

1. Raevsky O.A., Liplavskaya E.A., Worth A.P., Grigorev V.U.

Acute intravenous toxicity to mice calculations on the basis local regression models in superoverlapping clusters (LRMSC).

Modeling of quantitative structure - activity relationships between physicochemical descriptors of organic chemicals and their acute intravenous toxicity in mice have been presented. This approach includes three steps: structure-similarity chemicals selection for every chemical-of-interest (clusterization); construction of quantitative structure - toxicity models for every cluster (without including of chemical-of-interest); application of obtained QSAR equations for chemical-of-interest toxicity estimation. This approach has been applied for acute intravenous toxicity calculations of 10241 organic chemicals. For 7759 chemicals which has enough quantity of structural neighbours with the Tanimoto index (Tc) on the level 0.30 and over, a standard deviation of calculation vs. experimental $\log(1/LD50)$ values is equal to 0.51 at the estimation of experimental determination on the level 0.50. The results of calculations isn't so good for remain chemicals (~24%). It is connect with absence of sufficient number of structure similarity neighbours. It's assumed this QSAR approach can be useful for activity and toxicity prediction of chemicals large sets.

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2. Kornienko M., Ilina E., Borovskaya A., Edelstein M., Sukhorukova M., Kostrzewa M., Govorun V.

Strain differentiation of staphylococcus aureus by means of direct maldi tof mass spectrometry profiling.

Staphylococcus aureus - one of the most interesting for clinical studies of microbial species with extensive strain diversity, primarily due to the variability of virulence factors and pathogenicity. The aim of this study was approbation of a method for the rapid strain differentiation of S. aureus on the basis of bacterial cell direct protein profiling approach by means of MALDI TOF MS. Beta-lactamase and alpha-hemolysin productions, coding by the blaZ and hla genes, respectively, were selected as markers for the strain differentiation. Mathematical analysis of MALDI mass spectra from 53 isolates allowed the construction of two independent classification models that can differentiate the strains on the presence/absence of blaZ or hla genes. A number of the most significant peaks (masses), which can be considered as markers of the strain differences in S. aureus, were identified using a statistical contribution of each mass peak in the models. These diagnostic models differ the sensitivity and the specificity, which were 97.5% and 82.5% for the classification of strains on the basis of beta-lactamase production, and 90.0% and 88.7% by the presence of alpha-hemolysin.

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3. Pakharukova N.A., Pastushkova L.Kh., Moshkovskii S.A., Larina I.M.

Variability of healthy human proteome.

The purpose of this review is to analyze investigations devoted to characteristic of protein variability and diversity of their posttranslational modifications in healthy humans. The numerous researches have demonstrated that proteomic profile has a considerable both intra- and inter-individual variability, and quite often normal variability of some proteins can be comparable to changes observed in pathological processes. Results obtained by our research group have confirmed high intra-individual variability of serum low-molecular subproteome of healthy volunteers, certified by a special medial committee. Proteins characterized by high variability in normal conditions (e.g. haptoglobin - 0-40 mg/ml; lysozyme - 0,01-0,1 mg/ml; C-reactive protein - 0,01-0,3 mg/ml) should be excluded from the list of potential biomarkers. On the contrary, proteins and peptides characterized by insignificant dispersion in healthy population (such as albumin - coefficient of variation (CV) 9%; transferrin- CV 14%; C_3N complement - CV 17%, $\text{I}\pm\text{-1}$ acid glycoprotein - CV 21%, $\text{I}\pm\text{-2}$ -macroglobulin - CV 20%; transthyretin fragment - CV 28,3% and $\text{I}\pm\text{-2}$ -HS-glycoprotein - CV 29,7%) can provide us with important information about state of health. Thus investigations of plasticity in proteomic profiles of healthy humans will help to correct reference intervals used in clinical proteomics.

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4. Iskusnykh I.Y., Popova T.N., Musharova O.S.

Intensity of cardiac free-radicals processes and expression of glutathione peroxidase and glutathione reductase genes in rats with adrenaline.

The correlation between changes in activities of glutathione peroxidase and glutathione reductase in heart of rats during development of adrenaline myocarditis and intensity of free radical processes estimated by biochemiluminesce parameters and the content of lipoperoxidation products was demonstrated. The maximal increase of glutathione peroxidase and glutathione reductase activities (in 1.8 and 1.4 times accordingly) was observed t 24 h after the development of the pathological process; this coincided with the maximum intensity of processes of free radical oxidation. Using combination of reverse transcriptions with real-time polymerase chain reaction the cardiac mRNA levels of glutathione peroxidase and glutathione reductase genes were determined during the development of adrenaline myocarditis in rats. Analysis of expression of glutathione peroxidase and glutathione reductase genes showed, that the level of this transcripts demonstrated 2,8- and 7,3- increase in rats with adrenaline myocarditis, respectively. Obviously, overexpression of these enzymes can increase the resistance of cardiomyocytes to oxidative stress.

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5. Shmarakov I.A., Katan N.V.

The induction of guerin's carcinoma cytochrome P450 hydroxylase activity by retinoids.

The interconnection of tumor growth process and the provision of the body with vitamin A was studied. The replenishment of vitamin A stores of vitamin-deficient tumor bearing animals modulated Guerin's carcinoma growth rate in a dose dependent manner ($r=0,83$). The morphological parameters of tumor growth at different provision with vitamin A positively correlated with hydroxylase ($r=0,81$) and demethylase ($r=0,49$) activities of the Guerin's carcinoma cytochrome P450 system. The induction of hydroxylase and demethylase activities of cytochrome P450 in Guerin's carcinoma microsomal fraction, observed either under conditions of overdose supplementation, or selective liposomal form of all-trans-retinoic acid, suggests the stimulatory effect of retinoids on tumor growth.

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6. Kopylchuk G.P., Shmarakov I.A., Buchkovska I.M., Marchenko M.M., Blaner W.S.

Cytochrome P450 system components and nitric oxide synthase activity in mouse liver under conditions of retinoid stores absence.

p-Hydroxylase and N-demethylase activities of cytochrome P450 system, NO-synthase activity and the intensity of nitric oxide and superoxide anion production in mitochondrial, postmicrosomal and microsomal cellular fractions were studied in mouse liver under conditions of retinoid stores absence. It is determined, that under conditions of retinoid stores absence the activation of NO-synthase is occurring with decreased p-hydroxylase activity of cytochrome P450 system. The results of the generation intensity analysis showed the level of NO and \dot{O}_2^- in liver mitochondrial fraction of knock-out mice, and changes in NADPH-dependent \dot{O}_2^- production in microsomal fraction of mouse liver cells.

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7. Kuzmenko D.I., Burov P.G., Serebrov V.Yu., Fait E.A., Perevozchikova T.V.

Functional state of a sphingomyeline cycle and free radical lipid oxidation activity of a rat's liver during different phases of starvation.

The functional state of a sphingomyeline cycle and character of its mutual relations with the processes of free radical lipid oxidation during starvation of animals without any restriction of access to drinking water at 1, 2, 3 day (I phase) and 6 day (II phase of starvation) were studied at the liver of rats. The maximal values of the ceramide/sphingomyeline ratio and activity neutral sphingomyelinase and executive caspase-3 were reached in a liver of animals at the 3rd day of starvation. From the 3rd day of starvation the concentration of the tumour necrosis factor- α which is one of activators neutral sphingomyelinase was increase in rats blood serum. During the extent of large part of the I phase of starvation the intensity of free radical lipid peroxidation in a liver had almost the same level as in control group - that was a result of the high-grade functioning of antioxidant defense system. After transition the I phase of starvation into the II phase (6 day of experiment) the oxidative stress was developed as result of an exhaustion of system antioxidant defense potential in a liver. The results of this data can testify that during I phase of starvation in a liver the conditions was raised for display of the ceramide-mediated proapoptotic signalling. We assume that ceramide-mediated apoptosis is one of mechanisms of optimization of liver cellular population at the frames of metabolic adaptation. The I phase of starvation in a liver proves by the ceramide-mediated proapoptotic signaling developing. During the II phase of starvation the oxidative stress process were prevailed.

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8. Voskresenskaya A.A., Medvedeva N.V., Prozorovskiy V.N., Moskaleva N.E., Ipatova O.M.

The absorption features of glycyrrhizic acid in composition of drug Phosphogliv.

Glycyrrhizic acid (GL) - one of the active components of the Russian drug formulation Phosphogliv; possesses extremely low bioavailability. A sensitive method for GL determination in blood using high performance liquid chromatography coupled with mass-spectrometry (HPLC-MS) has been developed in order to investigate absorption characteristics of glycyrrhizic acid after peroral administration of Phosphogliv; and GL sodium salt. Separation of blood components was achieved on the analytical reverse-phase column C18 EcoNova; ProntoSIL, using a gradient mode. Detection of GL and an internal standard (IS) (glycyrrhetic acid) was performed using electrospray ionization with the selected ion monitoring in negative mode (SIM) using target ions at m/z 821.3 for GL and 469.3 for IS. The calibration curve was linear over the range of 50-5000 ng/ml (the correlation coefficient was 0.995). The detection limit for GL in blood was 25 ng/ml and the lower limit of quantification was 50 ng/ml. The developed method has been applied to compare absorption efficiency of glycyrrhizic acid as the component of Phosphogliv; composition and solution of GL sodium salt during first two hours after their single peroral administration to rats at the dose of 8.5 mg/kg. It was shown that GL absorption occurs several minutes after peroral administration. Moreover, GL bioavailability after administration of drug Phosphogliv; was higher than after administration of GL sodium salt. This difference may be attributed to incorporation of glycyrrhizic acid in the phospholipid nanoparticles structure.

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9. Volkova Y.V., Sukhova L.L., Davydov V.V., Goloborodko A.V.

The activity of the first line enzymes of the antioxidant defence in the liver of pubertal rats during stress.

The purpose of the work was to study the activity of the first line antioxidant defence enzymes in postmitochondrial fraction of liver of pubertal rats during immobilization stress. During short-term immobilization the activity of catalase and glutathione peroxidase (GPx) decreased. Long-term immobilization was accompanied by activation of GPx and superoxide dismutase in the liver postmitochondrial fraction of late pubertal and adult animals, but not early pubertal rats.

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10. Zharkova I.I., Efremov Yu.M., Bagrov D.V., Zernov A.L., Andreeva N.V., Shaitan K.V., Bonartsev A.P., Boschomjiev A.P., Makhina T. K., Myshkina V.L., Voinova V.V., Yakovlev S.G., Filatova E.V., Ivanov E.A., Bonartseva G.A.

The effect of poly(3-hydroxybutyrate) modification by poly(ethylene glycol) on the viability of cells grown on the polymer films.

A biodegradable polymer of bacterial origin, poly(3-hydroxybutyrate) (PHB), is intensively studied as biomaterial for tissue engineering. However, factors determining its biocompatibility still require better understanding. To analyze the PHB films biocompatibility, the polymer material was modified by hydrophilic polymer, poly(ethylene glycol) 300 (PEG). The blends PHB/PEG with different PEG content (10, 20, 30 and 50%) were produced by

subsequent incubation in water resulted in removal of 95% PEG. The surface roughness and hydrophilicity were studied by atomic force microscopy (AFM) and contact angle "water-polymer" measurement, respectively. The film biocompatibility on cell culture of COS-1 fibroblasts was studied in vitro. It was shown that both roughness and hydrophobicity are directly proportional to initial PEG content in the PHB/PEG blends. The growth rate of COS-1 fibroblasts on polymer films is determined by combination of two basic physicochemical properties of the polymer surface: the roughness and hydrophilicity. The optimal roughness required for COS-1 cells growth is the average roughness more than 25 nm, whereas the limit values of the contact angle "water-polymer" that was responsible for relatively high cell viability were not found. These data indicate that the film surface roughness had the greatest effect on the cell growth, whereas the increase in the polymer surface hydrophilicity caused the additional positive effect on viability of attached cells. Thus, the modification of PHB polymer material by PEG resulted in the improved viability of cells cultivated on the polymer films in vitro. The obtained data can be used for development of such medical devices as surgeon patches and periodontal membranes.
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11. *Razygraev A.V.*

Catalytic activity in rat blood plasma and erythrocytes that eliminates homocysteine with hydrogen peroxide.

The activity utilizing the free SH-form of homocysteine with H₂O₂ has been found in rat blood plasma and erythrocyte lysates with the use of the glutathione peroxidase assay with hydrogen peroxide and 5,5'-dithiobis-(2-nitrobenzoic acid) and with the substitution of glutathione by homocysteine. The presence of rat plasma or erythrocyte lysate in a reaction mixture containing D,L-homocysteine, and H₂O₂ resulted in a marked acceleration of homocysteine concentration decrease (the decrease of homocysteine concentration was initiated by addition of hydrogen peroxide). The data obtained suggest the presence of homocysteine peroxidase activity in plasma and erythrocytes. The observed activity may be attributed to some known thiol-dependent enzymes. In the rat brain tissue, the level of the activity is extremely low (at the detection limit). The increase of the activity in blood components during post-embryonic ontogeny has also been shown. Probably, this activity contributes to low concentrations of free SH-form of homocysteine in the blood components.
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12. *Fedchenko V.I., Buneeva O.A., Kopylov A.T., Kaloshin A.A., Axenova L.N., Zgoda V.G., Medvedev A.E.*

Mass spectrometry detection of monomeric renalase in human urine.

Renalase is a recently discovered secretory protein, which is suggested to play a role (which still remains elusive) in regulation of blood pressure. Earlier it was purified from urine of healthy volunteers by means of ammonium sulfate fractionation and subsequent affinity chromatography (Xu et al. (2005) J. Clin. Invest., 115, 1275). The resultant purified preparation of renalase contained 2 proteins with molecular masses of 35 and 67-75 kDa. The authors believed that the latter represents a dimerization (aggregation) product of the 35 kDa protein. In this study we have detected renalase in urinary samples of 2 of 6 volunteers only after immunoaffinity enrichment of urinary samples subjected to ammonium sulfate precipitation. Electrophoresis of the purified preparation also demonstrated the presence of 2 proteins with molecular masses of 35 and 66 kDa, respectively. Mass spectrometry analysis of these proteins identified 35 and 66 kDa proteins as renalase and serum albumin, respectively. Thus, our results do not support suggestion on formation of renalase dimers and they indicate that urinary renalase excretion significantly varies in humans.
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13. *Globa A.G., Alekseev Y.I., Arzumanyan V.G., Zaborova V.A., Guridov A.A.*

The use of real time PCR for quantitative determination of some propionic bacteria residing on human skin.

A test system has been developed for determination of propionic bacterial species residing on human skin. This system developed in the real time PCR format is applicable for quantitative determination and also detection of genomes of the following Propionibacterium species: P. acnes, P. granulosum and P. avidum. This system was used for analysis of wash samples from the skin of 17 pentathlon sportsmen and 16 students. All three species of propionic bacteria were found in all skin wash samples. However, contamination with P. acnes was two times higher in control group than in the group of pentathlon sportsmen.
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