Session 13. TOXICITY OF METAL IONS, INJURIES CAUSED BY METAL IONS AND THEIR MUTAGENICITY

ALTERED OPEN-FIELD PERFORMANCE IN DEPLETED URANIUM EXPOSED RATS

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Depleted uranium (DU) is a heavy metal extensively used in munitions and is the target of considerable controversy regarding its toxicity. DU has as its site of greatest toxicity the kidney with renal failure frequently being the cause of death in animals exposed to this metal. Neurotoxicity of DU has not been well studied. It would be predicted that DU would be neurotoxic in a manner similar to other heavy metals such as lead and mercury. Preliminary studies in this laboratory have described neurodevelopmental toxicity in mice. This study explored the behavioral toxicity of DU in adult rats exposed to DU in drinking water for two weeks or six months.

Male and female Long-Evans rats (3–9 months of age) were exposed to either control conditions (no DU exposure) or to drinking water containing 75mg/L DU for either 2 weeks or 6 months. After the appropriate length of exposure animals were testing in an open-field apparatus where activity, as measured by line crossing and rearing, as well as grooming and boli activity were measured for 5 minutes. After testing the animals were sacrificed and brains harvested.

There was a general increase in open field activity for both male and female rats that was dependent on length of administration. Both line crossing and rearing were greater, indicating an overall increase of the activity state of the animal. Boli formation was increased at two weeks exposure but decreased at 6months, indicating a change in the "emotional" state of the animal dependent on length of exposure. A similar change was also seen for grooming behavior.

Overall, these data indicate that exposure to DU can alter behavior in the rat in a time dependent manner. Additional analysis is planned to look at lipid oxidation status and DU content in the brains of these animals.

BEHAVIOR OF JUVENILE MICE CHRONICALLY EXPOSED TO DEPLETED URANIUM

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Depleted uranium (DU) has been described as having toxicity roughly equivalent to lead. That being the case it would be reasonable to expect that young DU exposed animals would exhibit behavioral changes in a manner similar to young animals exposed to lead. Young animals are especially vulnerable to the effects of heavy metals. Specifically, they should display differences in exploratory behavior, differences in reactivity to environmental stimuli, and differences in emotionality.

To explore this question we exposed female mice, housed in a standard laboratory environment, to drinking water containing DU (0, 19, 37, 75 mg/L) for 2 weeks prior to mating. DU exposure continued through gestation and the remainder of the animals' life. At 21 days of age the animals were tested on a variety of behavioral measures including open-field activity, water maze learning, and a general neurologic inventory.

DU exposed animals show dose related alterations in open-field activity. The DU exposed animals displayed less line crossing, increased rearing, and fewer boli. The DU exposed animals took greater time to complete the water maze. Treated animals also displayed differences in body weight. DU exposed animals displayed differences in behavior on a number of behavioral measures related to reactions to environmental stimuli.

These data suggest that chronic exposure of young animals to DU may adversely effect development, brain, and behavior. The affected behavioral spheres include learning, activity, exploration, and emotionality. Currently, tissue studies are underway.

MODULATION IN HEPATIC PARAMETERS OF CARP (*CYPRINUS CARPIO* L .) INDUCED BY COPPER AND THE METAL ION CHELATOR CHITOSAN

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Copper is used in treatment mixtures to control fungal diseases in vineyards and concentrations are relatively high in some aquatic ecosystems collecting vineyard runoff water (Gerbe, 1996). Better awareness

of the ecological and health problems associated with copper and its potential accumulation through the food chain has prompted the demand for alternative used of low toxic molecules in plant protection and for the removal of heavy metal ions from waste water.

Chitosan is the N-deacetylated derivative of chitin, a natural abundant polysaccharide. The numerous properties of chitosan (especially antifungal, and heavy metal ions chelating agent) offer a wide range of applications. On the one hand, chitosan could be used as a natural agri-bioactive substance controlling fungal diseases and contributing to reduce the use of copper in plant protection (Ravi Kuman, 2000). On the other hand, chitosan is a metal ion chelator already used in waste water treatment (No and Meyers, 2000). It is then necessary to investigate the potential toxicity of chitosan for aquatic animal health, alone and associated with copper.

In this study, Carp were exposed to sublethal concentrations of chitosan (0.5 % and 1 %) or copper (0.1, 0.25 $mg.L^{-1}$) or chitosan and copper (0.5 % and 0.1 $mg.L^{-1}$ respectively) for 5 and 10 days.

In chitosan-exposed carp, hepatic catalase and glutathion S-transferase activities and expression of metallothioneins were significantly increased in comparison with control. An increased of these parameters were also observed in copper-exposed carp. Moreover, physiological response of carp exposed to chitosan/copper mixture was modulated too. This study showed that chitosan is potentially noxious molecule for fish and its industrial and/or future agricultural uses will have to take care of this problem.

ACUTE TOXICITY OF METALS TO MAN

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The aim of this study was to find relationships between lethal toxicity of metals to man and their contents in different organs and tissues (all body, skin, liver, heart, hair, blood, pancreas, stomach, lungs, kidneys, urinary-bladder, paranephroses, spleen). For decision this task the following expression has been used: $lg(Q_i / LD_i) = B_0 + B_1\ lgQ_i$, where Qi / LD_i is relative lethal toxicity; Q_i is content of metal "i" in the organ or tissue of the man (K, Li, Ag, Fe, Ba, Cu, Mn, Ni, Co, Ga, As, Cr, Sb, Hg) mg/kg; LD_i is lethal dose of the metal "i", mg/kg. The results of this investigations are shown in the Table.

Organ or tissue	Model
All body	lg(Qi / LDi) = 1.20 + 1.06 lg(LDi) Model I n = 14; r = 0.95; s = 0.50; FC = 118.6; FT = 4.67; FC / FT = 25.4
Skin	lg(Qi / LDi) = 2.13 + 1.09 lg(LDi) Model II n = 7; r = 0.95; s = 0.56; FC = 51.4; FT = 5.99; FC / FT = 8.6
Liver	lg(Qi / LDi) = 2.02 + 1.06 lg(LDi) Model III n = 13; r = 0.97; s = 0.50; FC = 156.8; FT = 4.75; FC / FT = 33.0
Heart	lg(Qi / LDi) = 1.92 + 1.04 lg(LDi) Model IV n = 11; r = 0.97; s = 0.55; FC = 141.2; FT = 4.96; FC / FT = 28.5
Hair	lg(Qi / LDi) = 2.29 + 1.19 lg(LDi) Model V n = 11; r = 0.95; s = 0.51; FC = 79.6; FT = 4.96; FC / FT = 16.0
Blood	lg(Qi / LDi) = 1.87 + 1.02 lg(LDi) Model VI n = 13; r = 0.97; s = 0.52; FC = 169.3; FT = 4.75; FC / FT = 35.6
Pancreas	lg(Qi / LDi) = 2.17 + 1.11 lg(LDi) Model VII n = 11; r = 0.97; s = 0.52; FC = 147.8; FT = 4.96; FC / FT = 29.8
Stomach	lg(Qi / LDi) = 2.06 + 1.09 lg(LDi) Model VIII n = 10; r = 0.96; s = 0.54; FC = 124.2; FT = 5.12; FC / FT = 24.3
Lung	lg(Qi / LDi) = 2.20 + 1.10 lg(LDi) Model IX n = 12; r = 0.98; s = 0.44; FC = 215.1; FT = 4.84; FC / FT = 44.4
Kidneys	lg(Qi / LDi) = 2.21 + 1.11 lg(LDi) Model X n = 13; r = 0.97; s = 0.48; FC = 199.3; FT = 4.75; FC / FT = 42.0
Urinary-bladder	lg(Qi / LDi) = 2.65 + 1.23 lg(LDi) Model XI n = 7; r = 0.90; s = 0.65; FC = 20.6; FT = 5.99; FC / FT = 3.44
Paranephroses	lg(Qi / LDi) = 1.93 + 1.06 lg(LDi) Model XII n = 10; r = 0.96; s = 0.56; FC = 106.1; FT = 5.12; FC / FT = 20.7
Spleen	lg(Qi / LDi) = 1.99 + 1.05 lg(LDi) Model XIII n = 13; r = 0.97; s = 0.51; FC = 172.3; FT = 4.75; FC / FT = 36.3

Note. n — number of metal, r — correlation coefficient, s – standard error of estimation, F_C — calculated Fisher's variance ratio, F_T — Fisher's variance ratio for the level of significance 95%.

The data show that all models are adequate ($F_C > F_T$) and can be used for prediction because $F_C / F_T > 4$ (except model XI).

TABLE. RELATIONSHIPS BETWEEN RELATIVE LETHAL TOXICITY OF METALS TO MAN AND THEIR CONTENT IN DIFFERENT ORGANS OR TISSUES.

INFLUENCE OF LOW DOSES IRRADIATION ON ACCUMULATION OF HEAVY METALS IN THE ORGANISM AND BIOLOGICAL EFFECTS IN RATS

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Background: Recent publications consider mainly results of investigations after combined actions of heavy metal salts and irradiation with doses significantly higher than the permissible ones, however the data absent

practically after action of these environmental injuring factors with low doses, that can be met in everyday life.

The purpose of the present investigation is to reveal the consequences of the low doses ionising irradiation exposures on the lead and mercury content in blood and kidney of animals in case of the metal salt prolonged administration with drinking water in comparison with biotesting data of the early and delayed consequences after action of the same injuring factors.

Materials and Methods: The investigation was performed on the 225 male rats receiving with drinking water $Hg_2(NO_3)_2$ or $PbCl_2$ in concentrations — 0.7 mcg/l or 2.0 mg/l in account to metal, respectively, during 3 weeks before and 1 month after single total gamma-irradiation with 25 or 50 cGy doses on the "IGUR-1" unit (^{137}Cs, dose rate = 44 cGy/min). The metal concentration measurements in blood, kidney and fodder were performed for mercury — on the atomic-absorption analyser of mercury "RA-915+" with "RP-91" block (made in Russia), and for lead — by an inversed volt-ampere measurement on the ion-scanning system "ISS-82" (made by firm "Radiometer", Denmark).

There were studied the early (24 hrs after irradiation) hematological reactions and genotoxic effects on the base of the blood leukocyte DNA alterations, results of their restorations (30 days after irradiation), as well as delayed consequences — life span shortening. DNA content in leukocytes was determined occuringly during one's life-time by use of 4',6-diamidine-2-phenylindole (DAPI), and the DNA structure alterations by means of two-parameters fluorescent analysis, including DAPI and ethidium bromide application, as described earlier (Ivanov et al., 1999).

The ionising radiation with low doses (25 and 50 cGy) allows to potentiate the accumulation of mercury in kidney, but not in blood of rats. The prolonged exposures of heavy metal salts with low concentrations combined with the single irradiation with 25 cGy dose resulted in alterations of the natural behaviour activity, and life span shortening in case of the mercury administration and irradiation with 25 cGy dose. Moreover, there was revealed the belt of hypersensitivity, corresponding to irradiation with 25 cGy dose combined with chemical toxicant administration, since the combined exposure in higher dose (heavy metal + 50 cGy) resulted in the lesser damage of the organism. On the base of only alone metal biomonitoring in blood of animals it is impossible to prognosticate the early and delayed biological effects of radio-chemical exposures with low doses. At the same time, the genotoxicity biotesting allowed to evaluate the results of postradiation restoration, that may be used for prediction of delayed consequences after combined action of mercury and irradiation.

EFFECTS OF THE ORAL ADMINISTRATION OF SUB-LETHAL DOSES OF MERCURY ON TESTIS MORPHOLOGY AND TESTOSTERONE PRODUCTION

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Mercury (Hg) is a heavy metal that provokes structural and functional damage in several organs and systems, by altering transport and permeability properties of cellular membranes, and inducing cell death by mitochondrial hydrolysis. In order to study testicular and epididymal morphofunctional changes, induced by oral drinking of inorganic mercury, we administered $HgCl_2$ in deionized water, at concentrations of 0.01 μg/ml, 0.05 μg/ml, or 0.1 μg/ml for 30, 60 and 90 days, to male Sprague-Dawley rats with 250–300 g of body weight (b.w.). Control rats received deionized water alone. Animals were sacrificed and testes as well as epididymides were removed and processed for light microscopy, and for Hg quantification by plasma mass spectroscopy. Moreover, blood samples were collected for Hg and serum testosterone quantification. We detected Hg in serum, and accumulation of the metal in testis and epididymis. On the other hand, independently of the dose used we observed progressive degenerative lesions in seminiferous epithelium after 30 of treatment, that consisted in lack of germ cell cohesion and desquamation to the lumena, arrest at spermatocyte level and hypospermatogenesis. Multinucleated giant cells and cytoplasmic vacuolation in Sertoli cells were also observed. Furthermore, Leydig cells showed cytoplasmic vacuolation and nuclear signs of cell death, after 60 days of treatment. Testosterone serum levels were decreased after 60 days of treatment with 0.1 μg/ml of $HgCl_2$, which was in coincidence with the degenerative changes observed in Leydig cells. At epididymal level, we evidenced peritubular cell disgregation and giant cells, after 30 days of treatment with Hg. The histological modifications detected in the present work suggest that oral intake of sublethal doses of $HgCl_2$ induces changes in either seminiferous or epididymal tubules in Sprague-Dawley rats that are associated with impaired testicular steroidogenesis.

TRACE ELEMENT RESPONSES TO THERMIC AGGRESSION IN RATS

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Specific alterations in trace element metabolism and distribution occur in response to stress and trace elements may be part of an early mechanism to combat stress. Therefore, the objective of the present study was to measure the evolution of essential trace element distribution in kidney and liver following the thermic aggression or burn injury. Burn injury and sample collection were performed under halothane anaesthesia to alleviate any possible discomfort to the rats. A non-lethal third-degree burn injury involving 20% of total body surface was applied to 45 male Wistar rats, divided in 9 groups and 5 rats served as the control group. Animals were sacrificed 6 hours after thermal injury, and after 1, 2, 3, 4, 5, 6, 8 and 10 days. Liver and kidneys were removed, weighed, frozen in liquid nitrogen and stored at -80EC until analysis for Cr, Zn, Se, Cu, Mn, and Fe by atomic absorption spectrophotometry. Standard reference materials were run with each batch of samples to verify the accuracy of the analyses. There were the biphasic increases in liver Zn commencing within 6 hours of thermic aggression that continued to increase during day 1 and declined during days 2 and 3 followed by an increasing trend from day 4 and liver Zn was significantly elevated after 10 days. There were no significant changes in kidney Zn concentrations. There were significant declines in liver Se and trends towards increases of kidney Se. There were significant biphasic declines in the concentrations of manganese both in the liver and kidney. There was also a biphasic decline in liver Cr and liver Cr values dropped to non detectable during days 5 and 10. There appeared to be a biphasic increase in kidney chromium but changes were not significant. Changes in Fe and Cu both in the liver and kidney were largely nonsignificant and no specific responses were detected. These data demonstrate that there are specific responses of the trace elements, zinc, selenium, manganese and chromium, to thermic aggression related to combating stress and also a second phase of changes in liver and kidney levels during recovery. There were no obvious specific responses of iron and copper to thermic aggression under the conditions of our study.

TOXIC EFFECTS OF LEAD, CADMIUM, AND ARSENIC MIXTURES IN MALE RATS

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Lead, cadmium, and arsenic are among the three most common elements found in chemical mixtures at Superfund sites. In order to investigate the toxic effects of these metal mixtures, eight groups of male Sprague Dawley rats were administered deionized water, 25 ppm lead (Pb) (as lead acetate), 10 ppm cadmium (Cd) (as cadmium chloride), 5 ppm arsenic (As) (as sodium arsenite), 25 ppm Pb x 10 ppm Cd, 25 ppm Pb x 5 ppm As, 10 ppm Cd x 5 ppm As, or 25 ppm Pb x 10 ppm Cd x 5 ppm As for 30 days in drinking water. Doses were selected based on LOEL values for these elements assigned from previously conducted 30-, 90-, and 180-day single metal drinking water studies. Standard toxicological endpoints were evaluated, along with heme pathway enzymes. Body weight changes in all seven metal groups were greater than that of the control group. Liver/body weight ratios were decreased in the metal combination groups compared to the control group and the single metal groups. Hematocrit levels were mildly elevated in the As and all metal combination groups compared to control, Pb, and Cd groups. 24-hour urine output was reduced in all seven metal groups compared to control values. Blood ALAD (aminolevulinic acid dehydratase) activity among Cd rats was elevated compared to that of the control group. In contrast, blood ALAD activity among all other metal groups was decreased compared to that of the control group, and was the lowest in the PbxCdxAs combination group (10% of control value). Kidney ALAD activity was decreased among all metal groups compared to that of the control group, and was lowest in the Pb single metal, CdxAs, and CdxPbxAs groups (approximately 32% of control value). Zinc protophorphyrin (ZPP) values were elevated in all metal combination groups compared to the control group, and were highest in the PbxCdxAs combination group (144% of control value). Elevated ZPP values in all metal combination groups compared to single metal groups reflected a less than additive toxic effect. Decreased 24-hour urine volumes among animals from the PbxAs group demonstrated the occurrence of additivity. Inhibition of blood ALAD activity reflected the occurrence of synergism in the metal combination groups compared to the single metal groups, while kidney ALAD activity showed a similar pattern, but to a lesser degree. Histopathological evaluation of kidney sections from all groups is currently underway, as is HPLC evaluation of urinary porphyrins.

The results of these studies demonstrate a variety of interactive effects involving essential biochemical systems following drinking water exposure to combinations of Pb, Cd, and As at LOEL dose levels. These data indicate that interactions among Pb, Cd, and As should be considered in human health risk assessments.

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TOXICITY OF DIVALENT METAL IONS TO HYDROBIONTS

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The aim of this study was to select the significant descriptor to deriving quantitative structure – toxicity relationships. For decision this task five types of aquatic organisms (*Gasterosteus aculeatus L., Daphnia magna, C. elegans, T. pyriformis, P. caudatum),* fourteen divalent metal ions (Ca^{2+}, Sr^{2+}, Mg^{2+}, Ba^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Pb^{2+}, Fe^{2+}, Sn^{2+}, Cu^{2+}, Hg^{2+}), and twenty three different descriptors (Pauling ionic radius, absolute value of he log of the first hydrolysis constant, entropy of hydration, enthalpy of formation etc.) have been used. In order to choose a more informative descriptor a treatment of experimental LC_{50}, LC_{min}, EC_{50} values has been done. According to the "Okkama's razor: do not multiply essence without necessary" in all cases only linear models have been used. The results of this investigation showed that the most informative descriptor is covalent ion characteristic (C, kJ/mol) which can be calculated as follows:

$$C = F_1 + F_2 - L \qquad (1)$$

where F_1, F_2 are the first and the second ionization potentials accordingly; L – heat of hydration. For example, the following model has been obtained:

$$\log 1/ LC_{50} = 7.75 - 0.007 \mid C \mid \qquad (2)$$

$n = 14$ $r = -0.86$ $s = 0.91$ $F_C = 30.9$ $F_T = 4.8$ $F_C / F_T = 6.4$

where LC_{50} mean lethal concentrations of metal ions to *Daphnia magna*, mol/liter; n — number of metal ions, r — correlation coefficient, s — standard error of estimation, F_C — calculated Fisher's variance ratio and F_T — Fisher's variance ratio for the level of significance 95%. The statistical data show that model (2) is adequate ($F_C > F_T$) and can be used for prediction because $F_C / F_T = 6.4 > 4$.

EFFECT OF METAL IONS ON THE LIVER NUCLEI

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Metal ions coud inhibite or stimulate enzymes or some other proteins as metalothioneins and to cause changes in plasma membranes. Fast all of the metals may have a mutagenic affect. The aim of the research was monitoring the effects of the long-term exposure of animals to the subtoxic concentrations of elements.Carp were separately treated with 0.1 mg/L magnesium, selenium and lead salts during 80 days. Liver tissue was sampled in intervals of 7 days and prepared for histological observations. In all three treatments the presence of metal induced increase in number of nuclei with two or three nucleolus. There vere also noticeable changes in structure and size of the nucleus. Enlarged nuclei with intensively spread chromatin appeared particularly often after treatment with lead and selenium, indicating increased synthetic activity. Prolonged contamination has lead to formations of very dense pycnotical nuclei and finaly to their destruction.

A NEW APPROACH TO RISK ASSESSMENT OF LEAD INTOXICATION

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Lead is one of basic technogenic toxicants being constantly released into the environment via wastes discharged by high temperature technologic processes, automobile emissions, sewage from metal extracting and processing factories. It is known to pose the most toxic hazard to humans. They are exposed to lead mainly via air and food stuffs. When making evaluations of risks to humans, the development and introduction of new effective analytical methods for revealing interconnections between the environment pollution and human health is necessary. The study of the body biological media is one of the perspective trends in this context. With an increase in sensitivity and selection of chemical analysis these media may serve as a safe biologic indicator reflecting "health level" of both man and his environment.

In the process of dynamic clinic-experimental studies we have revealed the effect of a number of nonspecific therapeutic methods (hypnotherapy, acupuncture as well as an intake of ascorbic acid or adaptogens) on urinary excretion of lead. The content of lead in urine was determined using the method of atomic-absorption spectrometry of "Varian" company.

The method of lead intoxication risk assessment depending on lead content in urine following either hypnotherapeutic effects, or acupuncture, or ascorbic acid, adaptogens has been developed on the basis of data obtained.

It has been established that:
– if lead content in urine is increased to more than 10% as compared to the initial one the risk of lead intoxication development is evaluated as low and human adaptive capacity is evaluated as safe or satisfactory;
– if lead content is decreased to more than 10% the risk is high and adaptive capacity of the body is exhausted;
– the absence of significant dynamics of lead content (its concentration in urine is not changed) testifies about moderate risk and adaptive capacity of the body is strained.

INFLUENCE OF LEAD AND CADMIUM ON THE ELECTROLYTE EXCHANGE AND MORPHOLOGICAL CHARACTERISTICS IN RAT'S MALE GAMETES

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Presented are the experimental data about disturbances in Ca, Mg a turnover and morphological parameters in the gonadal cells of mature male rats against the background of administration of 1/200 LD_{50} lead acetate and cadmium chloride in experiments of 48-days.

Administration of lead and cadmium to adult rats resulted in an increase of its level in blood and spermatozoa, alteration in the contents of intracellular Ca, Mg. The disturbance of turnover of electrolytes was assumed to result in impairment of biochemical processes in spermatozoa and negative influence on their fertility.

ESTIMATION OF DNA-PROTEIN CROSS-LINKS, ABNORMAL SPERM HEADS AND MICRONUCLEI IN MICE CONTINUOUSLY EXPOSED TO HEAVY METALS AND GAMMA-RADIATION AT LOW DOSES

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Background: The global pollution of the environment has led to the fact that humans and biota are frequency exposed to heavy metals and ionizing radiation at low doses. The data about combined action of heavy metals and irradiation at low doses on genetic structure of mammals are rather fragmented and contradictory.

Aims: To study of influence of continuous exposure to heavy metals and gamma-radiation at low doses on genetic structure of mice.

Methods: CBA/lac male-mice 6 weeks old were exposed to low dose-rate gamma-radiation (0.07 cGy/day) and/or heavy metals (lead and cadmium) with drinking water (0.3 mg Pb^{2+}/l; 0.01 mg Cd^{2+}/l) for different time (20–80 days) and compared with control mice. The DPC level was determined by K/SDS assay. The percentage of ASHs and the percentage of peripheral blood normochromatic erythrocytes (NCE) with MNs were evaluated by standard cytogenetic tests.

Results: The results of our studies have demonstrated that the dependence of the DPC level on the total dose (exposure time) of gamma-radiation and/or heavy metals is nonlinear. The pattern of changes of DPC level was similar for different agents. The exposure to cadmium or γ-radiation or the combined exposure to gamma-radiation and lead caused an increase in the ASH frequency at 80-th day of the experiment. No increase was found in the frequencies of MNs in NCEs and reciprocal translocations in spermatocytes.

Conclusions: Summing up the results obtained it can be concluded that combined action of gamma-radiation and heavy metals at the applied doses do not result in pronounced cytogenetic effects. Non-linear shape of DPCs dose-response dependencies is strongly support the idea that DPC participate in overall response of the exposed cells to low doses of heavy metals and ionizing radiation.