, at present, hygienic rationing of lead, as well as other chemical compounds, is performed in isolation for various objects of the environment, which does not reflect the complex nature of its action on the body. Thus, the maximum permissible concentration of lead in the atmospheric air of populated areas - 0,0003 mg/m^3 cf) (8, 36 p.). The maximum permissible concentration of lead in the water of domestic and household water use is 0.03 mg/l (6.p.5). MPC in the air of the working zone - 0.01 mg/m^3 m^3) and 0.0007 mg/m^3 (5, 180 sec.). Maximum lead levels in food: milk; products for newborns - 0.02 mg/kg; fruits, vegetables, the meat of cattle, sheep and pigs, poultry; animal and poultry fat vegetable oils; milk fat 0.1 mg/kg, small fruits, apples and grapes: cereal grains, beans, wine - 0.2 mg/kg; edible by-products of cattle, pigs and poultry - 0.5 mg/kg (18, pp. 136-140 .).

Consequently, in real-life conditions, a person may be exposed to lead simultaneously aerogenically and intragastrically when it enters the body with air, water and food products. Therefore, hygienic regulations of chemicals only at isolated intake of substances are insufficient (1, p.75-78; 7, p.74; 15,pp.31-36). In this connection, there is a need to study the complex action of chemicals in environmental objects, in particular, constantly present in the air, water, food products in various concentrations and doses of lead at its oral and inhalation intake (9, pp.528-531; 11, pp.5-9).

Objective: experimentally determine the features of the biological response of experimental animals with simultaneous aerogenic complex intake of lead and the development of its permissible values in air, water and food products.

Materials and methods of research. One of the approaches allowing to study the nature of complex action of poisons at inhalation and intragastric intake is to study the dependence of "concentration (dose)-time-effect" (13, pp.3-6). Toxicological experiments on experimental animals on complex hygienic rationing of lead at inhalation and oral intake were conducted. The following set of tests was used (SH-group of whole blood, number of red blood cells, summation-threshold index (STI), time of sperm motility).

Considering that to evaluate the complex action, it is necessary to take into account the sufficient iso concentrations not only in inhalation but also in oral intake of substances. The experiment was carried out on 240 male rats WISTAR weighing 100-130 g, as in a separate oral intake by the dependence "dose-time-effect" with 6 doses of lead acetate 100, 20, 5, 05, 0.05 and 0.005 mg/kg, and 4 concentrations of lead acetate at the level of 80, 20, 2 and 0.5 mg/m^3 in inhalation by the dependence "concentration - time effect". The research was conducted followingthe European Convention for the Protection of Vertebrate Animals used for Experimental or Other Scientific Purposes (Strasbourg, 18 March 1986 ETS N 123.). The 200-liter chambers proposed by B.A. Kurlyandsky were used in the experiment for inhalation. The determination of lead content in the air of seed chambers was carried out daily by the calorimetric method. Data on the resorptive action of lead acetate in the experiments were statistically processed, calculating the Student's criterion (t) and error probability (P). The difference in mean values was considered reliable at significance level $P < 0.05$.

Results. With daily oral administration of lead acetate in a dose of 100 mg/kg in white rats showed symptoms of acute poisoning (refusal of food, lethargy, immobility, the untidiness of appearance, diarrhea, impaired movement coordination, weight loss), and in one rat at the end of 3 x day, there was paresis of the hind limbs. By the end of the fifth day, of those animals with convulsive contractions of the body muscles, cyanosis, shortness of breath, one rat died. The morphological study revealed a full-blooded internal organ, a bloated intestine. Thickening of interalveolar partitions due to histiocytic elements were found in the lungs, oedema was found in some alveoli. In the spleen and liver diffuse proliferation of reticuloendothelium with necrobiological changes in some cells.

Under daily exposure to lead acetate in a dose of 20 mg/kg for more than 12 days (280 h) and 5 mg/kg for more than 18 days (450 h) in some animals, there were signs of intoxication: movement coordination disorders, weight loss, poor appetite, and under the influence of 20 mg/kg for 10 days in one of the rats, even the paralysis of the hind limbs.

Fewer doses - 0.5; 0.05; 0.005 mg/kg - even with prolonged exposure (41, 90, 180 days, respectively) did not show any changes in animals' general state and behavior.

Under the action of lead acetate in a dose of 0.05, 0.005 mg/kg in white rats was observed, on the contrary, statistically significant weight gain on the 45th and 60th days of the experiment, maintained until the end of the experiment.

Both high (100, 20, and 5 mg/kg) and low (0.5, 0.05, 0.005 mg/kg) doses of lead acetate caused a decrease in STI, SH-group and red blood cell content, as well as changes in the functional state of spermatozoa in animals. At the level of low doses - 0.005 mg/kg - functional changes in spermatozoa occurred much earlier than changes in other indicators (STI, SH-group, erythrocytes). At the level of high doses, changes in the CNS and blood were observed earlier.

The study results showed that as the level of exposure to lead acetate decreases, the time of occurrence of toxic effects increases. (Table 1) Thus, reduction of SH groups by 25-30% in comparison with control ($p < 0,001$) was observed after 58 hours at exposure to 100 mg/kg, and at 20: 5: 0,5: 0,05 and 0,005 mg/kg these changes ($p < 0,05$-$0,001$) were observed after 165, 310, 680, 1420 and 4324 hours respectively.

Table 1

Study results of biochemical, physiological, hematological and gonad toxic indices in white rats at intragastric intake of lead acetate by dependence "dose-time-effect."

№	Dose, mg/kg	Deviation from control (25-30%)							
		SH group in the blood (gr %)		STI (in units)		Erythrocytes (million/μL)		Sperm movement time (min)	
		Deadline research. (Hour.)	M±m p<	Deadline research (Hour.)	Mm p<	Deadline research. (Hour.)	M±m p<	Deadline research. (Hour.)	M±m p<
1	100,0	58	52,68±2,40 <0,010,001	80	5,72±0,15 <0,001	110	5,41±0,44 <0,01	120	240±13,90 <0,01
2	Control	58	73,8±2,46	80	7,84±0,10	110	7,41±0,27	120	321,4±18,24 <0,01
3	20,0	165	57,2±3,58 <0,01	165	5,40±0,17 <0,001	260	5,61±0,44 <0,01	280	253,6±11,80

4	Control	165	77,6±2,86	165	7,42±0,30	260	7,53±0,20	280	369,8±20,38
5	5,0	310	53,74±3,86 <0,001	310	5,70±0,15 <0,001	600	5,34±0,42 <0,001	450	258,0±13,94 <0,01
6	Control	310	76,16±1,82	310	7,66±0,17	600	7,82±0,25	450	356,8±21,45
7	0,5	680	53,64±2,63	680	5,26±0,10 <0,001	1280	5,39±0,54 <0,01	940	228,0±21,03 <0,01
8	Control	680	76,00±1,71	680	7,32±0,15	1280	7,60±0,20	940	358,3±17,38
9	0,05	1420	55,3±3,81 <0,001	1420	5,44±0,19 <0,001	2300	5,70±0,50 <0,01	2160	241,3±18,24 <0,001
10	Control	1420	77,1±2,55	1420	7,26±0,32	2300	7,81±0,17	2160	358,2±13,51
11	0,005	4324	62,8±3,60 0,05	4320	6,34±0,60 0,05	4240	6,56±0,43 <0,05	4100	258,01±7,16 <0,01
12	Control	4324	74,2±2,23	4320	7,30±0,12	4240	7,76±0,21	4100	

Short-term exposure to high lead acetate concentrations (80 and 20 mg/m^3) caused some animal appearance changes and behaviour changes. In this case, the rats observed anxiety, excitement, increased reaction to externalirritants, aggressiveness, which were later replaced by lethargy. The animals also registered diarrhea, salivation, loss of appetite; meanwhile, the study of lead acetate concentration in a short-term experiment caused the same physiological (STI), biochemical (reduction of sulfhydrilic groups of whole blood), hematological (reduction of red blood cells), gonadotoxic (reduction of sperm movement time). (Table 2).

Thus, the SH-group content in whole blood of rats that inhaled 80 mg/m^3 of lead acetate after 10 hours decreased by 26.4% ($p<0.001$), 20 mg/m^3 by 28.9% - after 54 hours, 2 mg/m^3 by 27.8% after 150 hours ($p<0.001$), and 0.5 mg/m^3 by 27.7% after 280 hours ($p<0.001$). With a decrease in lead acetate concentration from 80 mg/m^3 to 0.5 mg/m^3, the rate of occurrence (25-30%) of deviations from control, ($p < 0.05$-0.001) of functional

changes in the state of the nervous system (STI) increased from 9.5 to 255 hours, spermatozoa (decrease in the duration of sperm movement and their osmotic and acid resistance) from 72 to 600 hours, peripheral blood (erythropenia) from 70 to 672 hours.

This data suggests that the time of occurrence of reliable changes in the studied parameters increases to a lesser extent compared to the level of concentration decrease. Thus, with a 160-fold decrease in lead concentration (80.0 to 0.5 mg / m^3), the decrease in SH-group time increased 28-fold (from 10 to 280 hours), the decrease in blood erythrocyte content increased 9.6-fold (from 70 to 672 hours) and the increase in sperm length time was marginal-8.33-fold (from 72 to 600 hours).

Establishment of experimental data on lead acetate in oral (Table 1) and aerogenic intake (Table 2) allowed us to compare them and establish iso effective, biologically equivalent doses and drug concentrations. Simultaneously, using the same time as a criterion, we determined biologically equivalent doses and concentrations. equivalent concentrations and doses of lead acetate. In this case biologically equivalent concentrations of lead acetate at the level of 6.5 mg/m^3 were equal to 110 mg/kg in the intragastric way of intake, 0.42 mg/m^3 - 4.0 mg/kg, 0.05 mg/m^3 -03 mg/kg, 0.018 mg/m^3 -0.05 mg/kg and 0.008 мг\м^3 - 0.029 mg/kg The complex action of lead acetate inhaled (6.5 mg/m^3) and intragastric (110 mg/kg) caused acute poisoning in rats.

Table 2

Study results of biochemical, physiological, hematological and gonadotoxic indices in white rats at inhalation intake of lead acetate by dependence "concentration - time - effect"

Indicators	Concession, mg/m^3	Deadlines Research (hour)	Statistic indicators						% Deviation from control
			M	Paз	σ	m	+	p	
SH-group whole of blood (gr %)	80,0	10	55,4	14,7	6,30	3,15	5,67	<0,001	26,4
	control	10	75,2	7,12	3,05	1,52			
	20,0	54	53,2	14,5	6,2	3,11	6,12	<0,001	28,98
	control	54	74,9	7,89	3,33	1,69			
	2,0	150	55,1	21,7	9,31	4,65	4,26	<0,01	27,8
	control	150	76,3	4,81	2,06	1,30			
	0,5	280	56,3	15,7	6,73	3,36	6,09	<0,001	27,7
	control	280	77,8	5,01	2,15	1,07			
STI (in units)	80,0	9,5	5,3	2,6	1,15	0,57	3,98	<0,01	31,2
	control	9,5	7,7	0,6	0,36	0,18			
	20,0	56	5,4	2,4	1,05	0,52	6,9	<0,001	28,16
	control	56	7,6	0,8	0,37	0,17			
	2,0	150	5,7	1,8	0,77	0,38	5,43	<0,001	26,89
	control	150	7,9	0,3	0,14	0,07			
	0,5	285	5,4	1,8	0,78	0,39	5,51	<0,001	29,01
	control	285	7,7	0,5	0,23	0,11			
Eritroquotes of blood (million/μL)	80,0	70	5,58	2,08	0,89	0,44	4,10	<0,01	25,39
	control	70	7,48	0,62	0,26	0,13			
	20,0	210	5,12	2,47	1,06	0,50	3,96	<0,01	28,44
	control	210	7,16	0,59	0,25	0,12			
	2,0	400	5,58	1,65	0,70	0,35	5,26	<0,001	26,48
	control	400	7,59	0,51	0,21	0,10			
	0,5	672	5,43	1,98	0,84	0,42	4,77	<0,01	28,53
	control	672	7,60	0,76	0,32	0,16			
Sperm motion time(hour)	80,0	72	220	105	45,0	22,5	5,47	<0,001	37,15
	control	72	350	60	26,7	12,8			
	20,0	140	230	76	32,61	16,3	5,18	<0,001	30,30
	control	140	330	48	20,6	10,3			
	2,0	450	220	108	46,3	23,1	4,96	<0,001	37,80
	control	450	354	65	27,8	13,9			
	0,5	600	237	105	45,0	24,5	4,02	<0,001	30,91
	control	600	343	45	19,3	9,6			

At simultaneous action of lower concentrations and doses of 0.05 mg/m^3 and 0.3 mg/kg; 0.018mg/m^3 and 0.08 mg/kg; 0.008 mg/m^3 and 0.029 mg/kg rats were active, externally no different from control animals.

The complex action of lead acetate at high concentrations and doses (Table 3)

Table 3

Study results of the biochemical, physiological, hematological and gonads toxic indices in white rats under complex inhalation and intragastric exposure of lead acetate in dependence of "concentration (dose) - time - effect"

Level of effective IEC concentrations and doses		STI			SH-group			Sperm movement time			Erythrocytes		
mg/m^3	mg/kg	Deadline	M+m	%	Time	M+m	%	Time	M+m	%	Time	M+m	%
6,5	100	40	5,32±0,42	28,5	30	52,16±4,50	25,9	120	235± 30,8	31,08	100	5,48±0,45	27,5
Control		40	7,44±0,27 <0,01		30	71,86±2,68 <0,01		120	345± 16,8			7,56±0,13 <0,01	
0,42	4	210	5,14±0,21	31.8	200	54,86±5,21	26,9	400	248± 27,4	25	450	5,47±0,46	29,0
Control		210	7,54±0,21 <0,001		200	75,14±2,31 <0,01		400	331± 13,4			7,71±0,13	
0,05	0,3	760	5,28±0,3	26,6	860	55,28±2,06	26,9	1000	238± 33,9	32,3	1200	5,42±0,44	30,3
Control		760	7,2±0,3 <0,01		860	74,52±2,31 <0,001		1000	352±21,0			7,78±0,16	
0,018	0,08	1600	5,26±0,47	27,0	1860	51,98±4,1	26,7	1620	238± 33,0	29,3	1800	5,42±0,44	29,2
Control		1600	7,2±0,17 <0,01		1860	70,98±1,54 <0,01		1620	337± 13,4			7,67±0,16	
0,008	0,0029	2500	5,6±0,45	29,7	2800	54,28±5,12	28,1	2500	250± 26,6	28,7	2800	8,29±0,29	27,2
Control		2500	7,96±0,17 <0,01		2800	75,5±1,95 <0,01		2500	351± 11,2			6,52±0,64	

led to a decrease in STI, SH-groups, a decrease in the number of erythrocytes, hemoglobin, a violation of the functional state of sperm, morphological changes in the lungs, liver, kidneys, stomach, similar to those in the separate inhalation and intragastric supply pathway. However, all changes, in this case, were expressed much more strongly than in the isolated action. Analyzing the data obtained from inhalation intragastric and complex effects of lead acetate in subacute and chronic experiments, it should be noted that changes in the studied parameters (STI, SH-group of blood, functional state, spermatozoa) are unidirectional, and the degree of severity of effects and time of its occurrence depends on the level of influencing doses and concentrations. Thus, under the complex action of high concentrations (6.5 mg/m^3) and doses (110 mg/kg) the reduction of SH-groups in relation to control reached 26% after 30 h, under the action of 0.008 mg/m^3 + 0.029 mg/kg respectively - only after 2800 h. Registration of time of occurrence of toxic effects under simultaneous exposure to different concentrations and doses of lead acetate allowed to calculate the coefficients of complex action. (Table 4)

Table 4

Coefficients of complex action (C_{ca}) at simultaneous inhalation and intragastric intake of lead in different equivalent concentrations and doses

Lead pathways		Index			
Inhalation mg/m^3	Intragastricmg/kg	SH-groups whole blood	Reducing erythrocytes	STI	Sperm motion Time
6,5	110,0	0,90	0,48	0,60	0,97
0,42	4,0	0,98	0,84	0,75	0,97
0,05	0,3	0,95	0,87	0,84	0,99
0,018	0,05	0,92	0,89	1,06	0,92
0,008	0,029	0,88	0,97	1,01	1,05

At the same time, it was found that the complex action coefficients (C_{ca}) of lead acetate at the level of relatively high isozoaffective concentrations and doses fluctuated from 0.48 (on the reduction of erythrocytes) to 0.97 (on the time of sperm motility) and at the level of small concentrations and doses fluctuated from 0.88 (on the reduction of blood SH-groups) to 1.05 (on the time of sperm motility) and is estimated as an effect close to "summation".

Conclusion

1. Complex effect of lead acetate on the body simultaneously at inhalation and intragastric intake at the level of small concentrations and doses within the limits of acceptable hygienic norms has a negative impact on the experimental animals and causes functional changes in a number of sensitive indicators.

2. Coefficients of complex action of lead acetate at the level of small concentrations (0.008 mg/m^3) and doses (0.029 mg/m^3) ranged from 0.88 (reduction of blood SH-groups) to 1.05 (sperm movement time) and is estimated as an effect close to summation.

3. In case of joint intake of lead acetate into the organism by inhalation and intragastric activity, its content in the air, water, food products should not exceed 0.33 MPC in each dose with isolated action.

4. The nature of complex lead action must be taken into account when assessing the real risk of environmental pollution, including atmospheric air, for the health of the population living in areas where sources of lead and its compounds are located.

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