



Abstracts

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**TRANSGENIC SOURCES OF FOOD:
SITUATION IN UKRAINE AND IN THE
WORLD. TRANSFORMATIONAL
CONSTRUCTS AS AN OBJECT OF
DETECTION**

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Since 1986, when first GM plants have undergone the first field trials, the commercial GM crops have been widely cultured all over the world. They caused so-called 'Trangenic revolution' – the effectiveness of cereals cultivation has risen almost in 4 times (from 0.6 billion tons in 1950 to 2 billion ton in 2000, with tendency to achieve the level 3-4 billion tons in 2050). The analysis of world area under GM crops shows the 20% increasing in 1-year period (from 2003 to 2004), which makes 13.3 mln hectares difference. Nowadays 17 countries in the world are culturing GM-crops officially, 14 of them are called 'Biotech mega-countries' under their GM/non-GM ratio.

High efficiency of GM crops convinces more and more farmers to change their agricultural traditions, and to increase level of its cultivation. It explains 56% part of GM crops in total crops of soybean, 28% part in total crops of cotton and 14% part in total crop of maize.

During GMO development specific transformational constructs are implanted into plant genome. The main parts of transformational constructs are promoter (usually CaMV-35S), specific gene, marker genes and terminator (usually NOS). Depending on targeted sequences of PCR primers we can detect presence of exact piece of transformational construct, which is defined by objective of exact GMO monitoring stage.

There are three main stages of GMO monitoring analysis: 1) screening on GMO presence, 2) identification of GMO strain, 3) quantification of GMO contents.

**TO PROBLEM OF THE COMBINED
ACTION OF PESTICIDES**

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Intensive chemization of agriculture results in contamination of environment by the chemical substances. One of the ways of diminishment of the negative influencing of pesticides on biocenose and man is an application of the combined preparations on the basis of the already known chemical substances. This further in minimization of norms of expense, warning of resistance to preparations and increase of efficiency of fight against wreckers, illnesses and weeds on sowing of agricultural cultures. However here is possibility of simultaneous influence on the organism of man of a few pesticides. It can take place at application of pesticides when there are inhalation and dermal ways of exposure and at consumption of food and water containing the remaining amounts of chemical substances stuffs. The special danger arises up in the case of potentiation of toxic action, when a joint effect exceeds the sum of effects of each of the substances included in combination. By the researches conducted by us during a few decades, it is set that toxicity potentiation is observed only at influence of combination of organophosphorus compounds and synthetic pyrethroids at the level of lethal doses. The expressed of effect of potentiation goes down with diminishment of doses of pesticides. There is only more early display of changes of biochemical changes and their less harmoniousness as compared to the control in the chronic experiment that can tell on adaptation possibilities of organism. According to this it is expedient to conduct research of the combined action at the level of threshold doses in the chronic experiment in future and to study adaptation of organism to influence of environment at their joint simultaneous administration in organism that will allow to giving objective estimation of the safe use of pesticides in agriculture.

**SUBCHRONIC ORAL TOXICITY OF
METHSULPHURON-METHYL FOR
WISTAR RATS**

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The aim of this study was evaluation of oral subchronic toxicity of Methsulphuron-methyl technical (96%) from the firm China Chemical Industrial & Research Co., LTD (China). The study performed on adult male and female Wistar rats. The rats were instilled by a syringe with a metal probe. Doses of Methsulphuron-methyl in water emulsion with the emulsifier "OP-10" were 0, 25, 75, 400 mg/kg of body weight. The exposition time was 13 weeks. The observations of behavior changes, the clinical symptoms of intoxication, the lethality, food and water consumption were performed daily. The registrations of individual weight and body weight growth were realized weekly. The functional condition of central nervous system (CNS), the functional condition of kidney (daily diuresis, pH, specific gravity, protein and glucose concentrations), the liver (alkaline phosphatase activity, alanine- and aspartateaminotransferase activities, total protein, urea, total cholesterol and glucose concentrations), the macroscopic changes, absolute and relative weight of the internal organs were studied on the 4th, 9th and 13th weeks. Any clinical symptoms of intoxication, lethality, behavior changes and changes of water and food consumption were not found. CNS status was studied by the behavior reactions characterized the orient-investigate activity, the passive-defensive reflex and the emotional condition of animals and there were not any significant changes. Methsulphuron-methyl at 25, 75 and 400 mg/kg of body weight doses has not negative influence on kidney of male and female rats. There were not any significant changes of absolute and relative weight of the internal organs at all the time of examination. The body weight gain was at control level on all of doses. The macroscopic changes of the internal organs were not detected for all the time of examination. It was found the significant increase of body weight on 400 mg/kg dose after 1 week from the start of the experiment (male – 6.1 %, female – 5.9 %). We registered the significant increase of alkaline phosphatase activity in male and female serum on the 4th, 9th and 13th weeks (35.4 %, 37.8 %, 29.5 % and 35 %, 30.4 %, 26.4 %, accordingly). The absolute

weight of male spleen and the relative weight of male brain had a tendency to decrease (19.6% on the 4th week for spleen and 15.8% on the 13th week for brain); the absolute and relative weight of female spleen weight had a tendency to increase on the 13th week (9.9 % and 17.2 %, accordingly). On 75 mg/kg dose it was found a tendency to increase of the absolute (34.1 %) and the relative (42,3%) weight of male spleen on the 9 week only. There were not any changes of the body weight gain and significant changes of the serum and the urine parameters on 25 and 75 mg/kg doses during the study. Thus Methsulphuron-methyl at subchronic oral study make general toxic effects and cause liver cholestasis on 400 mg/kg dose. Methsulphuron-methyl technical (96 %) NOEL for male and female rat – 75 mg/kg (general toxic rates).

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**BIODEGRADATION AND
BIOREMEDIATION OF POLYCYCLIC
AROMATIC HYDROCARBONS**

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Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous contaminants that are found in high concentrations in contaminated soil and sediment at sites associated with several industrial activities. They are always found as complex mixtures rather than as individual compounds. In the United States, the Environmental Protection Agency regulates 16 PAHs ranging in size from two rings to six rings, with seven of these compounds considered to be human carcinogens. Many microorganisms have been found to metabolize PAHs, so we know they are inherently biodegradable. However, their removal from contaminated soil is often not as extensive as required to meet cleanup goals, suggesting that bioremediation might not be a feasible cleanup strategy at some PAH-contaminated sites. Poor removal during bioremediation is a particular problem for the higher-molecular-weight four-, five-, and six-ring compounds, which includes the

carcinogenic PAHs. Limited bioavailability has been invoked as an explanation for poor removal of the PAHs, but bioavailability is rarely measured for specific soils. Furthermore, several studies have provided evidence that limited bioavailability does not explain poor removal of the five- and six-ring compounds during bioremediation of field-contaminated soils. Therefore, other factors must control the degradation of these compounds. This presentation will explore such factors and current methods for evaluating them in field-contaminated soil. Topics will include methods of measuring bioavailability, cultivation-independent methods of identifying and quantifying PAH-degrading microorganisms, and measurement of genotoxicity as a potential factor influencing the degradation of PAHs during bioremediation.

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THE EVALUATION OF DANGER OF MODULATING FUNCTION OF SEX HORMONES PESTICIDES FOR HUMAN

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Hormonally active agents, also termed "endocrine disruptors", have become a widely debated issue in toxicology and related fields due to concerns that exposure may result in developmental, reproductive, oncological effects. EPA estimates the universe of potential endocrine disruptors chemicals, EDCs, numbers more than 87,000 items. Many active ingredients of pesticides can have such **properties**. On the basis of literary data analysis made a list of such chemicals, which could enter the environment of Ukraine.

Analysis of these data was shown that estrogenic or androgenic effects can be induced by a variety of mechanisms, but they most commonly occur through binding of endocrine active compounds to nuclear receptors. These effects is realised under the exposure of organism to low doses. In most doses EDCs can to involve other mechanisms as metabolic inhibition or induction affecting steroidogenesis, enzymes that modify hormones, plasma transport proteins, and neurotransmitter levels. The data about the interactions of

pesticides with the sex hormone receptors of man was found in many publications. The results of these studies were analysed. Transactivation or reporter gene assay, which is a wide used tool for testing receptor agonists and antagonists among chemicals, has been established as a method for evaluating the receptor activity of chemicals. By the different modification of these methods many pesticides were studied.

The most representative was studies Hiroyuki Kojima et al. [Environ. Health. Perspect. 2004.112, 524], which were tested 200 pesticides, including some of their isomers and metabolites, for agonism and antagonism to two human oestrogen receptor (hER) subtypes, hER α and hER β , and a human androgen receptor (hAR) by highly sensitive transactivation assays using Chinese hamster ovary cells (CHO). It was shown that several pesticides exert estrogenic and antiandrogenic activities through interaction with estrogen (ER) and androgen receptors (AR).

The integral index of safety pesticides for human is acceptable daily intake (ADI). The aim of our study was to evaluate whether the Ukraine standard for ADI are adequate to prevent risk of these effects. Margin of safety was determined as the percent ratio of the ADI to the lowest observable effects level (LOEL), which were set in above-mentioned studies. On such principles the danger of the pesticide, which can meet in the environment of Ukraine and had setting the ADI, was analyzed.

These data of 90 active ingredients of pesticide preparations, which were used in Ukraine, were studied. 16 of the 90 pesticides were found to induce estrogenic activity in the ER assay. 25 of 90 pesticides exhibited antiandrogenic activity in the AR assay. The data of ER and AR assays show that 24 pesticides possessed both estrogenic and antiandrogenic activities, indicating pleiotropic effects on hER and hAR. It was shown that only 4 pesticides (methoxychlor, prothiophos, propanil, procymidone) of the 90 were found to induce estrogenic activity in the ER / AR assay as receptor agonists or antagonists through direct interaction with hormone receptors at doses ADI. Methoxychlor has more strong effect. In the present time these pesticides did not used in Ukraine. The Ukraine standard for ADI pesticides

provides adequate margin of safety against adverse endocrine effect associated with the interactions of pesticides to the sex hormone receptors of man.

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CLINICAL AND HYGIENIC ASPECTS OF RISK PROGNOSIS OF DEVELOPMENT OF CHRONIC PESTICIDES INTOXICATIONS OF AGRICULTURAL WORKERS

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The protracted influence of pesticides complex and agrochemicals on agricultural workers quite often results in the origin of chronic pesticides intoxication. However even at the identical terms of productions in one cases intoxication develops in relatively short time, in other cases its signs appear only in 25-30 years or quite absent, that testifies to the large role of individual sensitiveness in its development, providing the state of the promoted receptivity (promoted risk) or tolerance (to stability) to the protracted professional influence of pesticides. In work prevalence of acute and chronic intoxications is studied by pesticides for the last 15 years among agricultural workers. In the structure of the acute poisonings pesticides poisoning herbicides on the basis of a 2,4-dichlorophenoxyacetic acid is predominated (47.4 %, eight groups cases), rarer marked poisoning herbicides on the basis of sulphonilurea (7.7 %), organophosphorus substances (3.5 %), pirethroids (1.7 %), by preparations on the basis of carbaminic acid (1.3 %), copper containing pesticides (0.9 %), phenilpyrozol derivates (0.4 %) and other substances, mainly because of hygienic regulations violations. Chronic intoxications of the protracted influence of pesticides complex (OPS, OCS, herbicides, pirethroids, copper containing and other substances) found out in agricultural workers mainly at experience of work over 10-15 years, frequency of exposure depended on a profession, amount of the workings changing in a year, intensity of pesticides contamination of air of working area. More frequent chronic intoxications found out among workers of pesticides storages which had most of the workings changing in a year in touch with

pesticides (on the average 196.2 ± 6.8). Frequency of exposure of chronic intoxications in this group achieved 30%, thus middle experience of work to development of disease made 14.2, thus 7.7 % cases diseases exposed already at experience of work 5 years, 15.4 % - at experience from 5 to 10 years. For tobacco growers, mechanization experts, fruit-growers, disinfectors and agricultural field crop growers the amount of changing in a year with influence of pesticides was less, and frequency of exposure of intoxications was considerably below.

Neurological disorders (toxic encephalopathy, asthenovegetative syndrome, vegetative-sensory polyneuropathy) predominated in the clinical picture of intoxications pesticides, toxic hepatitis, cardiomiopathy, hypochromic anaemia, toxikodermy, exogenous allergic alveolitis, bronhoabstrusive syndrome were rarer marked. The study of character of flow of disease showed that in 34.6 % cases development of disease was only in 42 % of cases connected with hygienic risk factors. In 58 % cases development of disease was related to expressed of cytolythic syndrome of liver disorder, endotoxicity level, small circulatory immune complexes and expressed endothelial dysfunction.

For the priority conducting of curative prophylactic measures in different professional groups the index of estimation of group weight of intoxication taking into account the days of disability is developed in a year with the temporal loss of ability to work and percent of proof loss of ability to work. The index of the length of service loading of the combined action of pesticides is developed taking into account multiplies of exceeding of MAC in air working area of different pesticides during work, their class of danger and amount of the workings changing in a year. The calculations of this index showed that at workers with influence pesticides with chronic intoxication its level is considerably higher.

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BIOMARKERS: CHALLENGES FOR CHEMICAL ANALYSIS

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Unambiguous identification, rigorous characterization and accurate quantitation are essential for meaningful measurement of biomarkers of exposure and of effect. The Chemistry and Analytical Core of the UNC-Chapel Hill Superfund Basic Research Program provides the infrastructure needed for analyses and assays that are critical for evaluating exposure to hazardous environmental chemicals and for understanding the role of oxidative stress in determining health outcomes. Chief among the biomarkers of interest are protein and DNA adducts; progress in analysis of markers of DNA damage resulting from oxidative stress has been particularly challenged by the lack of standards and the presence of artifacts. Our strategy has been to prepare, purify and unambiguously characterize synthetic standards for the putative adducts and other biomarkers. These enable rigorous assay development and validation, and in conjunction with analytical tools such as LC-MS/MS, highly specific and highly sensitive quantitation. We have been able to prepare S-arylcysteine and S-arylmercapturate adducts as standards for analysis of protein adducts of polycyclic aromatic hydrocarbons. The former conjugates as their 9-fluorenylmethoxycarbonyl (Fmoc) derivatives were also incorporated into defined oligopeptide sequences representing the head sequences of keratin proteins, for analysis of adducts formed in the skin. Another approach that has proven especially fruitful has been the synthesis of modified DNA bases, and bases and nucleotides labeled with stable isotopes. Thus the tricyclic adducts $N^2,3$ -ethenoguanine and $N^2,3$ - $[^{13}C_4, ^{15}N_2]$ ethenoguanine, $N^2,3$ -ethenodeoxyguanosine, ethenoadenine and their $^{15}N_5$ analogues were prepared and characterized. The ^{15}N and ^{13}C isotopomers served as internal standards for highly specific assays utilizing mass spectrometry detection. The methodology employed for incorporation of the stable isotopes into $N^2,3$ - $[^{13}C_4, ^{15}N_2]$ ethenoguanine also enabled preparation of guanine with C4, C5, N7 or N9 specifically labeled. This

approach was key in structural elucidation by nuclear magnetic resonance of a novel oxidation product of guanine, 5-carboxamido-5-formamido-2-iminohydantoin

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MEDICAL PREPARATIONS AS ENVIRONMENTAL RISK FOR HUMAN

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The threat of global environmental contamination requires more deep study of compounds the accumulation of which in a natural environment is directly related to the vital functions of human. Medical preparations (MP) to the present tense were not examined as pollutants of environment. A production and synthesis of new MP grows constantly. A consumption only of one antibiotic is 100-200 thousand tons annually. In work the analysis of MP is presented as a factor of risk for the human and biota health on the whole at their income to environment. Unlike other chemical toxicants contamination of objects of natural environment by the different forms of MP because of their wide individual use a population is constant and uncontrolled.

There are a few ways of their income to environment: through the sewage system in unchanging (cytotoxicants, 90-65% are antibiotics) or metabolized state (more than 17%) in the unrationed amounts depending on the courses of treatment and volumes of their use; as domestic wastes and wastes of pharmacological productions. In addition, contamination of environment by MP is constantly multiplied in connection with the wide use them in veterinary science (warfarine, aminoglycosides, β -lactams and macrolids, cholines, sulphonamids, tetracyclines), in agriculture, as antimicrobial preparations and for protecting from the insects and diseases of agricultural cultures, repellents (caffeine), for regulation animals and birds population (acetaminophen, paracetamol, 4-aminopyridin), as making ingredients of cosmetic products, at making of tooth-pastes (triclozan, tocopherol, tiamin, riboflavin), etc. Through soil they enter

underground waters, and at the use in the economies of fishes - in superficial reservoirs.

Modern technologies of flows of sewages, which are used on cleansing buildings, are not adjusted for clearing of MP. Majority of them determined in superficial reservoirs in the concentrations of 1 ng/l – 1 µg/l. Researches, conducted in some regions of the USA and Germany showed that such MP as clofibric acid, carbamasepin, iodine-contrasting agents pass through soil and determined in underground waters, in large concentrations more than to thirty MP are detected as antibiotics, febrifuge, cardiac and anaesthetic preparations.

Because in small concentrations some MP were detected in a drinking-water, it is considered that MP can act a population with a drinking-water daily during all life.

Possessing high and specific biological activity, by persistence to degradation the special danger is presented by cytotoxic preparations, antibiotics and disinfectants, hormonal preparations, and also preparations with a psychotropic and narcotic action. Unfavorable physiological effects of majority of MP on the living organisms of water environment, birds, beetles, mosquitoes and microorganisms are shown in very low concentrations (ng/l). Toxic effects of antibiotics for water-plants and daphnia shows up in the concentrations of 5-100 µg/l, cytotoxic agents are the source of mutagens in environment. A risk for the human health is related to their intake into organism with a drinking-water and by food chains. Antibiotics form development of multiresistance of pathogenic flora is founded, that is a serious medical problem in the whole world.

Biochemical cooperation of different MP results in the effect of toxicity potentialization. And the fact of continuous and protracted intake of such substances even with low persistence can cause the effects of stable pollutants, because their speed of transformation and elimination is compensated by speed and constancy of intake.

Contamination of objects of ecosystems by medicinal preparations (MP), metabolites, by the products of their transformation is dangerous by unforeseeable externalities and health of population and requires development of the special system of MP

management in the process of production, import, use and elimination.

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IMPACT OF DIFFERENT CLASTOGENES ON THE TYPE OF CHROMOSOMAL ABERRATIONS MEASURED BY FISH

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The pattern of chromosomal aberrations (CA) was studied by fluorescence in situ hybridization (FISH) technique (whole chromosome #1 and #4 painting) in workers occupationally exposed to either of the four following conditions: acrylonitrile (ACN), ethyl benzene (EB), carcinogenic polycyclic aromatic hydrocarbons (c-PAHs), and irradiation in nuclear power plants (NPP), respectively. A decrease in the relative frequency of translocations was observed in EB group, and an increase in reciprocal translocations in ACN and NPP-exposed groups. An increase in a relative number of insertions was registered under all four conditions (significant at ACN, EB, c-PAHs, quasisignificant at NPP-exposed groups). Significant differences in the percentage of lymphocytes with aberrations on chromosome #1 ($58.8 \pm 32.7\%$, vs. $73.8 \pm 33.6\%$ in the controls, $P < 0.05$), and chromosome #4 ($47.0 \pm 34.1\%$, vs. $29.4 \pm 32.2\%$, $P < 0.01$) were found in workers exposed to ACN. Similarly, a decrease in the proportion of cells with aberration on chromosome #1 ($61.0 \pm 24.0\%$, vs. $73.8 \pm 33.6\%$, $P < 0.05$) and an increase on chromosome #4 ($45.6 \pm 24.6\%$, vs. $29.4 \pm 32.2\%$, $P < 0.05$) were observed in workers exposed to EB. Frequency of aberrant cells (% AB.C.) as well as genomic frequency of translocations $F_G/100$ increased with age ($P < 0.001$). Aging also increased the percentage of translocations and reciprocal translocations ($P < 0.05$), but decreased the relative number of acentric fragments ($P < 0.01$). Smoking led to significantly increased $F_G/100$ ($P < 0.05$), but did not affect the pattern of chromosomal aberrations. Our results seem to indicate that different carcinogens may induce a different pattern of chromosomal aberrations.

HOUSEHOLD CLEANERS. SAFETY FOR HUMAN HEALTH AND ENVIRONMENT

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During manufacture and applications synthetic detergents and cleaners on the surfactants basis can come through environment, have negative effect on human health and environment. The wide range of application washing and cleaners in private life determines close contact of all population groups with them. At detergents and cleaner manufacturing about 80 % of total amount of the surface-active substances produced nowadays are used. Among all made detergents anionic substances occupy the greatest proportion. Thus, in 2000, 3,4 million tons of linear alkyl benzene sulphonates have been used that has made up one third of all usage volume of the basic types of surfactants. Pollution of water and ground by enterprises for manufacturing surfactants and with their wide application has been investigated. Air pollution around the household chemistry goods producing plants makes 0.03-0.045 mg/m³ within the 3 km distance. The average content of anionic surfactants in open reservoirs is within the limits of 0.05 mg/l, in rain and snow water is 0.14 mg/l, in ground 0.595 mg/l. Surfactants are low toxic for human and animals organism. Getting on skin, surface-active agents influence its functional state: change of pH level, lipids contents, total level of amino acids. The greatest danger of surface-active agents and preparations on their basis for human lies in their sensibilized action, ability to cause allergic reactions. The sensibilization may occur at any ways of surfactants entrance to organism. As a rule, detergents in concentration of 1 % and less do not show sensibilization.

The following hygienic demands are made of detergents and cleaners:

- Detergents and cleaners should have irritating and allergic effect on a human organism at observance of their use conditions according to the reference document. They should not have any teratogenic, carcinogenic, embriotoxic,

mutagenic and other negative effect on human organism;

- The formulation of detergents and cleaners should contain components issued under the reference document and coordinated with bodies of sanitary-epidemiological service of the country.

- Toxic chemical substances of 1 and 2 danger classes should not be used by manufacture of synthetic detergents and cleaners;

- Chemical compounds that are included to formulation of compositions, should be removed from surface of finished goods at their processing to the level of hygienic specifications after triple rinsing.

- Compositions should be made in aggregate states extremely reducing or excluding come to respiratory tract, a digestive tract and at mucous of human being at their use; by working out of new formulations of compositions surfactants with high biodegradation degree should be used;

- Synthetic compositions should not change physical and chemical properties of processable materials and to worsen their hygienic properties.

Synthetic detergents and cleaners are considered unsuitable on following one or several parameters:

- If substance has skin irritating and other biological effect during the work with it;

- If there are complaints from population at natural monitoring;

- If compositions have toxic effect in doses and concentrations of working solutions

- If during monitoring of volunteers, the composition causes change of parameters of a functional state of coverlets.

THE PECULIARITIES OF CHILDREN'S MORBIDITY DURING FIRST YEAR OF LIFE IN DEPENDENCE ON SEX IN INDUSTRIAL REGION

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Human health is formed in early childhood and is determined by age peculiarities of organism and by effect of the environmental factors. Environmental pollution leads not

only to appearance of pathological states in child's organism, but to appearance of adaptive processes, which is formed during period of embryogenesis too. The morbidity during first year of life, it's investigation in connection with data biological anamnesis and with environmental pollutions indexes were studied, since the main trait of adaptation is resistance of organism to damage environmental factors.

Different sensitivity of new-born's anthropometric indexes to change of pollutant concentrations in dependence on sex was established, using methods of mathematical simulation and sensitive coefficient, which was 2,43 for boys and 1,86 for girls.

The morbidity of respiratory organs is the most widespread pathology among children in industrial region (about 50 %). The exceed of morbidity level at boys in comparison with girls was established according to such nosologies as: acute respiratory infections of up-respiratory tract – 24,1 %, influenza and pneumonia – 9,2 %, bronchitis – 53,1 %, rhinitis – 16,5 % during sex analysis. There were not significant differences between sexes during analysis of the morbidity duration. These data confirmed, that there was the most strong sensitivity in boys in comparison with girls. So, the index of acute morbidity in boys was higher then comparison indexes in 1,3 times and in girls – in 1,8 times.

As to morbidity level according to an other disease classes, it was find the higher indexes in boys then in girls too. The diseases of blood were the most widespread in 1,8 times, nervous system – 2,2 times, osseous and muscular system – 2,7 times, organs of digestion – 1,3 times, congenital defects of development – 1,2 times.

The most important is determination of the following state of organism, the degree of it's reserves reaction, adaptive opportunities.

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DERMAL EXPOSURE TO JET FUEL JP-8 SIGNIFICANTLY CONTRIBUTES TO THE PRODUCTION OF URINARY NAPHTHOLS IN FUEL-CELL MAINTENANCE WORKERS

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Jet propulsion fuel 8 (JP-8) is the major jet fuel used world-wide and has been recognized as a major source of chemical exposure for the U.S. Air Force fuel-cell maintenance workers. Despite the increasing number of studies conducted on JP-8, knowledge of JP-8 exposure, uptake, metabolism, and its potential human health effects is limited. In this study, we investigated the contributions of dermal and inhalation exposure to JP-8 to the total body dose of the U.S. Air Force fuel-cell maintenance workers using naphthalene as a surrogate for JP-8 exposure. Dermal, inhalation, and exhaled breath measurements of naphthalene were obtained using tape-strip sampling, passive monitoring, and glass bulbs, respectively. Levels of urinary 1- and 2-naphthols were determined in urine samples and used as biomarkers of JP-8 exposure. Multiple linear regression analyses were conducted to investigate the relative contributions of dermal and inhalation exposure to JP-8. Our results show that both dermal and inhalation exposure significantly contributed to urinary 1- and 2-naphthol levels in all workers. The contribution of dermal exposure was also significantly associated with levels of urinary 2-naphthol (> 32%), but not to urinary 1-naphthol, among the fuel-cell maintenance workers who wore supplied-air respirators. We conclude that dermal exposure to JP-8 significantly contributes to the systemic dose and affects the levels of urinary naphthalene metabolites. Future work on dermal xenobiotic metabolism and toxicokinetic studies are warranted in order to gain additional knowledge on naphthalene metabolism in the skin and the contribution to systemic exposure.

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THE SAFETY OF FOOD-STUFFS. TOXIC COEFFICIENTS OF

ORGANOPHOSPHORUS AND CARBAMATES PESTICIDES

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The lack of traditional methods of the hygienical setting of norms of pesticides in food products consists that every new norm is established without taking into account possible presence in the food product of other pesticides. At the same time it is fully reasonable to assume in many cases, that influence on the organism of man of many residues of pesticides will carry additive character, for example, in the case of organophosphorus pesticides or pesticides – derivative carbamic acid which possess the same mechanism of toxic action (inhibition of cholinesterase).

For perfection of setting of norms of pesticides possessing the identical mechanism of action (development of the Maximum Residue Limits (MRLs) and Acceptable Daily Intake (ADI), it is suggested by analogy with polychlorinated dibenzodioxins to express toxic of organophosphorus and carbamates pesticides by the coefficients of toxic. For example, the toxic of organophosphorus pesticides can be expressed in relation to a parathion-methyl (metaphos) – most from the toxic organophosphorus pesticides applied in agriculture, the coefficient of toxic of which sets to 1 (one). The toxic of carbamates pesticides can be expressed in relation to carbofuran, the toxic of which also sets to 1 (one). For the calculation of coefficients of toxic the values LD_{50} for rats are used. The MRL and ADI values in these case must be expressed in a «metaphos» or «carbofuran» equivalent. It is necessary to produce the calculation of the organophosphorus or carbamates pesticides concentration in the analysed matrices, which in these case is named equivalent toxic concentration, by the multiplication of values of concentrations of separate pesticides on the values of coefficients of toxic proper to them. In the lecture is brought the expected coefficients over of toxic for some organophosphorus and carbamates pesticides.

OPTIMIZING THE MANAGEMENT OF PHYTOREMEDIATION FOR THE HYDRAULIC CONTROL OF A GROUNDWATER PLUME

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Worldwide reliance on groundwater and global municipal waste production intersect as a significant public health threat. Landfill leachate plumes often contain hazardous chemicals that are harmful to human, animal, and environmental health. Recent advances in phytoremediation suggest that deep-rooted vegetation may be more effective at remediating these sites than the traditional pump-and-treat method. Because phyto-remediation is a relatively new technology, optimized management practices have not yet been developed. It is hypothesized that hydraulic control of a leachate plume can be obtained using poplar trees (*Populus L.*) and increased management can improve root development and reduce the time to gain hydraulic control.

Recent studies at Kansas State University indicated that bare root eastern cottonwood (*Populus deltoides* Bartr. ex Marsh.) plantings treated with animal lagoon effluent produced significantly more biomass and used up to three times the amount of water during their first two years of growth compared with seedlings receiving only tap water. Plantings treated with the lagoon effluent also developed more extensive root systems as implied by soil water fluctuations deeper in the soil profile.

In the spring of 2005, seven rows of eastern cottonwood trees (*Populus deltoides* Bartr. ex Marsh.) were planted down gradient from a buried chemical waste landfill to impede plume migration and to enhance the uptake of the contaminant, 1,4 dioxane. The first step in assessing the potential impact of the tree plantation on plume migration was to conduct a complete water balance on the site, accounting for all inflow and outflow of water. By assessing the groundwater, precipitation, evapotranspiration, surface runoff, and vadose zone soil moisture in the system, it was possible to estimate the required evapotranspiration for plume control.

In addition to the water balance calculation to determine the effectiveness of hydraulic control, the effects of increased plant management will be studied. It is hypothesized that trees irrigated with nutrient-rich lagoon water will grow faster, requiring more water and enhancing potential for gaining hydraulic control at the site. Irrigation regimes with and without lagoon water from the Kansas State University Animal Science Farm will be studied at the chemical waste landfill site beginning spring 2006. The use of lagoon water not only serves as a nutrient source to enhance the growth of the trees and to reduce the time to gain hydraulic control, but also provides a beneficial use for animal waste.

15

ADVERSE REACTION OF DIETARY SUPPLEMENTS

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During the International nutrition conference in Rome at 1992, the deficit of nutrients was accepted as a most important problem that could bring population of Earth to the global crisis in XXI century. A monitoring of nutrition structure of modern human indicates the chronic deficit of irreplaceable food components (micronutrients). To achieve optimal provision of all group of population by energy and food substances using only expansion of foodstuffs is impossible. One efficient solution of population nutrition correction problem is using dietary supplements. Using of dietary supplements should be safe, that's why all they need to go through sanitary-epidemiological examination. But conclusion about safeness of dietary supplement could not guarantee absence of its adverse reaction. Last time, there are speculations about incidents of adverse reaction of dietary supplements. Particularly, this concerned to dietary supplements that used for body weight correction and include guarana, their content of caffeine is higher than in coffee in three times. Using these products brought healthy humans to arrhythmia and hypertensive strokes. Serious violations in human organism could be made by dietary

supplements with chitin. Decreasing absorption of fat, they decrease assimilation of liposoluble vitamins (A, E, D, K). Additional risk concerned with presence of tissues and animals organs in dietary supplements, that could be pathogens. Long time use of tea, that includes plants with diarrhea affect, could bring to decreasing of potassium level in blood and risk of arrhythmia. One reason of serious adverse reaction of some dietary supplements is high contents of vitamins. As practice showed, exceeding of vitamin A daily dose could bring to heavy liver complication. Usage it during pregnancy could bring to foetus defects. Usage vitamin D during several months in big doses could bring to potassium level increase and kidney injury. Even, presence in dietary supplement content only good explored components, doesn't leave out risk for health, in the case when dietary supplements using without a control, long time, and, what is especially dangerous, without considering contra-indications. As a result, during usage of dietary supplements, it is necessary to consider:

- possibility of adverse reactions;
- non-predictable interaction between dietary supplements components and drugs or other dietary supplements;
- risk of overdose;
- production of dietary supplements using exotic plants, which influence on human organism is unexplored;
- possibility of influence of dietary supplements components to embryo and foetus;
- fuzzy recommendations for dietary supplements usage;
- using of high-quality dietary supplements require medical monitoring and control.

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GENETICALLY MODIFIED MICROORGANISMS. THE METHODS OF DETECTION

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Genetically Modified Microorganism (GMM) is defined as a micro-organism in which the genetic material has been altered in a way that does not occur naturally by mating or natural recombination, or by a combination

of both. GMMs are promising for many environmental, agricultural and food application, and it is important to ensure the monitoring of them.

To determine the sufficient contents of the GMM examination the food should be classified to one of the three groups by the availability and condition of technological microorganisms in it:

- 1). Food and raw materials which consist of/ or contains viable microorganisms.
- 2). Food and raw materials which consist of/ or contains non-viable microorganisms.
- 3). Food and raw materials which were made by GMMs, but were purified from them during the technological process.

Depending where this food products or raw materials contain viable, non-viable microorganisms, or don't contain microorganisms at all, the structure of the analysis is changing. The essential part of molecular and genetic examination is provided using the method of PCR for the detection of specific markers - integral components of transformed genome (for example genes of antibiotic resistance). The analysis of the additional indexes of quality and safety of food products is provided in the terms of necessity.

The methods and stages of the GMM expertise are described into the review.

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STUDY ON OXIMES IN REVERSAL OF NEUROMUSKULAR BLOCK PRODUCED BY ORGANOPHOSPHORUS COMPOUNDS

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The toxic effect of organophosphorus compounds (OPC) is based on inhibition of acetylcholinesterase (AChE), enzyme which plays an important physiological role in the cholinergic nervous system. The drug therapy on intoxication with OPC included mainly combination of cholinesterase reactivators and cholinolitics. There is no single AChE reactivator having the ability to sufficiently reactivate inhibited enzyme due to the high variability of chemical structure of the inhibitors. Exposure to AChE inhibitors such as OPC impairs cholinergic neuromuscular transmission (NMT). The recovery of NMT is an important mechanism

of antidote action of the oximes. The present experiments were done to compare the effects of 2-PAM, TMB-4, Toxogonin, Toxidin (Bulgarian HI-6 ampoule), H-, BDB- and HGG - oxime reactivators of ChE in restoring in vivo nerve-induced muscle contraction blocked by intoxication with soman. A series of these oximes was synthesized in the Laboratory for Experimental Toxicology of Military Medical Academy, Sofia. The aim of present study was to evaluate the potency of those oximes to restore the neuromuscular transmission after block produced with soman and to follow the structure activity relationships (SAR). Toxidin – HI-6, were superior than other oximes. Among the HGG- and BDB- oximes tested here the optimal recovery was achieved with compounds with oxime group in position 4. The difference to the H- oximes can be explained with the size of the phenylcarbonyl- or cyclohexylcarbonyl-group compared with - CHNOH or - CONH2 groups. A different binding site in the cholinoreceptor may be proposed. On the base of the result obtained we tried to follow structure activity relationships for best restoration of NMT blocked with soman. Investigation of the recovery of NMT is one of the most important moments in studying of the antidote activity of reactivators of ChE like antidote of OPC intoxication.

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POSSIBILITY OF A DIETARY SUPPLEMENTS SIDE EFFECT CONCERNED WITH ENDOGENOUS SYNTHESIS OF FORMALDEHYDE

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Creatine, dimethylglycine (DMG), glycerol, caffeine, aspartam and pectins are used extensively as dietary supplements. These ones have same feature – they are substratum for the enzymatic synthesis of formaldehyde (FA) in an organism. They inserting into one or another catabolism path can essentially increase the FA production. Thus, creatine and DMG are the source of methylamine, which is transformed into FA, hydrogen peroxide and ammonia by semicarbazide-sensitive amine

oxidase (SSAO). FA is synthesized from glycerol and caffeine by P-450 cytochrome. Dehydration of methanol, which is an intermediary of aspartam and pectins catabolism, results in the FA formation too. FA evinces genotoxic, mutagenic, immunogenic and oncogenic activities. Therefore, the FA impact should be taken into account in the evaluation of the supplements side effect. FA synthesis from these supplements can be accomplished by a gastrointestinal flora and/or by way of cellular metabolism of those supplements, which can be passed through gastrointestinal tract without changes. Under the utilized supplement dose the second path of FA synthesis probably can't lead to the accumulation of the toxic quantity of free FA in cells and tissues of the organism because there is a very active system of one-carbon metabolism, which is enough for binding of free FA. The first path – the microbial metabolism, especially under dysbacteriosis and derangements of the gastrointestinal function, can result in the high local level of FA in the gastric tract, that lead to apoptosis and neoplastic transformation of slime layer cells. It is not inconceivable that in the result of microbial metabolism, intermediary-predecessors of FA (for example, methanol) are formed from these supplements in the gastrointestinal tract, whereupon they are soaked into the organism and toxically affect on cell's level through FA formation. Creatine used extensively as a part of a lot of dietary supplements for sportsmen may be dangerous because it is utilized in a high dose and faintly soaked from the gastrointestinal tract. Our clinical research has revealed that about 15 percents of patients (total 54) with gastrointestinal tract deceases had positive FA test in the gastric air after creatine was consumed. This result proves the possibility of the side effect of these dietary supplements.

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GENOTOXICITY OF COMPLEX PAH MIXTURES IN ANIMALS AND HUMANS

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Complex mixtures of polycyclic aromatic hydrocarbons (PAHs) are ubiquitous in the environment. PAHs are by-products of combustion. Cigarette smoke and cooked foods are perhaps two of the most common sources of exposure to PAH mixtures. However, PAHs are also common environmental contaminants at facilities contaminated with waste from petroleum production, manufactured gas plant residue and wood preserving industries. The observation by Sir Percival Pott in 1776 that chimney sweeps experienced an increased frequency of scrotal cancer was one of the first studies to recognize the carcinogenic potential of complex PAH mixtures. Extensive research since that time has confirmed that benzo(a)pyrene and several other PAHs are carcinogenic in animals. However, minimal information exists to define potential interactions of carcinogenic and non-carcinogenic PAHs, as well as appropriate biomarkers of exposure to these compounds. Research supported by the US Environmental Protection Agency and the National Institute of Health has been conducted to investigate potential interactions of PAH mixtures in animals. Data from the analysis of model PAH compounds and mixtures in animal studies suggest that unknown components of the mixture may contribute to genotoxicity. The genotoxicity of reconstituted mixtures may be more than 30% lower than the response observed for an equivalent complex mixture. Exposure studies in Azerbaijan and China have suggested a relationship between serum levels of PAHs and DNA adducts in white blood cells. The goal of these studies is to develop improved methods to identify exposed populations. In addition, knowledge of genetic factors affecting sensitivity and potential compound interactions could lead to improved methods for preventing diseases associated with exposure to PAH mixtures

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DIOXINS INTOXICATION IN HUMANS: THEORETICAL BASES OF THE TREATMENT

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The global danger of environmental pollution with dioxins and related compounds (PCS, PCDDs, PCDFs, PCBs) for health, medical and social well-being is gradually realized all over the world. The special urgency for Russia of fundamental and applied researches in this field is defined by unpleasant situation with dioxins in many regions of the country, and high probability of these superecotoxicants contribution in observable critical failure of the population health and lifetime.

The analysis of accumulated international experience on medical and social treatment of the people who have suffered the dioxins' influence proves that effective way of these problems decision still does not exist. One of the main causes of such dramatic situation in this field of medicine is the absence in a modern science of uniform idea about a pathogenesis of poisoning.

The development of the general theory of pathogenesis of human intoxication with dioxins, so-called "the theory of biological intensification of primary dioxins activity or hyperplastic theory", was the result of theoretical generalization of the outcomes of the study on the long-term medical consequences of chemical war in Vietnam, and also of other scientific publications.

Original principles of the theory are discussed in this report.

The approbation of the developed theory has shown its ability to solve adequately the scientific and practical problems of public health services. In particular, the theory of the pathogenesis has allowed developing:

- classification of the long-term medical consequences of dioxin influence;
- methodology for categorizing and distinguishing the dioxin-exposed population by a level of health loss;
- requirements for complexes of treatment-and-prophylactic and rehabilitation measures for the population with the long-term medical consequences;
- organizational principles for system of medical and social examination and care of the population exposed to dioxins.

MEDICAL CONSEQUENCES OF THE ENVIRONMENT CONTAMINATION WITH DIOXIN-CONTAINING HERBICIDES

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Investigations of the last decades revealed harmful influence of chemical environment pollution on different biological systems, including humans. The most alarming chemicals include new ecotoxicologically specific class of the "persistent organic pollutants" and, in particular, the most toxic "dioxins", which belong to the superecotoxicants.

In the last years, protection of the environment and human health from superecotoxicants became a matter of many national and international initiatives. This task is considered as an integral part of public health development ensuring the national safety, high life quality and sustainable development. However, the results of different investigations on the real health hazards of superecotoxicants still remain inconsistent and contradictory.

The large-scale spraying of dioxin-containing herbicides (Agent Orange etc.) by the USA army during the Second Indochina War (1961-1975) has generated unique conditions for studying the dioxins influence on humans in Vietnam. The comparative analysis of the health assessment of the exposed and not exposed with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) Vietnamese veterans has revealed the long-term health consequences of exposure.

The data of clinical examination of the 322 Vietnamese veterans testify to existence of pathology, which is characterized by various and persistent lesions all the organs and systems (cardiovascular, respiratory, alimentary, nervous, excretory, muscoskeletal, reproductive etc. systems), by authentic differences of anthropometrical parameters and also by reduction of lifetime.

The results of epidemiological, clinic and laboratory examination of the Vietnamese veterans convincingly testify to existence of pathology of a new kind, which is characterized: 1) by reduction of lifetime; 2) by a phenomenon of "premature ageing"; 3) by an extremely wide spectrum of the pathologies, involving practically all the

organs and systems of human organism; 4) by persistent various lesions - organical, functional and metabolic; 5) by of modulating influence on a disease of an "exposure scenario" (temporary, quantitative, qualitative features of concrete variant of an exposure, combined action with chemical and other factors of environment); 6) by modifying influence on occurrence pathology of individual features of human organism by mechanism of "locus minores resistentia". The results of the executed researches have allowed to determine the new kind of the pathology as a "dioxin disease".

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CYCLIC N-TERMINAL HEMOGLOBIN ADDUCT IN HUMANS, RATS AND MICE EXPOSED TO BUTADIENE

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1,3-Butadiene (BD) is an industrial chemical that is carcinogenic in rodents and probably humans. BD is oxidized by P450 to 1,2:3,4-diepoxybutane (DEB), the most mutagenic BD metabolite. DEB reacts with N-terminal valine in hemoglobin, forming the cyclic adduct (2,3-dihydropyrrolidin-1-yl)-3-methylbutanoic acid (pyr-Val), a potential biomarker that is specific for DEB. Sensitive isotope dilution mass spectrometric assays were developed to measure pyr-Val in globin from mice, rats and humans, exposed to BD or DEB. The procedure uses trypsin hydrolysis of globin, immunoaffinity (IA) purification of peptides (with antibodies specifically raised against the adducted human peptide), and quantitation of the N-terminal heptapeptides by capillary LC-ESI-MS/MS. The necessary internal standards (IST, D₃ labeled) for each species were synthesized and characterized by ESI-MS/MS sequencing. Quantitation was performed by LC-ESI-MS/MS in SRM mode, using both singly and doubly charged ions. This method readily detects 25 fmol of human analytical standard on column. The overall recovery was 50-90% for in vivo samples. Preliminary results show that the pyr-Val adduct was below the detection limit in 10 BD workers with exposures ranging from 0.1 to 4.2 mg/m³ when 200 mg of

globin was processed. In samples from rats exposed to 2.5 and 5 ppm DEB (4 weeks), the adduct was measured at 1.6 and 2.5 pmol/mg globin, respectively (using the human IST). In rats exposed to 1000 ppm BD (90 days) the amounts of pyr-Val adducts were 3-4 times lower than in the DEB exposed rats. In mice exposed to 62.5 ppm BD (4 weeks) and 1250 ppm BD (10 days) the amounts were 0.1 and 2.5 pmol/mg globin, respectively. These results provide preliminary data on the use of pyr-Val as a specific and selective biomarker for internal exposure to DEB. This novel biomarker represents a useful tool to study differences in the metabolism and carcinogenicity of BD in mice, rats and humans, as well as potential gender differences and possible effects of genetic polymorphisms.

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METHODICAL APPROACHES TO ECOTOXIC COMPOUNDS IDENTIFICATION

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Identification of toxic compounds in the environmental objects, industrial products with unknown composition, is one of the most complex and responsible problems of sanitary-chemical researches. On the basis of the identification results becomes possible to determinate of health hazard of these objects, to formation of environmental priority pollutants lists for regions. This information becomes especially important for extreme situations estimation

Methods and approaches used for identification have the specific, depending from the nature of investigated objects, their aggregate states, and supposed toxic substances contents. This specific shows up both in the use of instruments for compounds identification and in preparation of samples for the analysis. For solid samples industrial products with high percentage of the identified compounds, for example, unknown pesticides, pharmaceutical preparations, etc., the methods of qualitative chemical analysis, quantitative determinations of element composition, and spectral methods, such as atomic-emission spectroscopy, IR and NMR

spectroscopy are used. For water solutions analysis become preferable methods of liquid chromatography (TLC and columns), and HPLC in combination with diode-matrix and MS detectors. The volatile components of water solutions can be identified by gas chromatography. The method of gas chromatography is irreplaceable for toxic substances identification in the air. In this case success can be attained at the use IR-, MS- and atomic-emission detectors.

Preparation of water samples, as a rule, consists of extraction of different fractions of toxic substances by organic solvents or solid sorbent. Solid phase extraction in combination with subsequent thermodesorption of the analysed components can most widely be used for the analysis of air. The headspace analysis has the limitations related to volatility of organic compounds, and with the value of coefficient of distributing water / octane too. The analysis of samples with unknown composition after identification of toxic compounds must be accompanied by measuring of their contents, by quantitative methods, specific for these compounds. As a result must be obtained complete information about qualitative and quantitative contents of toxic substances in the investigated objects. In some cases it is expedient on the stage of identification apply quantitative methods for the some classes of toxic compounds with the purpose of determination their presence and quantitative contents in objects with unknown composition.

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**INFLUENCE OF CHEMICAL
SUBSTANCES ON HEALTH OF THE
POPULATION: APPROACHES TO AN
ESTABLISHMENT RELATIONSHIPS OF
CAUSE AND EFFECT**

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The variety of the factors influencing health the population, insufficiency of their estimation, wide spectrum of the biological answer of a population on action of adverse factors make estimations about their influence on health of the population frequently uncertain and poorly demonstrable. One of way out of this

situation is creation of system of criteria of a complex estimation of received results. For many years we use the modified criteria Hill's offered in 1975. The given approach can be used as for an estimation of influence on health of the population, and for an estimation of dependence of diseases from chemical production factors at concrete individuals.

At the proof of connection of infringements with influence of chemicals following criteria are used:

1. Experimental acknowledgement of the revealed effects.
2. Presence of similar changes in other groups of the population or workers (precedent).
3. Force of connection (excess of parameters of disease in the basic groups in 10 and more times, a degree of reliability of distinctions with the control not less than 0,01).
4. Presence of a gradient "doze-effect", "time-effect", "distance-effect" (the effect pays off both on average sizes, and on number of persons with presence of effect).
5. Increase in frequency of responses in groups of the increased risk.
6. Reduction of effects at elimination of the adverse factor.
7. Presence of substance or products of its metabolism in biotissues (specific oppression of enzymes, occurrence of infringements of an exchange and immune answers).
8. Uniformity of displays of responses at different individuals.
9. Simultaneous involving several systems or bodies
10. Specific symptoms.

At presence of 7 and more criteria connection of the revealed responses and influence of chemicals can be taken for granted, 5-6 criteria testify to possible connection with influence, and 4 and less speak about its absence.

Use of the specified criteria allows not only reduce uncertainty at an estimation of the received results of ecological researches, but also purposefully to plan scientific development.

The modern scientific tool for the decision of questions of connection of the revealed changes at the population with environmental chemical contamination are geoinformation systems, for example ArcInfo allowing to make a binding of the

received results to concrete territory and to carry out search of connections in multivariate space.

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EFFECT OF DIOXIN AND DIOXIN-LIKE COMPOUND ON REPRODUCTIVE SYSTEM

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Now structure diseases of female reproductive systems were changing. More attention of toxic substance such like as dioxins and dioxin-like compounds as a pathogenic factor disorders of reproductive system scientists were published.

The Mechanisms of disrupt action of dioxins and dioxin-like compounds are unknown. Investigators have discussing of initial role Ah receptor for pathological process. Hereinafter system of cytochrome P450 are involved in process. The mechanisms of damaging hypothalamic-pituitary-gonadal system, the system of reception and regulation of hormonal secretions, the processes of the metabolism and distribution hormone on the organs and tissues were described. Different effects influents of dioxins for animal's and human's organism were detected in experimental and clinical trials. Toxic effects for reproductive system has depend of study of development of system, doses depended, term of influence toxicity, conditions of organism and present of somatic disorders. Experimental animal teratogenic effects (disruptions of development reproductive organs, cleft palate, hydronephrosis, atrophy of thymus), disorders of spermatogenesis, loss weight of genitals, breaking of sexual differentiation of brain and metabolism steroid hormones were observed. It is significant this changing has interspecific, intraspecific and individual has differences.

Dioxin depended effects for human is discussing and studied as not enough. However relations between exposition of dioxin contaminants and endometriosis, breast cancer and leiomyoma of uteri was founded. There is foundation to suppose that effect of influence dioxin before and

during period formation reproductive system promotion alteration of menstrual cycle. Have depended same effects of dioxin for infertility (quality of sperm, inflammatory processes genital sphere, non-carriage of pregnancy etc.). Discussing role exposure of dioxins in pathogenesis other disorders of reproductive system. Consequently, dioxin and dioxin-like compounds is disruptor of function difference organs and systems involved regulation of reproductive system.

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THE SAFETY ASSESSMENT OF FOOD DERIVED FROM BIOTECH CROPS

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Global regulatory authorities require that food derived from crops produced through biotechnology be *as safe as* food produced from conventionally bred crops. There must be "reasonable certainty that no harm will result from intended uses under the anticipated conditions of consumption" (OECD). A variety of European/Global Scientific authorities (WHO, FAO, OECD, EFSA) have provided guidance on the safety assessment process for food and feed derived from biotechnology-derived crops. The safety assessment process considers two main categories of potential risks: those related to the properties and function of the introduced protein(s), and those resulting from insertion of the introduced gene(s) into the plant genome that could cause unintended effects. The safety assessment for a biotechnology-derived crop is a comparative process that uses conventional food with a history of safe consumption as the reference point for all comparisons. The outcome of this assessment is to determine whether the genetically modified crop is comparable to the existing conventionally bred crop. One category of the safety assessment process involves evaluating the safety of the introduced protein(s) that impart the desired trait to the crop. This evaluation includes testing for digestibility of the protein since readily digested proteins pose little risk for allergenicity. Bioinformatic comparison of the amino acid sequence of the introduced protein to known proteins in searchable data bases is done to confirm the absence

of similarity to known protein allergens and toxins. The United States Environmental Protection Agency requires insecticidal proteins with an established mode of action (e.g., *Bacillus thuringiensis* derived Cry proteins) to be subjected to high dose acute oral testing in rodents to confirm their safety to mammals. Other non-target safety studies are also completed (fish, birds, insects etc.) to confirm absence of toxicity to non-target organisms. Cry proteins have been extensively tested for safety over the years and exhibit selective activity against target insect pests and an absence of toxicity to non-target organisms.

The other category of the safety assessment process involves testing for potential unintended effects in the food/feed portion of the crop. This includes evaluating agronomic, compositional and feeding value of the biotechnology-derived crop using conventional crops as comparators. The feed portions of the crops are usually fed to a variety of farm animals under normal farming practices and the performance of the animals is carefully monitored. Some food crops have also been fed to rats in 90 day feeding studies to provide confirmatory evidence of food safety. An example of the practical application of the food/feed safety assessment process will be presented using YieldGard Cornborer® as a case study. This product provides protection against corn borer feeding on corn plants throughout the entire growing season. It also provides secondary benefits by reducing the use of chemical insecticides to control corn borers. In addition, mycotoxin contamination of corn grain often also is reduced. Protection of the ear against corn borer damage results in fewer ports of entry for mycotoxigenic fungi to infect the ear and produce fumonisin mycotoxins. A brief summary of the data supporting these benefits will be discussed as well as future products that may reduce mycotoxin contamination of grain even further.

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Children, due to their size, behavioral characteristics and other factors represent a sensitive subset of the population. Children may be exposed to pesticides from a variety of sources including drift from agricultural fields, ingestion of pesticides in food, and household usage. This project is a multi-year, multi-agency, multi-investigator study to determine if health education can reduce a child's exposure to pesticides. The study is designed to occur in four phases. In phase 1, a group of approximately 200 Promotora's (community lay health workers) will be administered training in home safety. The home safety module includes information on home safety, but focuses on sources of pesticide exposure. The second phase of the study will measure pesticide exposure (via urinary elimination of pesticide metabolites) in 80 children 2 to 6 years of age in four different South Texas colonia's. In the third phase of the study, the mother of each of the 80 children will be administered the home safety health education. The last phase of the study will consist of a second round of exposure measurements in the same group of 80 children. The utility of the interventions will be measured using knowledge and technical assessments. Knowledge assessments, a pre- and post-test, will be used to measure improvements in knowledge in Promotora's and mothers that received the health education. The technical assessment will include measurements of childhood exposure to pesticides and a visual assessment of pesticide use and storage within homes in the colonia's. The first and second phase of the study will begin in March and April, 2006. It is anticipated that the third phase will be conducted in June and the last phase of the study in July, 2006. Various portions of the study are supported by the USEPA Border 2012 program, the Health Resources and Service Administration, and the National Institute of Environmental Health Sciences.

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**HEALTH EDUCATION AS AN
INTERVENTION TO REDUCE
CHILDHOOD EXPOSURE TO
PESTICIDES IN RURAL TEXAS
COLONIAS**

Hart, Cynthia, Leslie Cizmas, N. Foreman,
G. Castillo, L. Gamm, J. Burdine,

TOXICOGENETIC ANALYSIS OF SUSCEPTIBILITY TO ACETAMINOPHEN HEPATOTOXICITY

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Background: The mouse is an invaluable model for study of linkages between the genome and phenome, facilitating a knowledge base for genetic diversity, gene-environment interactions and toxicological endpoints. Inbred mouse strains comprise diverse genetic lineages that may be conducive to modeling human outbred populations. By utilizing several strains in our research, we aim to develop biomarkers that are predictive of susceptibility to toxic injury. Acetaminophen (APAP) was selected as a model hepatotoxicant because much information exists regarding the mechanisms of toxicity and conventional clinical markers largely fail to connect toxicity and clinical outcome. **Methods:** A panel of 37 inbred strains from the Mouse Phenome Project was selected for this study. Male mice were fasted for 18 hrs, administered an acute dose of APAP (300 mg/kg) or vehicle (0.5% methylcellulose), and sacrificed at 4 or 24 hr post-dosing. **Results:** A dramatic gradient of APAP-induced toxicity was detected across strains. Serum enzyme markers indicated that some strains have a more rapid response to APAP treatment, with higher values at 4 hrs than at 24 hrs. Additional doses (30, 100, 200, 600, 900, and 1200 mg/kg) were tested in non-responder and high-responder strains. The dose-response profiles vary by genetic background, indicating that susceptibility to injury is not simply a function of dose, but is due to complex genetic or gene-environment

interactions. We report candidate loci that may contribute to progression of liver injury following APAP exposure as identified by haplotype-associated genetic mapping. **Conclusions:** The data indicate that strain-specific liver injury research may be useful for risk assessment and predicting individual susceptibility to toxicant exposure. Grants supported by NIEHS: ES11391, ES11660, ES10126, T32-ES07126, N01-ES-35513, N01-ES-25497, N01-ES-65406.

NUTRITIONAL MODULATION OF ENVIRONMENTAL TOXICITY

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Nutrition and lifestyle are well-defined modulators of chronic diseases, and evidence is accumulating that dietary components can modulate toxic insults mediated by environmental pollutants. Poor dietary habits, such as high intake of processed foods rich in fat and low in fruits and vegetables, as well as a sedentary lifestyle are clearly contributing to today's compromised quality of life in many parts of the world. The diet is a major route of exposure to environmental toxins, such as persistent organic pollutants and heavy metals. Since many of these pollutants are fat soluble, fatty foods usually contain higher levels of persistent organics than vegetable matter. Once absorbed, environmental toxins distribute themselves to tissues, especially adipose, where they are in dynamic equilibrium with the blood. Many pollutants, such as persistent organics, bioaccumulate in our bodies, and "bioremediation" is extremely difficult. Furthermore, many environmental toxins induce signaling pathways that are oxidative stress-sensitive and similar or the same as the ones associated with the etiology and early pathology of many chronic diseases. Studies derived from epidemiological and basic research and clinical data are evolving which suggest that diet or nutrition, as well as life-style changes, can modify pathologies of chronic diseases as well as diseases associated with environmental

toxic insults. Furthermore, nutrition can dictate the cellular lipid milieu, oxidative stress and antioxidant status, and thus modulate mechanisms of cytotoxicity mediated by environmental pollutants. For example, certain dietary fats may increase the risk to environmental insult induced by polychlorinated biphenyls (PCBs) and fruits and vegetables, rich in antioxidant and anti-inflammatory nutrients or bioactive compounds, may provide protection.

There is now increasing evidence that exposure to persistent organic pollutants, such as PCBs, can contribute to the development of inflammatory diseases such as atherosclerosis. Activation, chronic inflammation and dysfunction of the vascular endothelium are critical events in the initiation and acceleration of atherosclerotic lesion formation. Our studies indicate that an increase in cellular oxidative stress and an imbalance in antioxidant status are critical events in PCB-mediated induction of inflammatory genes and endothelial cell dysfunction.

There is a great need to further explore this nutritional paradigm in environmental toxicology and to improve our understanding of the relationship between nutrition and lifestyle, exposure to environmental toxins and disease. Because early nutrition can dictate risk of diseases in the adult population, there is a need to include nutrition and dietary habits as a variable in studies that involve environmental toxins and disease development. Nutrition may provide the most sensible means to develop primary intervention and prevention strategies of diseases associated with many environmental toxic insults. (Supported by grants from NIEHS, NIH (P42ES07380) and the University of Kentucky AES).

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Concerns about the quality and safety of our environment have evoked an awareness of the hazards associated with diverse pollutants in groundwater and foods destined for human consumption. Many of these environmental contaminants can have severe and long lasting effects on human health. Research in our laboratory focuses on the development and application of clay-based technologies for detoxifying and detecting various environmental contaminants in food and groundwater. In previous animal studies, NovaSil (NS), a calcium montmorillonite clay, has been shown to prevent the adverse effects of aflatoxins in a variety of animals when included in the diet. NS provides significant protection from the adverse effects of aflatoxins by decreasing the bioavailability of these contaminants in the gastrointestinal tract. Intervention studies with NS clay are currently ongoing in human populations that are at high risk for aflatoxicosis. In related in-vitro studies, nanostructuring techniques have been utilized to construct various formulations of clay-based composite media for the selective cleanup and analysis of target chemicals from contaminated matrices. The formation of these hybrid sorbents is based on electrostatic attraction between oppositely charged components and allows for the systematic control over film composition, structure and thickness. Experiments have shown that clay-based media developed in the laboratory may provide an alternative and cost-effective method for the cleanup and concentration of aflatoxins from contaminated grains. Similar research focusing on groundwater contaminants showed that clay-composite sorbents can be immobilized onto the surface of a solid support to enhance water permeability and flow rates. These multifunctional composites are prepared from cetylpyridinium-exchanged clay in combination with other diverse sorbent materials and are effective in the removal of a variety of toxic contaminants from groundwater. Laboratory data and field studies indicate that these composite sorbents can be used to reduce pentachlorophenol and PAH loads in oil-water separator effluent streams by at least 95% as determined by GC mass

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**DEVELOPMENT OF CLAY-BASED
SORBENT TECHNOLOGIES FOR THE
CONTROL AND REMEDIATION OF
ENVIRONMENTAL CONTAMINANTS IN
FOOD AND GROUNDWATER**

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spectrometry. Overall, the results of these and other studies indicate that both naturally-occurring and chemically-modified clay minerals can be an integral component of practical strategies leading to decreased exposure to environmental toxins and prevention of toxin-induced disease.

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INFLUENCE OF AMOSITE AND GLASS FIBRES ON THE SELECTED INFLAMMATORY AND CYTOTOXIC PARAMETERS OF BRONCHOALVEOLAR LAVAGE IN EXPERIMENT

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The problem of the effects of industrial fibrous dusts remains topical and represents a potential health hazard for humans. Therefore it is necessary to substitute asbestos by fibers with less negative biological effects. We examined the effects of 2 types of industrial fibers: amosite and asbestos substitute - glass fibers on the inflammatory and cytotoxic parameters of bronchoalveolar lavage. The Fischer 344 rats were instilled with two doses (2 and 8 mg/animal) of fibrous dusts; the animals were intratracheally instilled with fibrous suspension in saline solution or only with 0,2 ml saline solution per animal (control group). They were sacrificed 4 or 16 weeks after last instillation. BALF cells were harvested by modified method of bronchoalveolar lavage according to Myrvik. Following parameters of bronchoalveolar lavage fluid (BALF) were investigated: a) Inflammatory response biomarkers: the number of BALF cells/ml, the number of alveolar macrophages (AM)/ml, the differential number of cells (% AM; granulocytes - Gr; lymphocytes -Ly), phagocytic activity of AM, multinuclear lung cells, the level of cytokines (TNF-alpha, IL-1 alpha), b) Cytotoxic parameters: phagocytic activity of AM, viability of AM, the lactate dehydrogenase activity, the acid phosphatase activity, the cathepsin D activity.

The aim of our study was to compare the changes of inflammatory and cytotoxic parameters of bronchoalveolar lavage after

exposure to amosite and glass fibers with the control group and so provide data of the impact of mentioned mineral fibrous dusts on the respiratory tract.

- Significant changes (in similar large extent) of inflammatory parameters were recorded after amosite instillation in both doses and time of exposure and were much more expressive than those after glass fibers instillation.

- The inflammatory parameters after glass fiber exposure were the most significantly changed after 2mg/ 4 week exposure.

- Cytotoxic parameters in amosite treated groups were the most statistically changed after dose 8 mg in both times of exposure. The number of changed cytotoxic parameters after exposure to glass fibers was evidently lower in comparison with amosite exposure.

Because of the wide use of fibers for industrial purposes and their negative effects on respiratory tract it is necessary to test their biological effects and select these which are less harmful for people and environment.

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VEGETATED SOLUTIONS FOR NONPOINT SOURCE POLLUTION CONTROL

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Nonpoint source pollution is the leading cause of water quality problems in the United States, and its reduction is a major challenge facing society today. Since the approval of the Clean Water Act of 1972, the United States has made great advances in reducing point source pollution from industrial and municipal wastewater systems. Unfortunately, not enough has been done to control nonpoint source or diffuse pollution, resulting in approximately 40% of rivers, lakes, and estuaries being unfit for fishing and swimming. As of 1998 over 290,000 miles of river, almost 7,900,000 acres of lake and 12,500 square miles of estuaries failed to meet water quality standards. The integration of

biological technologies used by ecologists and agronomists with traditional engineered pollution control and remediation technologies appears to offer a cost effective, timely, and aesthetically pleasing solution for nonpoint source pollution. In recent years, it has become evident that the establishment and presence of vegetation can mitigate nonpoint source pollution and enhance the remediation of contaminated soils and water. Kansas State University is currently conducting numerous field, mesocosm (column) and laboratory studies to assess the effectiveness of vegetated systems for NPS pollution control in several settings, from agricultural fields to military training lands and urban centers. Preliminary results indicate that vegetated bioretention cells (urban NPS pollution management practice) can have a significant impact on urban stormwater quality and riparian buffer strips reduce sediment and nutrient transport into streams in both rural and urban areas. Vegetation selection based on climate and required function in addition to the site physical characteristics are the primary factors effecting system effectiveness.

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SYNTHESIS OF WATERSOLUBLE AND WATER SWELLING POLYMERS OF VINYLTRIMETHYLPYRIDONE IN THE MEDIA OF WATER AND THEIR SORPTION ABILITY RELATED TO ENDOTOXINES STUDY

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During last time great attention of investigators was attracted to the polymer materials, which are sensitive to small changes in external sphere conditions. These properties are more characteristic to water soluble polymers and hydro gels, extremely sensitive to fluctuations in pH, temperature, ionic power, light, electric fields and etc. Such systems are very cuddy to fields like biotechnology and medicine. There are some examples of practical implementation such polymers for the purpose of separation and purification of

biologically active compounds and immobilization of biocatalysts. They could also be practiced in concentration of proteins' extracts, in dehydration of slips, in making membranes with adjustable permeability, in making sensory systems and systems with controllable excretion of medical compounds. One of the perspective classes of monomers to be used for the synthesis of water soluble and water swelling polymers purposes is derived ethinyl piperdole, which due to the presence piperdole group can be quartzied until ionized state of monomer or corresponding polymer. Due to the all abovementioned facts the main goal of this investigation was performing polymerization of one of the members of monomers that belongs to one of such classes – vinyl-ethinyl-threemethyl-pipperidole (VETP) in water and understanding its sorption characteristics with regard to edogenic toxins. The process of polymerization was carried under the room temperature and with the change of concentration of monomer ranging from 0.7 – 2 mol/l. Concentration of initiator – ammonium persulphate was taken 0.006- 0.02 mol/l. As catalyst for this reaction we used tetraethylendiamine at the pH= 3. Also special sewing reagent (BIS) in concentration of 0.03- 0.13mol/l was added in order to receive cross-linked polymers. The structure of polymers was identified by the means of IR- and NMR spectroscopy. Line structured polymers after the process of quartz formation of the nitrogen atom by hydrochloric acid were used for complex formation with serum albumin, heparin and bilirubin. In all cases formation of solid or swelled phase was observed. Quartzied cross linked polymers were investigated on the subject of their capacity of bilirubin sorption from the model solutions with 0.001 M of NaOH at the static conditions. In all cases linked polymers showed high sorption ability of bilirubin even exceeding 1 kg per 1 g of polymer used.

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PRODUCTS OF OXIDATION AS MEASURABLE INDICATORS OF OXIDATIVE STRESS: VALIDATION OF BIOMARKERS FROM RODENT CCL4 AND OZONE EXPOSURE

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Oxidation products of lipids, proteins and DNA in plasma and urine of rats were measured as part of a comprehensive, multilaboratory validation study searching for non-invasive biomarkers of oxidative stress. The goal of the study was to find the most sensitive, selective and specific markers of oxidative stress that are applicable to different oxidative insults and stored specimens. Investigators from 24 labs worldwide are participating in this study. The focus of this presentation will be on the findings from measurement of oxidative stress in experimental animal models of CCl₄ poisoning and ozone exposure. The time and dose-dependent effects of CCl₄ and ozone exposure on concentrations of lipid hydroperoxides, TBARS, malondialdehyde (MDA) and isoprostanes were investigated with different techniques. In addition, measures of oxidation products of proteins (protein carbonyls, methionine sulfoxidation, tyrosine oxidation products) and DNA (strand breaks, 8-OHdG, M1G) were carried out as well.

It was found that plasma concentrations of MDA and isoprostanes (measured by GC/MS) and urinary concentrations of isoprostanes (measured with an immunoassay) were increased in CCl₄ treated rats in a time- and dose-dependent manner. All other products were not changed by CCl₄ or showed only high-dose and/or single time point effects. In the ozone exposure model, however, plasma concentrations of MDA and isoprostanes (measured by GC/MS) were not changed whereas urinary concentrations of isoprostanes (measured with an immunoassay) were increased. In addition, measures of oxidation products of proteins (protein carbonyls, methionine sulfoxidation, tyrosine oxidation products) and DNA (strand breaks, 8-OHdG, M1G) were not changed in a time- and dose-dependent manner by CCl₄ and ozone. Therefore, at this time, there are no good markers of oxidative damage to DNA or proteins with CCl₄ poisoning and ozone exposure. It is concluded that measurements of free radical mediated lipid peroxidation products

- MDA and isoprostanes concentrations in plasma (by GC/MS) and urinary isoprostanes (by immunoassay or GC/MS) are promising candidates for general biomarkers of oxidative stress. The pattern of oxidative stress biomarkers seen in these two exposures will offer insight into the specificity and sensitivity of the markers and will provide evidence that a given product of oxidation may be a marker for some type of oxidative stress but not others.

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METALS, METALLOTHIONEIN AND OXIDATIVE STRESS

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Oxidative stress plays a key role in the development of cardiovascular disease, neurodegenerative diseases, cancer and inflammatory disorders. Many metals associated with increased risk of these diseases also induce oxidative stress. According to literature data, both Cd and As cause oxidative stress. However, it had not been directly shown that these inorganics are capable of generating free radical metabolites *in vivo* even when high level exposure is used. Our group has successfully developed and applied ESR spin-trapping assays that permit detection of molecular free radical metabolites as markers of oxidative stress in biological specimens. For example, using electron spin resonance (ESR) in conjunction with the spin traps phenyl-*N-tert*-butylnitron (PBN), α -(4-pyridyl 1-oxide)- *N-tert*-butylnitron (POBN) and 5,5-dimethyl-1-pyrroline-*N*-oxide (DMPO) we investigated free radical production by cadmium chloride and inorganic arsenicals sodium arsenite (As^{III}) and sodium arsenate (As^V) in a whole animal mouse model of acute poisoning. In addition, the role of free radicals in the *in vitro* cytotoxicity of dimethylarsinic acid (DMA^{III}) using murine TRL 1215 liver cells was also examined. In order to define the mode of action of DNA damage induced by DMA^{III}, this study investigated free radical generation by DMA^{III} in *in vitro* experiments with supercoiled ϕ X174 DNA. Administration of PBN and As^{III} to adult male 129/Sv mice

resulted in the generation of free radical metabolites detected in liver lipid extract by ESR spectroscopy. Free radical generation was subsequently observed in TRL 1215 liver cells subjected to an acute high concentrations of DMA^{III}. The complete system containing \emptyset X174 DNA, DMA^{III} and DMPO also gave a characteristic spectrum of a DMPO-hydroxyl radical adduct.

Cd is not a redox-active metal, and thus the radical production by Cd must be mediated through indirect mechanisms. We found that in the rat, depletion of hepatic glutathione by diethyl maleate greatly enhanced Cd-induced POBN-radicals, consistent with diethyl maleate's aggravation of cadmiums' hepatotoxic effects. In another important pathway, Cd-induced oxidative stress is thought to be mediated through the activation of Kupffer cells, the resident macrophages in the liver. Cd-induced POBN-radical formation was significantly diminished by the phagocytic toxicant gadolinium chloride, suggesting that Cd-induced radical formation is an important aspect of acute Cd hepatotoxicity, and that activated Kupffer cells and/or neutrophils are an important source for Cd-induced oxidative stress in the liver. MT did not play role in the free radical generation. This presentation will describe the identification of oxidative stress-derived free radical metabolites and their application as biomarkers of oxidative stress *in vivo*.

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**THE PLANT GROWTH REGULATORS
INFLUENCE ON THE LIVER
MICROCIRCULATION. COMPARISON OF
INDIVIDUAL AND SIMULTANEOUS
ACTION**

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Liver is the main organ in the processes of pesticides transformation. The condition of hepatic microcirculation is an important index of this organ health. The influence of the plant growth regulators on the liver vessels, especially sinusoids, is not studied enough until now. Simultaneous action of these pesticides was not analysed at all.

There were investigated the morpho-functional changes in the rat liver blood vessels after the herbicide 2,4-

dichlorophenoxyacetic acid (2,4-D, 10 mg/kg) and the plant growth stimulators 2,6-dimethylpyridine-N-oxide (ivon, 50 mg/kg) and complex of 2,6-dimethylpyridine-N-oxide and Na-succinate (potatin, 50 mg/kg) action during the month. These chemicals were administered intragastrally in 1 ml of distilled water in the morning before feeding. For histological analyses livers were fixed in Buen mixture, paraffin slides were stained with Bemer hematoxylin, eosin and orange G. The morphometry was realized on microscope Olympus BX-41 (Japan) using the program Olympus DP-Soft. The obtained data showed that herbicide 2,4-D provoked hepatitis. The inflammation focuses were located predominantly around vessels: portal and central veins and hepatic arteries. There took place vessels thrombosis, hemorrhages and sinusoids constriction. The sinusoids diameters lessened threefold (from 5.6 ± 0.3 mkm in control group to 1.9 ± 0.4 mkm), the heights of endothelium cell nuclei decreased almost in half (from 2.5 ± 0.1 mkm to 1.9 ± 0.1 mkm). Ivon caused conjunctive tissue overgrowth around vessels in centrolobular and periportal regions, sometimes perivascular edema. Ivon influenced on the width of sinusoids, but less than herbicide 2,4-D. The sinusoids diameters were 3.2 ± 0.6 mkm. Just the same time the size of endothelium cell nuclei decreased to a greater extend and theirs heights changed to 1.3 ± 0.1 mkm. Data analysis of the morpho-functional changes in liver vessels after simultaneous action of 2,4-D and ivon showed that the last partly prevented injuries, provoked by 2,4-D. Simultaneous action of 2,4-D and ivon led to results more like ivon alone. The sinusoids diameters lessened to 2.3 ± 0.4 mkm, the heights of endothelium cell nuclei decreased to 1.5 ± 0.1 mkm.

Potatin provoked significant changes in the liver circulatory system. Portal and central veins and hepatic arteries were full of blood. The sinusoids located under capsule contain predominantly erythrocytes, and sinusoids closer to central area of the liver were filled with lymphocytes. The sinusoids diameters lessened only to 3.9 ± 0.3 mkm, the heights of endothelium cell nuclei remained without changes (2.5 ± 0.1 mkm). After simultaneous action of herbicide 2,4-D and potatin the influence of pesticides was less than after their individual action. The sinusoids diameters are 3.2 ± 0.3 mkm, the

heights of endothelium cell nuclei – 2.2 ± 0.1 mkm. Thus it was described the differences in liver vessels reaction effected by individual and simultaneous action of the plant growth regulators 2,4-D, ivin and potatin.

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FORECASTING OF PROFESSIONAL FUNCTIONABILITY IN DANGEROUS AND EMERGENCIES

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The progress of a science and engineering considerably has expanded the areas of activity of the people. The environments are mastered in which in the man cannot work without special individual or collective means of protection.

This problem is actual also for many kinds of industry, military divisions (subdivisions), civil defense and liquidators of emergencies.

Because of high mental pressure (voltage, stress) and threat to life the activity on liquidation of emergencies it is necessary to select in the special group.

The researches have allowed to determine the main (basic) behavioural responses of the man on the dangerous conditions. It preventive and excessive protection. The preventive the use of modern means of protection considerably reduces losses at origin of emergencies. However their preventive use can upset a functional condition or to call diseases. These disturbance and diseases are necessary to considering as an outcome of inexpedient use of means of protection. Subjectively disturbance of state of the health are perceived by working people and ambient staff as indications of a defeat. It in its turn results in further inexpedient application of medical and evacuational measures.

The researches were conducted in some stages.

At first by results of inquiries of the experts, which possess experience activities on liquidation of emergencies their formal gradation was developed.

To the first level of danger the activities which are not danger to the life, but can call significant disorders of health in the case of rough violations of the rules of activity or safety precautions were referred. The

activities requiring the use of means of protection also were referred to them.

To the second level the activities potentially dangerous for life were referred, that is such, that without use of special means of protection bear threat to life.

To the third level the activities in conditions of emergency were referred, when there is a threat to life even under condition of use of means of protection.

The developed laboratory models have allowed rather adequately them to imitate and to reproduce mental strength connected with a various degree of confidence in rather satisfactory termination in dangerous conditions.

Taking into account special features of perception of danger in the work in the infected atmosphere the additional researches were carried out (spent). The dangerous conditions were imitated by activity of monitoring devices, actuation of the alarm signal and in other ways.

The received results have allowed to make a conclusion, that the psychoemotional pressure in a nominal situation is adequate to a degree of danger of conditions of activity and does not call a significant drop of functionability. In emergencies the psychoemotional pressure not adequately and calls an essential reduction of functionability.

Emergencies, connected with the necessity to work, in the infected atmosphere call large changes of psychoemotional condition especially, when the means of protection are used on a signal of danger.

The insufficient physiological and hygienic characteristics of majority of modern means of individual protection require development of effective systems of forecasting of functionability of staff at their use, and also monitoring systems of a functional condition.

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MEDICAL ASPECTS OF CHEMICAL TERRORISM: ANTIDOTES OF PHOSPHORORGANIC COMPOUNDS

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At present time, mass terrorism acquires a progressively growing scale all over the

world. As a result of acts of terrorism, a lot of people perish, and extensive damage is caused to the ecosystems. Scales of terrorism threat can be evidenced by the known cases in Matsumoto (1994), Tokyo (1995), Amman (1997), New York, Moscow (2002-2004). Among chemical substances that are potential substances for terrorist actions, a special place belongs to cholinesterase blockers, particularly to organophosphorous compounds, which are either in arsenal of many countries (sarin, soman, tabun, V-gases, etc.). Besides, the usage of chemical substances of other destination (such as industrial chemicals, pesticides, etc.) cannot be excluded because of their greater accessibility. The usage of some of them even in small amounts can affect a large contingent of the population, cause death or invalidization, and do damage to the environment as well. The usage of modern knowledge does not exclude the synthesis of toxic OP substances by underground laboratories. Mechanisms of toxic action of organophosphorus compounds as potential agents for chemical terrorism and the contemporary approaches to therapy of acute poisonings induced by blockers of cholinesterase. Since OP compounds block cholinesterase selectively in every cholinergic structure (M- and N-cholinoreceptive systems), practically all physiological systems and organs can be involved in a pathological process. At that, changes in activity of the central and peripheral nervous systems as well as the resulting impairments in respiratory and cardiac activities have a critical influence on an outcome of the poisoning. Some OP compounds are produced the delayed neurotoxic effect. Till present time, near 40 000 cases of pareses and paralysis developed in human beings as a result of their exposure to OP compounds have been described. A principle of the therapy for acute poisonings with anticholinesterase compounds lies in the complex performance of specific antidotic therapy including methods for poison excretion. The specific therapy consists in concurrent use of two antidotes differing by mechanism of action: cholinolytics eliminating anti-cholinesterase effects on central nervous system, and cholinesterase reactivators ensuring the restoration of inhibited enzymatic activity. Modern

approaches to medical treatment of poisoning caused by neuroparalytics anticholinesterase compounds will be considered in the report. The prospect of development of combined antidotic means composed of central action cholinesterase reactivators and cholinolytics and tranquillizers will be substantiated. In view of possible use in terrorist acts of neuroparalytic OP compounds the development of antidotic and therapeutic means in Ukraine is an extreme relevant problem.

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**USE OF ENDOTOXICOZUM
PARAMETERS IN QUALITY
PRESCRIBING METHODS OF
XENOBIOTICS EMBRYOLOGIC ACTION
DETECTION**

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According to the data of some authors (Dyban A.P., 1987; Sanotskij I.V., 1997; Kotova T.E., 2003; Chernyh A.M., 2003; Velichkovsky B.T., 2004) the big number of chemical substances influencing on mammal organism during pregnancy can render direct or indirect by products of biotransformation of xenobiotics or circulating immune complexes (CIC) damage of a placental barrier that is accompanied by anomalies of development of embryos of a various degree of expressiveness, including incompatible with a life (Tompson R.A., 1983). Pregnancy, being as a matter of fact process physiological, is provided with intense functioning of various systems of mother organism, including endocrine, nervous, immune and many others, that is accompanied by increase in blood serum of level of biologically active substances including a level middleweight peptides (MWP) and the CIC that is a part of normal mutual relations between a parent organism and fetus. At the same time there are interesting researches about increase in quantity of the CIC at background of preeclampsic toxicosis at which disease and death rate of fetus during the early postnatal period grows (Tompson R.A., 1980). It allows regarding substantial growth of a level of the CIC, as one of the important

parameters of immune biological disbalance between an organism of mother and a fetus, and also as one of possible prescribing parameters of embryotoxic action of xenobiotics. The submitted work is a fragment of researches on development of serologic markers of embryotoxic action of xenobiotics on the basis of use of some endotoxocosum parameters, in particular: detections of MWP level (Gabrieljan N.I. and coauthors, 1985) and total of the CIC (Digeon M., and all., 1977) with an indirect estimation of their size (Struchkov P.V. and all, 1985). Researches are carried out on 120 Wistar rats receiving per os with 6 for 15 day of pregnancy xenobiotics - carboxin in dozes 10, 40 or 160 mg / kg. Detection MWP level λ_{280} and λ_{254} nanometers and the CIC was carried out for 7-th, 14-th and 21-st day from the beginning of preparation administration that corresponds to 13, 21 days of pregnancy and 5-th day of the postnatal period.

The revealed system disorders of embryos development (increase of postimplantational death, decrease in fetus body weight) at dozes of preparation carboxin - 40 and 160 mg / kg associated with strengthened disintegration of protein - increase of level of MWP λ_{254} nanometers and nucleotides - level MWP λ_{280} nanometers the most expressed on 13 day of pregnancy. The maximal increase of CIC level was observed in blood serum of pregnant rats for 21 day of pregnancy at carboxin doze 160 mg / kg, thus in blood serum of the pregnant rats receiving carboxin at all tested dozes, the percent of individuals with primary formation of the CIC of the small sizes increased. Increase of MWP and CIC level on background of carboxin administration exceeded limits of physiological fluctuations of researched parameters at controlled rats of similar terms of pregnancy.

Thus, detection MWP and CIC level in blood of pregnant laboratory animals promotes objectification in estimations of condition of pregnant organism, and also allows estimating the contribution of factors of external ecological aggression to processes of embryotoxic action initiation.

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USE OF AUTOHEMOPERFUSION OF UV-IRRADIATED BLOOD FOR THE

TREATMENT OF CHRONIC DERMATOSIS

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The use of external ultra-violet irradiation (UVI) of skin has long-standing traditions. Thus Pototskiy I.I. (1979) offered to use the zonal UV-irradiation of skin in erythema and hypererythema doses at the psoriasis treatment and to use suberythema doses at the pyoderma treatment. UV-irradiation provides desensibilisation effect and increase protection power of an organism. With that the use of autoperfusion of UV-irradiated blood (AUVIB) at the skin diseases treatment (including chemical aetiology diseases) is limited at the present time. The modern data give evidence about the stimulation of cell-humoral immunity, non-specific reactivity, improvement of rheological properties of blood as a result of AUVIB action.

The aim of the work is to study the efficacy of AUVIB at the treatment of chronic dermatosis.

AUVIB treatment is carried out to 56 psoriasis patients, to 14 neurodermatitis patients and to 4 lichen ruber planus patients. AUVIB made with the "Isolda" MD-73M device at 20 ml/min blood velocity. The blood was irradiated by short 254 nm UV-rays (SUV) in the quartz cell. The blood was leaked through the cell by peristaltic pump. The volume of irradiated blood was 120-150 ml. The number of procedures for the course of treatment was 7-12 times. The period between the 1st and the 2nd procedures was 1 day, for the following procedures the period was 3 days. The condition of the cell and humoral immunity, non-specific reactivity and rheological properties of blood was investigated.

It's established, the overt disorders of cell and humoral immunity, non-specific reactivity of organism and rheological properties of blood was found at psoriasis patients especially at anthropotic psoriasis, at psoriatic erythroderma and at extensive psoriasis with the torpid run, at diffuse neurodermatitis patients and at hypertrophic forms of lichen ruber planus.

The rehabilitation of immunological and rheological parameters of blood with positive clinical dynamic is showed after the treatment course by AUVIB.

So, the use of autohemoperfusion of UV-irradiated blood is promising method of the treatment for chronic dermatosis.

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THE COMPLEX FORMATION OF CALCIUM ION WITH THE MACROMOLECULARS OF PECTIN

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Interaction of macromolecular polymers with small bulk molecules was the subject of many recent publications. The goal of such investigations is understand mechanisms of ions interaction with small size molecules and understanding results of conformation changing under influence of these substances.

Together with theoretical scientific interest such new complexes have many aspects of implementation. For the last time great attention was paid to the compounds of pectin nature as component for complex formation due to their possibility to form gels in the presence of metals cations.

Interest to the compounds like pectin grows because they are one of the food components. Having water saving ability they find implementation in medicine as drug for several illnesses. On the other hand pectin compounds due to presence of negative charged carboxylic function have ability to attract positively charged metal ions.

Mentioned pectin compounds open possibility to be used for the purpose of withdrawing heavy and toxic metals out of organism from one side and as container that brings different kinds of metals to the humans body especially calcium ions for purpose of curing osteoporosis illness. That is why investigation on mechanism of complex formation of pectin compounds with above mentioned metals and determination of maximum capacitance related to components of complex formation is indeed great scientific task. The goal of the

presentation is study of abilities of complex formation of sunflower's plant pectin compounds with calcium ions and determination of impact of different groups of monomeric chain and macromolecules to the common process. We used the pectin compounds separated from basket of sunflower. This pectin has in its composition galactouronic acid 85.2%, and degree of polymerization of 44.4%. The ion calcium sorption was carried out at the static conditions. The concentration of calcium ion was determined by trilon-B titration. It was found that isotherm of sorption has extreme characters. Achieved results clearly demonstrate that gel formation ability of pectin compounds strongly depends on concentration of calcium ion. The conformation and possible structure of pectin compound depends on distribution of free carboxylic groups and molecular mass of polymer. Ion of calcium, under appropriate conformations of di- and polymeric aggregates helps in formation of stable gels. Last property is very important to the practical case, because it open doors to highly concentrated pectins.

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ROLE OF CYTOCHROME P450 2E1 INDUCTION IN MALE REPRODUCTIVE TOXICITY IN RATS

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According to toxicological and epidemiological studies male reproductive system is very sensitive to the different hazard factors of the environment. Metabolism and access of chemicals to the reproductive tissues is an important toxicological consideration. Microsomal cytochrome P450 (CYP) monooxygenases play important roles in the biotransformation of both endogenous compounds and xenobiotics. Unfortunately, oxidative metabolism of xenobiotics generates a variety of reactive intermediates, metabolites, and oxygen-free radicals, that can damage cellular components, macromolecules modification and lipid peroxidation. CYP2E1 isoform is responsible for the metabolism and potential bioactivation of a number of low-molecular-

weight pharmaceutical and other xenobiotics, including acetaminophen, ethanol, acetone, benzene, carbon tetrachloride, N-nitrosodimethylamine, pyridine, pyrazine. Knowledge of how CYP2E1 induction affects male reproductive functions is very superficial.

Aim of the study is to analyze the effects CYP2E1 inductor pyrazinamide on the functional, morphological and biochemical parameters of male reproductive system in rats. All experiments were carried out on male Wistar rats. Water solution of pyrazinamide was administered per os during period of spermatogenesis (60 days) at the doses of 500, 1000 and 2000 mg/kg b.w. Disulfiram, specific inhibitor of CYP2E1, was administered per os, 30 mg/kg b. w. The levels of CYP and p-nitrophenolhydroxylase activity (marker of CYP2E1) in liver microsomal fraction, histology of the testis and functional state of spermatozoid in epididymis cell suspensions were investigated. Pyrazinamide per oral administration (500, 1 000 and 2 000 mg/kg) for spermatogenesis period decreased sperm number and compensatory increased spermatocyte meiotic activity (1.21, 2.42, and 2.48-fold, respectively). These alterations may be due to induction of CYP P450 by pyrazinamide, that is confirmed increasing p-nitrophenolhydroxylase activity (1.5, 1.8, and 1.87-fold, respectively) and CYP levels in liver microsome fraction. Pyrazinamide at 2000 mg/kg caused degenerative changes in testis seminiferous tubules (desquamation of epithelial cells into the lumen of the tubule, epithelial exfoliation from basal membrane, "windows"). Administration of disulfiram to male rats considerably decreased degenerative changes and recovered spermatogenesis of testis, that shows role CYP2E1 induction in reproductive toxicity.

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DETERMINATION OF ACETALDEHYDE AND FORMALDEHYDE IN WATER AND MODEL ENVIRONMENTS WITH METHOD OF LIQUID-GAS CHROMATOGRAPHY

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Level of consumption of polymeric products in our country is increased every year. Rapid growth of consumption is caused mainly by swift development of food industry with the use of packing materials (polymeric tapes, packages, plastic bottles, throw-away tableware), which became our life's companions. Unfortunately, it is accompanied with no less hasty growth of problems, related to the use and utilization of the spent polymeric container. Therefore, safety control of application of polymeric materials becomes more and more necessary in these industries for the health of human, and also safety control of contamination of environment with harmful compounds.

Aldehydes are related to basic substances that require permanent control after their migration to contacting environments. The purpose of our research was a study and determination of optimum methods of determination of acetaldehyde and formaldehyde at their joint presence as the most toxic matters that are migrating to contacting environments.

The most modern methods of determination of aldehydes were tested – chromatography methods. Determination of formaldehyde and acetaldehyde is studied in a thin layer with 5.5-dimethyl-1.3-cyclo-hexo-dion (dimedon), liquid-gas method – equilibrium steam phase and reactionary liquid-gas chromatography. We determined that among all approved methods on the specificity, exactness, and repeatability most optimum is a method of reactionary liquid-gas chromatography. This method is based on the reaction of interaction of aldehydes with 2.4-dinitrophenylhydrazine in a sour environment with formation of derivative aldehydes of 2.4-dinitrophenylhydrazone, then by extraction them from water or other model environment (solution of citric, acetic and lactic acids, saliva imitation liquid) by an organic solvent – toluene. Chromatography was obtained using gas chromatograph with detector based on the capture of electrons. Basing on data from literature, determination of formaldehyde with method mentioned above is widely used in practice, and its determination in situation of simultaneous presence of acetaldehyde is used extremely rarely.

We studied the conditions of chromatography of derivatives of

acetaldehyde and formaldehyde with 2,4-dinitrophenylhydrazine on a few prepared hard carriers, modified with different immobile liquid phases. It is set experimentally that the best separation level of acetaldehyde and formaldehyde is achieved at the use of column (1m x 3 mm) filled with 5% SP 2100 using chromosorbe W-AW with $T_{\text{column}} = 190 \text{ }^{\circ}\text{C}$, $T_{\text{detector}} = 250 \text{ }^{\circ}\text{C}$, $T_{\text{vaporizer}} = 250 \text{ }^{\circ}\text{C}$ on gas chromatographer "Tsvet 500M". These conditions provide implementation of measuring with an error, not exceeding $\pm 20\%$; the lower limit of determination for formaldehyde was 0,01 ug, for acetaldehyde – 0,05 ug, what provides the level of determination of these matters at their maximum permissible concentration in water; time of output of formaldehyde – 1 min 12 sec, time of output of acetaldehyde – 2 min 48 sec, what provides sufficient separation on chromatogram.

The method we developed allowed estimating the level of migration of formaldehyde and acetaldehyde in contacting environments from the explored polymeric materials, textile materials and production.

The result of research is that migration of formaldehyde, acetaldehyde more often observed from polymeric raw material to more aggressive environments, such as solutions of acetic and citric acids.

Achieved results allow recommending the developed method for introduction in practice of sanitary-chemical researches.

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THE ROLE OF THE HAZARDOUS FACTORS STATE REGISTRATION UNDER CARRYING OUT THE SOCIAL & HYGIENIC MONITORING, ASSESSMENT AND MANAGEMENT OF RISK

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In accordance with the Law of Ukraine "On The Providing Sanitary And Epidemic Occupational Well-Being", that was put into action by the Decree of the Verkhovna Rada of Ukraine (Parliament) in February 24, 1994 N 4005-XII and the set of by-laws, it has been foreseen creating and

conducting the Unified State Register of the Hazardous Factors that is a file of systematized and scientifically analyzed information about exogenous substances that turn in Ukraine.

The Unified State Register of the Hazardous Factors represents a list of substances that passed through the procedure of the state registration as the hazardous factors in accordance with the current legislation, and allows to take a real stock of the substances of chemical and biological origin that turn in Ukraine, to evaluate a degree of safety at use and hygienic regulations availability for different media.

The Register contains the following information: the names of chemical substances and biological factors, data regarding their function, properties, methods of determination, biological action, hazardous degree for human health, behavior pattern in the environment, production, hygienic regulations etc.

The objective of the State Registration of Hazardous Factors maintenance in Ukraine is the solution of two main tasks, namely: protection of human health and environment from the adverse effect of potentially hazardous chemical and biological substances and possible adverse effect at their usage, and formation of the unified data bank regarding substances that turn in Ukraine [1]. It has to be underlined that both of the tasks – informational and preventive, are the parts of the whole and are integral parts of risk evaluation and risk management.

The availability of such data bank is necessary condition for the formation of an informational fund, provided by the Procedure of Carrying out the State Social&Hygienic Monitoring, adopted by the Decree of the Cabinet of Ministers of Ukraine of February 22, 2006 N182. It facilitates showing up cause-and-effect relations between the status of occupational health and an impact of the factors of human vital medium, in particular of chemical and biological origin [2].

It seems to be advisable to draw and analyze data of the State Register of Hazardous Factors for determination of the criteria for selecting priority pollutants among the chemical substances which pollute industrial and natural surrounding, for selecting the priority group of the extremely hazardous chemical substances

(highly toxic and persistent substances in the environment and those that cause the long-term effects); for working out the system of medical measures of chemical safety management.

On the basis of the above mentioned data bank the Data Card of Hazardous Factor was developed (analogue of Material Safety Date Sheet that was developed in accordance with the Directive 91/155 EEC) and was put into action by the Decision of the Chief State Medical Officer of Ukraine of May 20 2002 N19. The Data Card of Hazardous Factor became an integral part of an informational document which confirm the fact of the State Registration of The Hazardous Factor. Owing to the information that contains the Data Card of Hazardous Factor producers and users have the possibility to prevent the negative impact of the substances of chemical and biological origin on human health and the environment and to take the necessary measures for protection of workers' health at the production sites [3].

1. The Decree of the Cabinet of Ministers of Ukraine of June 13, 1995 N420 "On the Approval of the Provisions of Hygienic Regulation and State Registration of the Hazardous Factors and the Procedure of Remuneration of the Works on Conducting the Hygienic Regulation and State Registration of the Hazardous Factors".

2. The Decree of the Cabinet of Ministers of Ukraine of February 22, 2006 N182 "On the Approval of the Provisions of Conducting the State Social&Hygienic Monitoring".

3. Commission Directive 91/155 EEC. Official Journal of the European Communities. - Vol. 22, No L 76.- P. 35-41.

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**TRACEABILITY OF GMO-DERIVATIVES
IN THE FOOD PRODUCTS.
COMPARISON OF DIFFERENT
DETECTION METHODS**

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Recent changes in European Union law together with requirements of consumer's rights protection organizations sent a challenge to world scientific society to develop control methods of GMO in food and feed.

All methods that are used for qualitative and quantitative GMO analysis could be divided in following groups: 1) methods build on detection of GMO proteins and 2) methods that are build on detection of genetic material (DNA, RNA).

Historically methods for protein detection are considered as de facto standard for North and South America countries, methods for DNA, RNA detection - for European countries.

Each of these two approaches has its own advantages and disadvantages. According to experiment conditions one can use most suitable and precise.

Protein based methods are cheap, fast and simple. These includes ELISA, lateral flow sticks. This group of tests do not require expensive equipment and allows automation. At the same time sensitivity of protein based methods depends on matrix and can not be used for identification of GMO transformational events.

Methods that are based on detection of DNA and RNA use polymerase chain reaction in different modifications (conventional, nested, multiplex, etc). For quantitative analysis competitive PCR and Real-Time PCR are used, which allow determination of number of genome copies in sample. Detection of PCR product with hybridization in situ makes the requirement to laboratory simpler and can be automated. Still the questions about sensitivity and reproducibility are open, as well as applications of other GMO detection method - biological chips. However, a possibility to run several analyses simultaneously encourage further investigations of this method.

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**INFLUENCE OF MOTHER MALNUTRITION
IN OVER SALT CONDITION ON
FORMATION OF DIGESTION FUNCTION
IN OFFSPRING**

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The ecological disasters connected with the drying of the Aral Sea, stated before mankind a number of problems of global importance. One of them is the protection of the mother's and child's health in conditions

of the increased contents of fertilizers, pesticides, mineral salts etc. in air, ground, food and water as well as deficiency of drinking water. Earlier according to results of our experiments it was established, that the infringement of ecological balance in the Aral Basin region has a negative effect on development and health of the people and animals living in this region. The specific condition of Aral Basin influence on organism as a long-time stress-factor, which is the reason of the changes of the mother hormonal status, reduction of hormones and enzymes content in breast milk and breaking normal development of breast feeding

In this work in experiments on animals it is shown, that the deprivation protein in food and increased salt content in drinking water in lactating mother, rather precisely affect on the quantitative and quality of breast milk. In experimental lactating females the secretion of milk and content of protein are decreased on 32 % and 23 % in comparison with the animals, consumed balanced diet and pure drinking water correspondingly.

Quantitative and qualitative changes of breast milk are connected with high death-rate, sharp growth reduction of suckling during milk feeding and after weaning. The development of posterity delays in terms of eye opening, tooth and hair occurrence, functional formation of various organs and systems. For example, the consumption of «poor- protein» diet in combination with «poor-quality» drinking water by nursing mother results in sharp reduction of structural and functional development of pancreas and small intestine. Such reduction is shown in decrease of intestine mucous weight, villy height, crypt depth, quantity of cells on villy, content of mucous protein as well as in striking repression of pancreatic (complex of proteases, alpha-amylase) and enteral hydrolases activity, participating in initial and final stages of proteins and carbohydrates hydrolysis and final (dipeptidhydrolases, sucrase, maltase, alpha-amylase, lactase). The backlog in rates of morphological and functional formation of digestion function in growing organism is observed not only during milk feeding, but after wearing too.

Thus, the simultaneous consuming of «poor-protein» food and drinking salt water by nursing mother results in change of

quantity and quality of breast milk, i.e. promotes deterioration of breast-feeding. The deterioration of milk feeding causes repressing of activity of cavity and membrane hydrolysis digestive enzymes, i.e. ability of digestion organs to assimilate proteins and carbohydrates. Low ability of digest function results in growth and development suppressing in posterity. Finally, adaptive opportunity and viability of developing organism are decreased, increasing risk of different diseases in later periods of individual development.

Hence, one of the important problem of bioecological researches in conditions of Aral Basin - to study structure both properties of woman milk and milk of home animals, with the purpose of optimization of nutrition in lactating mothers and growing organism, decrease of risk of child's diseases as well as children mortality.

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**PHYTOTECHNOLOGIES:
INNOVATIVE METHODS TO CLEAN-UP
OR STABILIZE ENVIRONMENTAL
CONTAMINANTS USING VEGETATION**

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Phytotechnologies use vegetation to accumulate, degrade, or stabilize environmental contaminants in soil, sediments, surface water, or groundwater. Compared to other clean up methods, phytotechnologies can be cost effective requiring lower capital costs for installation; however, more time may be needed to achieve environmental management objectives. For over 10 years, development, testing, and application of phytotechnologies has resulted in considerable experience in benefits and limitations of using vegetation to manage risk from environmental contamination. Some applications have demonstrated promise for practical application while other applications must still be considered experimental. Some promising applications include:

Phytoremediation of organic compounds such as petroleum hydrocarbons to enhance microbial degradation.

Phytostabilization of organic and inorganic contaminants by revegetation of contaminated sites.

Hydraulic control and remediation of chlorinated hydrocarbons in groundwater using deeply rooted trees.

Riparian buffers and filter strips to manage surface water run-off to reduce non-point source pollution.

Evapotranspiration landfill covers to reduce leachate and protect groundwater.

- Constructed wetlands for municipal and industrial wastewater treatment and stormwater management.

Some experimental applications include:

- Phytoextraction of heavy metals.
- Phytoextraction of organochlorine pesticides, PCBs, and PAHs.

Successful design, installation, management and monitoring of phytotechnologies will benefit from application of local knowledge of agricultural practices and ecosystems. Selection of plant species is a critical decision for successful application of phytotechnologies. Over 1000 plant species have been investigated for phytoremediation capability for more than 40 contaminants. This information is being assembled in to a database that will be accessible online. This presentation will review several case studies illustrating the current state of knowledge and potential for application of phytotechnologies.

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MICROBIOLOGICAL SAFETY OF THE FOODS - WHAT IS TO BE DONE

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Three principals have been used to control microbiological hazards of foods. These are: 1) education and training, 2) inspection of facilities and operations, and 3) microbiological testing. Effective programs utilize combinations of all three approaches. A microbiological criterion for food consists of 1) a statement of the food to which the criterion applies, 2) a statement of the contaminants of concern (species or groups of microorganisms and/or their toxins), 3) the analytical methods to be used for its detection and/or enumeration, 4) the sample to be taken from a lot of food or

from a source of concern such as a point in a processing line, 5) the microbiological limits appropriate to the product, that is, the values of n (samples number), m (the level of test organism which is acceptable and attainable in food as it reflected by Good Manufacturing Practice (GMP), or is a hazardous level for 2-class plan (quality testing), M (a hazardous or unacceptable level of contamination caused by poor hygienic practice – used for 3-class plan only (quantative testing) and c (number of results between m and M). The stringency of sampling plans (the particular choice of sampling procedure and the decision criteria) is based either on the hazard to the consumer from pathogenic microorganisms, or potential for quality deterioration to an unacceptable state. Some microorganisms merely spoil a product, others can cause illness, and others are taken to indicate the likelihood of contamination by pathogens. The choice of a sampling plan must therefore consider: the type and seriousness of hazards implied by the microorganisms for which the test is to be made, and the conditions under which the food is expected to be handled and consumed after sampling. It may be classified 15 different cases of sampling plans on a two-dimensional grid taking into account these factors. The stringency of the sampling plan increases with the type and degree of hazard: from a situation of no health hazard but of utility only, through a low indirect health risk (as implied by the presence of indicator organisms), to direct health risks related to disease of moderate or severe implication. The stringency of the sampling plan also changes to the conditions under which the food is expected to be handled. Hazards may remain unchanged, be reduced by cooking, or increase because of subsequent growth of microorganisms. The most lenient plan is case 1 (3-case plan, $n=5$, $c=3$), case 15 is the most stringent (2-class plan, $n=60$, $c=0$). If the food is ordinarily subjected to conditions that permit bacterial growth, thereby increasing hazard, the case would be 3, 6, 9, 12 or 15. If conditions would not cause a change in the number of relevant bacteria (e.g., frozen storage) the appropriate case would be 2, 5, 8, 11 or 14. If a food is expected to be fully cooked later, one would choose case 1, 4, 7, 10 or 13 since cooking reduces the hazard. Poultry,

pasta and many dried products fall into this category. Any practicable system of bacteriological examination of a food product in commerce can never provide complete certainty that a desired bacteriological state has been attained: it can indicate this only with a particular degree of probability. In certain cases this degree of probability is either barely adequate, as in trying to detect salmonellae, or even totally inadequate, as in trying to detect *Clostridium botulinum* in canned foods. In such situations it is always wise to use other safeguards besides microbiological examination of the end-product. Thus, for optimal control of microbiological hazards at source, a more complete system is necessary. One such is the Hazard Analysis Critical Control Point (HACCP) system. Many of the processes used in food manufacture, such as heat treatment, acidulation, fermentation and salting will destroy or inhibit the growth of harmful microorganisms. Hazards associated with these procedures must be evaluated, and the consequences of failure of processing steps designed to destroy harmful microorganisms must be understood.

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EARLY-LIFE EXPOSURE TO DIETARY FAT AND AROMATIC HYDROCARBONS CAUSES METABOLIC SYNDROME, MORPHOLOGICAL CHANGES IN THE MAMMARY GLAND AND INDUCTION OF P450 PATHWAY IN DBA/2J MICE.

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The prevalence of childhood and adult obesity is increasing worldwide, contributing to increased numbers of individuals with metabolic syndrome and precocious mammary development along with increased cancer risk. The increased food intake associated with weight gain can further increase disease risk since, either through fat content or contamination by chemicals such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), it is a

major source of exposure to endocrine disruptors. However, exposure to TCDD retards weight gain and mammary development, yet increases diabetes and cancer risk. Prototypic carcinogens TCDD and 7,12-dimethylbenz[a]anthracene (DMBA) bind the Ah Receptor (AhR) and are transactivated by CYP1A1, CYP1A2, and CYP1B1, with the latter thought to be the primary enzyme responsible for formation of mutagenic metabolites. Consequently, we hypothesized that exposure to dietary fat should increase body weight, body fat, blood glucose, and mammary gland development, while TCDD should have opposing effects on body weight, body fat, and mammary gland development but similar effects in potentiating an increase in blood glucose. Furthermore, these exposures may interact to modify DMBA- induction of the AhR pathway. To test this, we examined the susceptibility of DBA/2J, a mouse strain highly resistant to ligand activation of CYP1 transcription. Pregnant DBA/2J mice were dosed with 1 µg/kg of TCDD (or vehicle) on gestational day 12.5, and when pups were born, the cage was put on a high or low fat diet. On post-natal day 35, mice were weighed, x-rayed for percent body fat, dosed with 60 mg/kg of DMBA, and fasted; 24 hours later blood glucose was measured and liver and mammary glands collected for real time PCR and whole mount analyses, respectively. High fat diet increased body mass and body fat relative to low fat diet, referred to as obese and lean mice, respectively. TCDD decreased body mass and percent fat in obese mice only. Blood glucose was depressed in obese and TCDD-exposed lean mice, while TCDD increased blood glucose in obese mice. Obese mice had greater mammary gland branch extension and terminal end buds (TEBs) than lean mice and TCDD depressed extension and TEBs in obese mice only. Molecularly, DMBA caused induction of CYP1A2, CYP1A1, and CYP1B1 mRNA. TCDD and low-fat diet heightened DMBA-induction of CYP1A2 and CYP1A1. Additionally, DMBA increased the ratio of CYP1B1/CYP1A1, but exposure to TCDD or low dietary fat eliminated this trend. We conclude that high fat diet increases DBA/2J susceptibility to body composition effects of TCDD. DBA/2J may be a useful model to elucidate the obese-

specific influences on cancer risk, since most obese models are also diabetic. The decrease of CYP1A2 in obese mice suggests that their adipose stores a greater portion of TCDD relative to liver. TCDD and low fat diet both favor formation of benign DMBA metabolites relative to mutagenic DMBA metabolites. In sum, this expression data suggest that DBA/2J susceptibility to DMBA-induced mammary cancer is increased by high fat diet and decreased by exposure to TCDD.

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PSYCHOSOCIAL RISK ASSESSMENT AND RISK MANAGEMENT IN ENVIRONMENTAL DECISION MAKING

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Since the Chernobyl accident and disintegration of the Soviet Union, storage of nuclear waste is recognized as a significant environmental and economical problem for Ukraine and other countries in Eastern and Central Europe. A strong local opposition, Not in My Back Yard (NIMBY) attitude, towards the attempt to establish nuclear waste facilities exists in most, or all, countries of the world. Extensive findings confirm that fear of potential exposure to ionizing radiation and long term negative health effects is a key NIMBY component. Numerous studies show that existing public fear and opposition to nuclear waste disposal plans also arise from the crisis of confidence, a loss of credibility, and a profound breakdown of trust in the scientific, governmental, and industrial managers of nuclear technologies. The substantial psychosocial impact on people and communities in close proximity to proposed sites for nuclear waste repository were reported in a number of studies. Recent research suggests that the well-being of individuals and communities could be impacted as much by the decision-making process as the outcomes themselves. In

this light, increased understanding of the psychosocial impacts of the siting process on the community members and society as a whole is essential in making successful environmental and remediation policy decisions. Awareness of the emotional, psychological, social, and behavioral consequences associated with the waste facility site and the siting process could help decision-makers to improve risk communication efforts, prevent unnecessary negative effects on people well-being and lead to less polarized relations. Future more, improved communication could increase the degree of trust in the authorities, foster resilience and positive outcomes. A Canadian chemical, biological, radiological, and nuclear (CBRN) psychosocial risk assessment and management (P-RAM) framework articulating risk assessment with public perception and psychosocial dimensions for managing the psychosocial aspects of CBRN risks that includes specific guidelines for psychosocial risk assessment, psychosocial risk communication, and psychosocial interventions was recently proposed. The P-RAM framework and related P-RAM Tools could provide decision makers with a structured approach to identify and recognize the full range of psychosocial aspects potentially associated with radioactive/nuclear threats, the factors influencing individual and community vulnerability to these effects, and the options for general and targeted interventions to manage negative psychosocial effects on individual and community well-being across the nuclear waste risk management process.

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TOXICOLOGICAL EFFECTS AND HUMAN RISK ASSESSMENT OF NEW FUNGICIDE FENHEXAMID

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Derivate of cyclohexancarboxamide – fenhexamid is the perspective new fungicides for use in agriculture. Fenhexamid is a highly effective protective fungicide for the control of Botrytis diseases

on grapes, strawberries and peaches. The fate of fenhexamid and safety of grown products have been investigated in different agroclimatic zones of Ukraine. The toxicological assessment of formulations and their active ingredients have been studied in Ukraine during State trials. Residual quantities of fenhexamid in the products have been studied by high-performance liquid chromatography (HPLC). Assessment of acute toxicity of fenhexamid formulation has shown that it may be referred to the pesticides of 3 class of hazard in accordance with Ukrainian Classification of Pesticides. In subchronic experiment (90 day) NOAEL for rats (2500 ppm), mice and dog (1000 ppm) have been established. In chronic experiment (2-years) NOAEL for mice - 800 ppm, for rats and dog -500 ppm. Fenhexamid is considered to be neither mutagen, carcinogen or teratogen. Hepatotoxic and nephrotoxic effects are the main toxicological effect of fenhexamid. On the basis of toxicological assessment of active substance, the ADI were recommended and approved in Ukraine. Field trials were conducted in Ukraine during 1999 – 2004. Dynamics of fungicide residues were studied in different agroclimatic zones of Ukraine. As a result of conducted experiments we establish that the rate of degradation of active ingredient is not stable. In some cases character of decrease of pesticide residues may be described as a wavy type. Fenhexamid more stable in plants then other group of fungicide. Residues of fenhexamid were found in plant products during the harvest time at the level of 0,1-0,2 mg/kg in grapes. Simulated industrial preparation of juice allowed us to study the fate of residue during processing. On the basis of conducted experiments, an MRL and post-harvest interval has been recommended, providing safe use of new fungicides in Ukraine. Theoretical maximum daily intake of new fungicides with food products did not exceed 2 % of acceptable daily intake. Based on conducted researches we consider that a dietary intake of fenhexamid residues is unlikely to present public health concern.

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USE OF THE EXPRESS-METHOD AS AN ALTERNATIVE TO ANIMAL

EXPERIMENTATION FOR PROGNOS OF TOXICITY

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For toxicological tests alongside with classical experiments on animals the increasing application is found the alternative methods. The argument to their application are the ethical motives of the attitude to an animal, economic aspects of cost of researches, and also complexity of an establishment of parameters toxic metric of extracts of unstated structure from products in experiment on animals.

As is well known, agrees of conclusions of the international program MEIC on check of efficiency of alternative methods the recommendations about an opportunity of application for tests on toxicity only of methods with use are given as tests-objects of crates of mammals.

As the given literatures testify, all these requirements to the full are responded with an express-method of a rating toxicity with use as test-object short-term of suspension culture of mobile crates-sperm of the bull. The authors of the publications convincingly show advantages of use of this method having the developed specifications for a rating toxicity of various groups of products, and testify to the high toxicology-hygienic importance of received results.

The specified express train a method of a rating toxicity is successfully used by us for examination of various kinds of products from polymeric materials on an extent more than 5 years. The experience of use of an alternative method in a complex with other researches has shown an opportunity of interpretation of the received results for development and updating of the hygienic rules of application of products of medical application, judgment about presence or absence of biological activity, spermicidal lubrications and other properties inherent in a researched sample.

Besides use it the express-method of a rating toxicity has allowed to determine total toxicity or non-toxicity of a complex of harmful chemical substances, which can migrate from products on modeling environments, at levels, which were not identified existing chemical-analytical

methods, or are identified at levels below allowable hygienic rules.

Use the express-method of a rating toxicity also promoted reduction of terms of researches and decrease of their cost at toxicology-hygienic examination of products used various areas of a national economy.

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MEASUREMENT OF EXPOSURE TO COMPLEX MIXTURES OF POLYCYCLIC AROMATIC HYDROCARBONS IN HUMAN POPULATIONS

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Polycyclic Aromatic Hydrocarbons (PAHs) are released from the incomplete combustion of organic materials such as gas, oil, and wood. PAH contamination occurs as complex mixtures that often contain over one hundred chemicals. Humans may be exposed to PAHs in the environment from many sources, including tobacco smoke, diet, and industrial processes. Animal studies have clearly linked exposure to PAHs with a variety of cancers. Human populations may also be at increased risk of cancer if the dose and duration of exposure are adequate. However, there is limited information regarding the absorption and distribution of PAHs from non-occupational exposures. Biomarkers have been measured in plasma and urine from three generations in a total of 70 families (37 urban, 33 rural) from the country of Azerbaijan. Measurements collected from these populations include the concentration of PAHs in plasma, PAH-DNA adducts in peripheral lymphocytes, and 1-hydroxypyrene in urine. The median serum concentration for total PAHs in the urban population was 148 ng/mL, while a median level of 67 ng/mL total PAHs were detected in the rural population. Total DNA adduct

levels were significantly higher in the urban population than in the rural population. Analysis of urine samples from urban and rural populations indicate that 1-hydroxypyrene concentrations are highly variable. Cotinine levels are also being measured to account for PAHs from tobacco smoke exposure. Overall, the results indicate there is a correlation between PAHs in environmental samples and PAH adducts in exposed populations.

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COMPARABLE STUDY OF SODIUM SUCCINATE HEPATOPROTECTIVE EFFECTS UNDER 2,4-D AND IVIN ACTION

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The large-scale agricultural application of pesticides is a reason of study the pesticides influence and to look for the way of the organism protection from the pesticides harmful influence. The detoxification mechanisms that take place in liver after the action of herbicide 2,4-D (2,4-dichlorophenoxyacetic acid) and plant growth regulators ivin (2,6-dimethylpyridine-N-oxide) and potatin (complex of 2,6-dimethylpyridin-N-oxide and sodium succinate) is a main problem. Studying of the sodium succinate features helps to find ways of prevent the toxic influence of these preparations.

Therefore the purpose was to investigate the hepatoprotective effects of sodium succinate under 2,4-D and ivin action. White rats obtained the preparations intragastrally daily for one month. Plant growth regulator ivin administered in dose 50 mg/kg, potatin - 50 mg/kg, herbicide 2,4-D - 10 mg/kg, sodium succinate - 25 mg/kg, 2,4-D - 10 mg/kg with sodium succinate - 25 mg/kg. The control group received in the same way distilled water. Liver for histological analysis was subjected to the standards histology processing. In the rat liver we evaluated the relative number (percents) of polyploid hepatocytes, hepatocytes which contain two nuclei and the information characteristics of system complication and organization were determined. It was displayed that 2,4-D leads to significant changes in liver.

Herbicide 2,4-D provokes decreasing of relative coefficient of systems organization and increasing of entropy, particularly in periportal zone of liver lobule. The regeneration processes also take place. Plant growth regulator ivin also causes decreasing of relative coefficient of systems organization and increasing of entropy. However, the changes in all zones are rather similar in this case. The sodium succinate leads to changes of the system information characteristics. Also the activation of hepatocytes take place. The changes in centrolobular and periportal zone of liver lobule are different. Simultaneous action of 2,4-D and sodium succinate leads to decreases of destructive influence of 2,4-D, particularly in periportal zone of liver lobule. Just the same time compensatory processes take place in liver. Plant growth regulator potatin causes (compare to ivin) increasing of relative coefficient of systems organization and decreases entropy, particularly in centrolobular zone of liver lobule. Analysis of the results obtained shows that sodium succinate decreases damages provoked by 2,4-D and ivin in the rat liver. But hepatoprotective effect of sodium succinate under 2,4-D and ivin action has some peculiarities in each case.

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**STUDY OF ONCOGENIC AND
CYTOTOXIC
EFFECT OF CARBENDAZIM IN RATS**

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Carbamate fungicides are well-known and have been used in agriculture all over the world. Nevertheless, the information about its carcinogenic activity is still contradictory. The purpose of this work was to determine the potency oncogenic and cytotoxic effects in short-term tests.

To evaluate the cytotoxicity effect we used the "micronuclei test". Oral administration of Carbendazim to rat at a dose 300 mg/kg body weight during 4 weeks with following hepatectomie have shown slight increasing the number of micronuclei in hepatocytes with respect to control animals. To determine oncogenic activity we evaluated induction of preneoplastic foci in

diethylnitrosamine-initiated hepatocytes, by positive gammaglutamyl-transpeptidase (GGTase) staining in liver slides. The male non-bred albino rats (10 rats in each groups) were initiated with 200 mg/kg diethylnitrosamine (NDEA) intraperitoneally. After three weeks animals were hepatectomized. As a positive control we used Phenobarbital instead of Carbendazim. All rats from treatment groups were given pesticide in dose level close to 1/5 LD₅₀ - 300 mg/kg. At the end of the 10th week all rats were sacrificed, and liver slices are fixed in ice-cold acetone for examination of GGTase. The number and areas of GGT-positive foci are measured using of the computer by the help of the polygraph programs "Adobe Photoshop" for processing a color image. Significant decrease in number and area per slide unit area (cm²) of GGTase-positive foci could be observed in pesticides-treated rats in experiment with respect to positive control. Conclusion: Carbendazim in toxic dose level (1/5 LD₅₀) is not caused oncogenic effects in liver cells of rats ("NDEA-hepatectomie" test) and demonstrated slight cytotoxicity in rat hepatocytes (micronuclei test). That is why it is necessary to continue our investigation in low dose levels in order to find no observed effect level.

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**CONTAMINANTS IN ENVIRONMENTAL
SAMPLES FROM RESIDENTIAL AREAS
IN SUMGAYIT, AZERBAIJAN**

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Azerbaijan is one of the independent republics of the former Soviet Union (FSU). Like other recent members of the FSU, Azerbaijan is struggling with economic, social, and political changes as it adapts to global market economy. At the same time, Azerbaijan is faced with severe pollution problems as a result of environmental practices during the Soviet era. The detected high level of environmental contamination in Sumgayit is due to petroleum hydrocarbons as a result of

centuries of oil exploration, transportation, and refining. In addition to the detected petroleum hydrocarbons, other chemical contaminants include pesticides, heavy metals, and other industrial products and by products. The main focus of this study is to determine if the environmental contaminants being detected in the soil, sediments, and water are being detected in the human and wildlife communities residing near the industrial complex. In addition to quantifying the suspected contaminants of concern (COC), other goals of the research are identifying possible emission and transport mechanisms and determine if the detected COCs are at levels that could cause possible risk to the exposed populations.

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**IMPACT OF DISTANCE OF RESIDENCE
OF MOTHERS FROM HAZARDOUS
WASTE SITES(HWS) ON THE
BIRTHWEIGHT OF THEIR
NEWBORNS.A SLOVAKIAN PILOT
STUDY**

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HWS are a big reservoir of hazardous substances with a potential of impact on human's health. This problematic is poorly studied in Slovakia. Pregnant women and their fetuses are especially vulnerable. The objective of this study was to create a methodology for evaluating the relationship between the distance of mother's residence from HWSs and a chance of having a low-birthweight baby.

We used data on birthweight of newborns and on mother's residence from the Slovakian birth-registry for years 1997-2002. We have chosen three HWS and we included every birthweight from our database being within 10km around the three HWS included. GIS were used to localize HWS and mother's on the map. The birthweights and the corresponding mother's residence-information from the registry were extracted and the distance of mother's residence has been applied as a surrogate for exposure because of lack of exposure data. We computed correlation coefficients(CC) for the distance of mother's

residence and the birthweight of their newborns both as continuous variables. As an additional analysis CC for the distance of the settlements from HWSs and the rates of low-birthweight in the settlements included as a dependent variable has been carried out (we considered birthweight below 2500g as a low birthweight). By analysing birthweights as a continuous variable we computed a CC=0,035 statistically significant ($p=0,000$, $N=12314$). Based on this we could say that there is an extremely small risk to deliver a baby with a lower BW when the mother lives closer to one of the HWS included in the study as compared to those living further. By correlating rates of low-birthweight in the settlements to their distance from the HWS we computed a CC=0,099 statistically not significant ($p=0,445$, $N=62$). We could say that in settlements closer to one of the HWS included in the study are the rates of LBW lower as compared to those living further. Because of the design of the study and data protection issues we did not have data to control for confounding factors. This fact decreases further the significance of the study.

Although the statistical significance of the results is very limited, the study achieved its objective by raising awareness concerning the topic. Under conditions of Slovakia where limit based evaluation is still the major method for environmental health issues, this is an important benefit. The study also serves as a knowledge base for further studies in the field.

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**THE STATE OF SKIN IN THE
CONDITIONS OF INFLUENCING OF
NATURAL AND SYNTHETIC IRRITATING
AGENTS**

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Irritating agents repeatedly used in a war-time. Use of the special irritating compounds with a military purpose, but not as to the means of conduct of battle actions, and now does not conflict with Convention on the prohibition of the development, production, stockpiling, and use of chemical weapon. In a current time,

due to the toxicological properties, irritants are known as the effective so-called "constabulary gases" or riot control agents intended for preventing and stopping of mass civil disturbances.

The mucous membrane of eyes, nose and respiratory tract are the primary organs affected by irritants. The opened areas of skin are also often involved. Influence of irritating agents on a skin shows up the signs of its inflammation, sometimes with formation of oedema and also accompanied by sensation of pain. Among synthetic irritating agents CR (dibenz[b, f]-1, 4-oxazepine) differs as the most expressed pain effect on a skin. Researches of Capsaicin, which is irritant of natural origin, are in proceeding. At creation of new, more effective irritating wares, the basic requirement must be harmlessness for the health of their active components.

We studied in a comparative aspect the toxicological indexes of the specific influence on the skin of such irritating agents as Capsaicin and CR, and also morphological consequences in areas of skin hit by these compounds.

The estimation of comparative activity of Capsaicin and CR was conducted coming from the value of EC_{50} – concentration which caused primary erythema of skin in 50% experimental animals. It is necessary to mark, that an account was conducted only for those animals in which a positive reaction appeared during 3 - 5 minutes from the moment of application of irritant. To conduct the experiment it was used such methodical approach which enough exactly allowed to adhere to the identical closeness of irritant for different animals. Such dilutions of substances were tested, that their closeness on a skin increased from 0,002 to 1,000 mg/cm².

It was determined, that by ability to cause primary erythema of skin the middle-effective concentration of CR was equal to 0,015 mg/cm² and of Capsaicin - 1,010 mg/cm². Comparing the noted indexes of EC_{50} it is necessary to specify on higher activity of Capsaicin. However these divergences were not of much substantial value.

These results found the confirmation at pathomorphological researches. Morphological researches were executed on white rats. There were used those areas of skin of animals on which solutions of

Capsaicin and CR were inflicted with the closeness of 0,100 mg/cm². The noted closeness was such which caused primary skin erythema practically in all experimental animals. Supervisions conducted in a dynamics in 3 hours, 1 and 10 days after the application of irritant.

After post-mortem examination in internal organs and cavities of animals, and also in places where studied substances were inflicted, in the noted terms of supervision, there were not macroscopically discovered pathological changes.

On survey preparations of skin in 3 hours after the application of Capsaicin there were not microscopically determined any dystrophic changes and haemodynamical violations. Approximately the same morphological picture registers in the skin of animals, which was explored in 1 day after the application of Capsaicin.

In animals on which skin CR was inflicted and explored in 3 hours, destructive changes and circulative violations were not observed. At the same time, in parts of experimental animals were defined the hearth changes of architectonics of the organ, epidermis and upper layers of derma compressed in a "accordion", that resulted in expressed disorderly wrinkles. Such phenomenon, possibly, is connected with reduction of muscular fibres of skin. It is confirmed by absence of such violations in a skin after 24 hours. At the same time in derma of animals hit by Capsaicin and CR, there was an increase of amount of cellular elements, which testifies to irritating effect of studied substances.

Thus, conducted researches of irritative action of Capsaicin and CR on skin of animals confirm the presence of high specific activity of the studied irritants. Moreover, at influence on a skin, the substance of natural origin Capsaicin surpasses by its specific potential the most drastic among known synthetic irritants CR. Morphological data testify to absence of organic violations in hit by Capsaicin and CR areas of skin, which determines possibility of creation on the basis of the noted compounds of potential special one component or combined irritative riot control agents.

HEART RHYTHM AND CONDUCTIVITY DISTURBANCES AT DISINFECTORS

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Insecticide facilities are widely used presently for implementation of fumigation and deratization. Formulations on the basis of pyrethroids - cypermethrin, permethrin and OPS – chlorpyrifos are widely used.

The changes of different ionic currents and conductivity lie in basis of normal heart electrogenesis and automatism. The last researches in area of electro-physiology and clinical cardiology exposed high meaningfulness of Na²⁺, Ca²⁺ and K⁺ of channels violations in myocardial cell in forming of arrhythmias.

It is described, that pyrethroids are another class of substances, influencing on modification of process of rapid sodium channels closing, able to block reduction, cause positive inotropic effects and contractions, violations of rhythm and conductivity. Ability of OPS to render the nonanticholine-esterase influencing, showing up in co-operating with ion potassium and by calcium channels, mainly related to N-CR, extending the electric systole of ventricles and interval of Q-T is presently confessed.

175 disinfectors (22-55 years old) were inspected in age, having a working contact with insecticides on the basis of pyrethroids - cypermethrin, permethrin («Sipaz-Super», «Arrivo», «Ribor», «Riapan») and OPS – chlorpyrifos («Chlorpyrimark», «Effect-Plus») with the purpose of finding of rhythm and conductivity disturbances. Method of electrocardiography in the 12 generally accepted leads with determination of corrected Q-T interval.

The purchased phenomenon of the extended Q-T interval (more than 0.440 sec.) is exposed at 59% of cases. It is set that at cases as compared to ones without the extended Q-T interval, arrhythmias confidently more frequent at 54% against 13% (p<0.05). At the persons of the same age group, not contacting with insecticide matters this disturbances were found much rarer.

Thus, the increase of duration of corrected Q-T interval was observed more than in

59% cases. Appropriate connection is traced between lengthening of Q-T interval and rhythm and conductivity disturbances frequency. The acquired lengthening of Q-T interval is arrhythmogenic substratum and correlates with insecticides expressed cardiotoxic effect.

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PREVALENCE OF CHRONIC CARDIOVASCULAR DISEASES IN A MINING AREA OF ROMANIA (ROSIA MONTANA)

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In Romania, cardiovascular diseases remain more prevalent than in the European Union. Relatively high rates of smoking, alcohol consumption, lack of exercise and a diet high in animal fats and low on fresh fruit and vegetables are direct contributory factors. The cardiovascular mortality rates (rates per 100000 inhabitants) at the country level in 2003 were 749.8 for males and 773.8 for females. At a European level, Romania's ischaemic heart disease mortality is comparable with a broader group of new EU member countries, such as Hungary, Slovakia, Poland and the Czech Republic. As regards the cerebrovascular diseases for all ages, these are particular problems in Romania, Latvia and Bulgaria. Rosia Montana area is located in west-central part of Romania (Alba county), in a mining district known as the Golden Quadrilateral of the Metaliferi Mountains. The Golden Quadrilateral was for more than 2000 years, the most productive auriferous area in Europe. The cardiovascular morbidity data (ICD10 codes I10-I15; I20-I25; I26-I28; I30-I52; I60-I69; I70-I79) collected from all family doctors (general practitioners) of an 120 square km area were processed as prevalences and represented using a Geographic Information System in order to get a spatial distribution of the investigated diseases. In general, Rosia Montana showed higher prevalences than other locations. Also, higher OR (for the above mentioned codes) have been recorded within the population living in Rosia Montana as compared to the

population from the other investigated localities, both, for localities with large and small numbers of inhabitants.

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**THYMUS HYSTOARCHITECTONICS AT
WISTAR RATS AT ACUTE
INTOXICATION BY 2,3,7-
TRICHLORODIBENZODIOXIN**

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The group of polychlorinated aromatic hydrocarbons is among the most toxic chemical substances is at the increasing attention of researchers [Tsyrllov I.V., 1990, Geyer H., Scheunert I., Kort F., 1987]. Among 75 isomers of polychlorinated aromatic hydrocarbons it is the most good investigated and the most toxic - 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). However alongside with 2,3,7,8-TCDD there is a wide spectrum of PCDD isomers which toxic action on an organism of mammals is investigated insufficiently. In the submitted work studying of thymus hystoarchitectonics at Wistar rats is carried out on a background of peroral administration of LD₅₀ of 2,3,7-trichlorodibenzo-p-dioxin (2,3,7-TriCDD).

Objects and methods of research. Object of research were white male Wistar rats (145-200 g body weight) which contained in vivarium at common diet. Experimental model was the pathological process developing in an organism of rats at intragastric administration of 2,3,7-TriCDD in doze of LD₅₀. For work solutions 2,3,7-TriCDD in the sunflower oil preliminary cleared with the help of activated coal are used. In dynamics the measurement of absolute animals body weight was carried out, and also thymus weights and the relative weight of this organ - mass factor was calculated. Morphological researches were carried out in dynamics at 1, 3, 7, 21, 30, 60 day after administration of 2,3,7-TriCDD. Morphological researches of thymus were done using survey histologic painting by hematoxiline-eozine (Lilly P., 1969) after fixing in neutral formalin with pouring in paraffin in the usual way.

The received results and their discussion. Detection of acute toxicity of 2,3,7-TriCDD has shown, that middle death doze at unitary intragastric administration to Wistar

rats was 32.0 ± 10.25 mg / kg. That 2,3,7-TriCDD is in 60-500 times less toxic for rats, than 2,3,7,8-TCDD (Poland A., Glover E., Rnutson J., 1985). Thus on a background of progressing reduction in body weight of rats at acute intoxication of 2,3,7-TriCDD progressing reduction in absolute and thymus relative weight was observed also. So for 7 day of intoxication the thymus absolute weight at tested rats was in 3.6 times less, than at controlled animals. Sharp distinctions between thymus weight at tested and controlled rats were kept for 14-21-30 day of supervision (reduction was 3.0; 3.0; 2.6 times, accordingly), and even for 60 day of an intoxication the gland absolute weight was in 1.7 times less, than at control animals. Accordingly, distinctions of thymus mass factor were very sharp. It agrees to the data of morphological researches at rats at acute intoxication by 2,3,7-TriCDD in thymus quickly developed expressed hypoplasia of lymphoid parenchyma: from pauperization of cortical substance of lymphocytes and its thinning up to becoming desolate. Reduction of lymphoid parenchyma body was accompanied by increase in the sizes of epithelial corpuscles in medullar substance, strengthened macrophage reaction and proliferation of stromal elements. Attributes of restoration of thymus structure, shown in occurrence of lymphocytes congestions in subcapsule areas of separate lobules, were observed only for 30 day of intoxication.

Conclusion. Summarizing the received results about a thymus tissue condition of animals at acute intoxication of 2,3,7-TriCDD, it is possible to draw conclusion that this polychlorinated dioxine is similar to TCDD and some other dioxins (1,2,3,4,6,7,8-Hepta - CDD and 1,2,3,7,8-Penta-CDD) renders the expressed influence on thymus, causing development of accidental involution (Kerkvliet N.I., Brauner J.A., 1987; Greenlee W.F., Dold K.M. and Irons R.D., 1984).

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**USE OF WILD PLANTS FOR
DETOXICATION CHLORORGANIC
PESTICIDES IN SOIL**

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In Kazakhstan, clean up or remediation of land polluted by obsolete pesticides is a serious problem. Most physical and chemical technologies for cleaning soils polluted with pesticides are too expensive for countries like Kazakhstan. Phytoremediation is a promising group of innovative technologies that may be both effective and relatively low-cost compared to other remediation options. Phytoremediation uses vegetation to accumulate, degrade, or stabilize environmental contaminants. Most pesticide storage warehouses from the collective farming system of the former Soviet Union have been destroyed leaving the stored obsolete pesticides and their containers unattended and open to the environment. Land near these former warehouses has become "hot points" of contamination and represent a serious ecological danger. The goal of our research is to develop phytoremediation technologies for "hot spots" contaminated with obsolete pesticides and to study mechanism of plant facilitated detoxification of pesticides. In a series of experiments under greenhouse conditions, we estimated the accumulative ability of dominant plant species that naturally colonize contaminated soil near a former pesticide warehouse. Soil collected from three contaminated sites, called 'hot points' one, two or three, were characterized by high concentrations of pesticide mixtures and fertilizers. The greenhouse study compared treatments of different plant species grown in contaminated soil from each of the three hot points with an unplanted control from each hot point. Accumulation and distribution of pesticides in the soils and plants was used to estimate pesticide mass balances. Soil sample analysis showed pesticide contamination included metabolites of DDT (2,4 DDD; 4,4 DDD; 4,4 DDT; 4,4 DDE) and isomers of HCH (α - HCH; β - HCH; γ - HCH).

Concentrations of these compounds exceeded limits of Kazakhstan's maximum acceptable concentration (MAC) (most of the chlororganic MACs are 100 $\mu\text{g}/\text{kg}$). In this study, soil treatments without vegetation resulted in residual pesticide concentrations at the end of the trial that varied from 48,37% to 59,25% of initial pesticide concentrations at the beginning of the trial. Soil treatments with vegetation resulted in decreased pesticide concentrations ranging from 21,89-58,19% for hot point one, 27,56-79,72% for hot point two, and 33,53-58,38% for hot point three. The study established the process of uptake of pesticides from soil to of plant tissue directly dependent on their initial concentration in the soil and the mass of plant tissue. From 13 investigated species, *Solanum dulcamara* showed the highest biomass production (0,58 kg) and possessed the ability to accumulate up to 176,96 μg (1,21 %) pesticide in plant tissue. *Xanthium strumarium* produced 0,01 kg biomass and accumulated 13,1 μg (0,36 %) pesticides in plant tissue. This information can be used for technology development of phytoremediation of soils polluted with pesticides.

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DERMAL EXPOSURE: MOVING BEYOND QUALITATIVE ASSESSMENT

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Quantitative understanding of the contribution of external dermal exposure to internal dose is lacking for occupational and environmental exposure scenarios. The main limitation has been the lack of reliable measurement techniques and data for dermal exposure and quantitative risk assessment. Thus, standardized methods for dermal exposure and risk assessment are non-existent. We have developed quantitative tools to measure dermal exposure and investigation of the contribution of dermal and inhalation exposure to jet propulsion fuel 8 (JP-8) to the total body dose of the U.S. Air Force fuel-cell maintenance workers using naphthalene as a surrogate marker for JP-8

exposure. We have also developed a PBTK model that quantifies the relationship between external environmental measurements and biological markers of human exposure to JP-8. These studies underscore the importance of the dermal route for exposure assessment in occupational, epidemiological, and toxicological studies. By understanding the relationship between human exposure to harmful chemicals and internal dose metrics, the PBTK model may be used to integrate complex chemical exposure and biomarker data into an improved assessment of human health risks. Future work on dermal xenobiotic metabolism and toxicokinetic studies are warranted in order to gain additional knowledge on individual differences in the metabolism of xenobiotics in the skin and the contribution to systemic exposure and risk.

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EFFECTS OF ARSENIC EXPOSURE FROM DRINKING WATER ON RESPIRATORY ILLNESSES IN A BANGLADESH POPULATION

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Arsenic from drinking water has been associated with many adverse health outcomes including malignant and non-malignant respiratory illnesses. Several studies reported higher prevalence of chronic obstructive pulmonary disease (COPD), chronic cough, chest pain and other respiratory symptoms among people drinking arsenic contaminated water and with visible skin lesions. In majority of these studies, the assessment of respiratory symptoms was based on self-report or clinical evaluation of individuals with other visible arsenical skin lesions, thereby may have been biased. In this study, using several biomarkers for arsenic exposure and chronic epithelial lung damage (i.e.,

Clara cell protein 16) we have examined the respiratory effects of arsenic in a group of non-smoking people (N=241) who have been chronically exposed to a wide range of arsenic (0.1 µg/l to 761µg/l) from drinking water in Bangladesh. Overall, we have observed an inverse association between serum Clara cell protein 16 (CC16) and urinary arsenic ($r=-0.11$, $p<0.07$) in this population. Logistic regression analyses revealed a dose response association between CC16 and urinary arsenic (OR=1.46, CI: 1.006-2.12, $p<0.04$) for trend of increasing dose. Linear regression analyses also showed strong associations of serum CC16 levels with urinary ($\beta=-0.13$, $p<0.01$) and cumulative arsenic index ($\beta=-0.04$, $p<0.06$) among individuals with arsenical lesions. We have also observed strong associations between CC16 and secondary arsenic methylation index (SMI = DMA%/MMA%) ($\beta=0.12$, $p<0.05$) in this population, indicating that individuals with increased methylation capability are at reduced risk of arsenic-induced alveolar epithelial damage. In a subset of individuals on whom we obtained spirometric lung function measures (N=31), we observed strong associations of urinary arsenic with predictive FEV1 ($r=-0.37$, $p<0.03$), FVC ($r=-0.35$, $p<0.04$) and FEV1/FVC ratio ($r=-0.36$, $p<0.04$). Our data also show strong negative association of FEV1/FVC with primary arsenic methylation index ($r=-0.42$, $p<0.01$) and positive association with SMI ($r=0.29$, $p<0.1$). This is the first study that used a novel biomarker for epithelial lung damage and has demonstrated the effects of arsenic exposure on respiratory illness at a lower concentration than earlier studies.

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ENHANCED REMEDIATION OF DNAPL-CONTAMINATED SUBSURFACE ENVIRONMENTS

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The Superfund program in the United States is focused on reducing risk to human and ecological systems caused by exposure to

chemical contaminants, which most frequently result from sources existing beneath the Earth's surface. Subsurface contamination caused by dense nonaqueous phase liquids (DNAPLs) are not only the most common class of contaminants found within Superfund sites but are the most challenging to remediate. These contaminants, which include trichloroethylene (TCE), tetrachloroethylene (PCE), and polynuclear aromatic hydrocarbon (PAH) mixtures, such as coal tar and creosote, are both a long-term source of groundwater contamination and are assumed to pose a health risk to humans at low concentrations. Thus, the quest for an effective DNAPL remediation strategy is an important environmental goal and motivates this work on physicochemical remediation approaches. We report on a variety of experiments to investigate brine-based remediation methods. In this approach, a dense brine solution is injected into the subsurface to control the movement of a DNAPL contaminant. Mobilization of the DNAPL is then accomplished by injecting solutions such as surfactant or cosolvent mixtures, or lowering the water table, to overcome the capillary forces that trap the DNAPL in an initial stationary state. Once mobilized, the DNAPL is removed from the top of the brine barrier. A tertiary removal process of vapor extraction is also explored. Our results demonstrate a high rate of removal in controlled laboratory studies for a variety of systems. Mathematical modeling is also used to demonstrate the behavior of these complex systems.

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PUBLIC ATTITUDE TO ENVIRONMENTAL PROBLEMS AND ENVIRONMENTAL HEALTH: CASE FROM POLTAVA, UKRAINE

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Effective environmental health and protection programs depend on developing and utilizing constantly traveled communication bridges, connecting a wide variety of groups and agencies involved [1]. From that perspective public involvement in

a process of environmental decision making, strengthening public access to information and level of education are among priorities, in particular across Eastern European countries where limited traditions exist in these issues [2]. We have researched public attitude to environmental problems and environmental health in Poltava region, Eastern Ukraine. This area is typically agricultural with constantly reported environmental threats caused by agriculture (soil erosion, water and soil contamination, biodiversity loss) reflected in aggravation health state of inhabitants. Among regional environmental problems a negative impact of warehouse of obsolete pesticides is essential: region rates third position across the county in terms of DDT loan per inhabitant recently estimated as 0,055 kg/per person [3]. We investigated soil and water contaminations close to obsolete pesticides places in two selected places. An intensive contamination of soil by DDT and products of it's decomposition was fixed, and the highest concentrations were shown at the distance of 1 m from storages. Surface water samples from closely located small river were also tested and water contamination by chlororganic substances were fixed [4-5]. The obtained results of contamination of soil and water tests were presented for local community. The fact of interconnection between water and soil contamination and health problems was discussed. Surveys of women in childbearing age were accomplished in two rural communities in Poltava region in order to investigate to which extend women understand the influence of environmental contamination as potential threat to the health. Results from one rural community indicated that women were not strongly concerned with pesticide exposure and there was a little environmental awareness. The attitude to environmental health problems in another rural community where results of water and soil contaminated were preliminary presented was different from first ones. High awareness raising was fixed among inhabitants at the second rural community which was resulted in cleaning up of one obsolete pesticides storage by local activists.

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THE SANITARY LEGISLATION IN UKRAINE IN THE SPHERE OF TOBACCO CONTROL

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The analysis of results of many years control for levels of tar and nicotine content in the tobacco production in Ukraine witnesses about the tendency to the increasing the specific weight of cigarettes with relative low content of tar and nicotine both in the imported and home origin production.

The levels of content the organochlorines and organophosphates pesticides, dithiocarbamates, synthetic pyrethroids, derivatives 2,4-dichlorophenoxyacetic acid and radionuclides in tobacco raw materials as well as in the tobacco rim cigarettes does not exceed maximum allowed doses.

It is necessary to do the toxicological and hygienic regulations of the other chemical compounds, which are present in tobacco smoke.

This in the first place concerns to monooxide carbon, compounds of nitrogen and benz-a-pirene. It is elaborated the approaches to scientifically substantiation of hygienic standards of content the mentioned substances in tobacco smoke, as well as chemical-analytical methods of control.

In Ukraine it is acting the sanitary legislation in the sphere of the tobacco control. This legislation regulates not only the maximum allowed levels of tar and nicotine content in the cigarettes, but as well as a number of the other indexes of safety of tobacco production for health of men. In particular:

- the maximum allowed levels of pesticides and radionuclides in tobacco, raw materials and its mixtures, used in the process of production the tobacco products, as well as in the tobacco strap cigarettes (for sell);
- the allowed levels of migration the toxic compounds from materials for the production the tobacco products (cigarettes rims, pasteboard and packing paper, cardboard, filter cigarette holder, foil, glue, paint, polymers and other materials and products) used for their production;
- the recipe of sauces and the aromatic compositions of tobacco (the content-

composition, relationship of separate compounds, materials and products, including the synthetic and natural origin), their conformity to home-origin and the international requirements.

The project of sanitary requirements to tobacco products and sold in Ukraine was scientifically substantiated and proposed to the approval.

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DIETARY FATTY ACIDS: NUTRITIONAL MODULATORS OF CANCER RISK

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Humans in modernized countries are increasingly exposed to environmental pollutants and contaminants that can increase the risk of human diseases such as cancer. Moreover, as the prevalence of obesity in these developed countries continues to grow at alarming rates it has lead to mounting concerns as to how nutrition modulates the risk of chemical-induced carcinogenesis. A contributing factor to the growing obesity epidemic is the disproportionate intake of calories from fat. Historical records have shown that Western countries have significantly altered their intake ratios of ω -6 and ω -3 polyunsaturated fatty acids (PUFA) from 2:1 to 15:1. Epidemiological and experimental data have linked a high dietary intake of ω -6 PUFA to increased risk for cancers of the breast, colon, and possibly prostate while intake of ω -3 PUFA are protective. A postulated mechanism for this observed difference between the two dietary fatty acids is their ability to modulate the cellular oxidant/anti-oxidant status. It is known that PUFA can lead to increased production of oxidants through several mechanisms which include lipid peroxidation and inflammation. Thus, we hypothesize that ω -6 PUFA contribute to carcinogenesis by modulating the production of reactive oxygen species, DNA damage and repair. To determine whether PUFA can modulate cellular oxidative stress, male C57BL/6J mice were

administered a high fat diet (23.5% from fat) containing corn (ω -6 PUFA) or fish oil (ω -3 PUFA) for up to 3 weeks. Oxidative stress and DNA damage in liver was evaluated by a panel of sensitive markers that included gene expression profiling, expression of base excision DNA repair (BER) genes, quantifying oxidative lesions in genomic DNA, and measuring lipid peroxidation. Gene expression profiling revealed that a diet rich in fish oil resulted in a significant increase in a number of anti-oxidant genes compared to low-fat control diet that was not observed with a diet rich in corn oil. Conversely, corn oil did lead to a significant accumulation of 8-hydroxy-deoxyguanosine (8-OH-dG) adducts with a concomitant 3- to 4-fold increase in expression of the BER genes, uracil DNA glycosylase and AP endonuclease 1. Interestingly, the fish oil diet resulted in a significant reduction in the number of 8-OH-dG adducts compared to control diet with no increase in expression of BER genes. Collectively, we have demonstrated that diet can modulate cellular oxidative stress and oxidative DNA damage. Many environmental contaminants exhibit human disease and toxicity through oxidative-stress signaling pathways. In this context, PUFA may exacerbate or attenuate chemical-induced carcinogenesis and warrants further study as its implications for human health could be significant.

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ALTERNATIVES OF DANGEROUS WASTE HANDLING

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The dangerous wastes may have a severe impact on ecology and human health. The Stockholm convention has defined the functions for EEC to provide application of the best practical means and the environment preservation technologies preventing the formation and the escape of persistent organic pollutants (POPs).

The ecology and medical safety of methods used in Ukraine has been analyzed on the base of sanitary-chemical investigations for the safe handling with domestic waste chlorine-containing, useless and banned pesticides (UBP) and transformer oils containing polychlorinated biphenils.

The repacking method with long-time preservation is of considerable current use in Ukraine for useless and banned pesticides. It should be noticed that this approach is a very relative solution stemming for lack of universal packing material and warehouses corresponding to ecological and sanitary standards of the monitoring system and involves huge investment. With the aim of the risk reduction at using of waste handling methods, the methodical recommendations for warehousing and treatment of the contaminated objects were derived.

The thermal method of waste destruction is practised extensively in present time. The numerous tests of ground, air, water and sewage taken from the territories nearest to destructor factories are evidence of contaminations by toxic wastes. As it was shown that POPs level (five isomers of tetrachlorodibenzo-p-dioxins and seven polychlorinated biphenils (di-, tri-, tetra-, penta-, hexa-, hepta-chlorobiphenil) of hard domestic waste burning in smoke before the electro-filter was $0.13 \times 10^{-9} - 7.3 \times 10^{-4} \text{ mg/m}^3$ and after the electro-filter – $0.07 \times 10^{-9} - 5.6 \times 10^{-9} \text{ mg/m}^3$ and $4.4 \times 10^{-4} - 6.7 \times 10^{-4} \text{ mg/m}^3$, POPs level in sewage was $5.8 \times 10^{-8} - 7.7 \times 10^{-8} \text{ mg/dm}^3$ and $5.8 \times 10^{-4} \text{ mg/dm}^3$. Besides, the problem of the mud recovery (20% total waste mass), requires a solution for the each case taken separately, not only pentachlorinebiphenils ($3.4 \times 10^{-2} \text{ mg/kg}$) but also heavy metals were discovered in amongst the contained ingredients, that is an indicator of the environment pollution.

The multicircuiting high temperature pyrolysis technology has been implemented at one factory, however it's power does not allow to remove all available dangerous wastes in Ukraine. In processing of removal, provision was made for pyrolysis gases purification from the second toxic pollutants in an absorber with quicklime, accompanied by heating up to temperatures 1200-1300 °C with purification by the 30% caustic sodium solution in gas-purifying camera. The results of joint work for improvements in technological regime indicate that the level of the second toxic pollutants at removing PHB and UBP was corresponding to the European standards (total amount of PCDD and PCDF does not exceed 0.06 ng/m^3). The other toxic substances SO_2 , CO , HCl , NO , NO_2 do not exceed limited (safety) concentrations in air.

There are industry technologies for the POPs waste-sources removal different from thermal method such as gas phase recovery (GPCR), basic catalytic decomposition (BCD), sodium reduction (SR), oxidation to extrawarm water (SCWO).

An analysis of these technologies and assessment based on data of distroyment ratio (DE), distroyment ratio and removment (DRE) are evidence of their efficacy in processing of the POPs removal and neutralization. Unfortunately up to now are not finding increasing use in Ukraine.

These alternative technologies prevent not only the formation and the unpremeditated POPs pollution but also provide explicit costs decrease in comparison with using of waste destructors equipped by not least modern monitoring devices.

Based on the alternatives stated above and analysis of methods used in Ukraine the waste handling system demands improvement both the executive power level and the legislative level in accordance with international standarts.

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**CLINICAL AND EXPERIMENTAL STUDY
OF TOXIC METHAEMOGLOMIEMIA
PECULIARITIES DUE TO ACUTE
HYDROXILAMINSULFATE POISONING**

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Peculiarities of toxic methaemoglomiemia formation in 154 patients with casual acute peoral hydroxilaminsulfate poisoning were studied. Mechanisms its toxic action in experiments using rat model also were studied. Main simptoms of acute poisoning with this xenobiotic in patients were headache, dizziness, weakness, nausea, vomiting, acrocyanosis, tachycardia, pain in the right hypochondrium, shortness of breath. In the majority of patients (96,1%) increased level of methaemoglobin (Mt Hb) was revealed, which was between 4% and 47%, its level was normalized in 2-3 days, but moderate acrocyanosis and shortness of breath during moderate physical activity most of patients were noticed for 7 – 10 days.

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**OVERVIEW OF EU, US, RUSSIAN AND
UKRAINIAN LEGISLATION ON GMO**

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Over the past few years there were a lot of discussions on GMO legislation in a number of countries all over the world. These discussions focused almost exclusively on genetically modified foods and tried to answer questions how to handle genetic modified organisms and whether there is a need to have a system of identification or labelling.

The main questions in relation to labelling includes:

1. should the system be voluntary?
2. which GMOs or products of GMOs have to be labelled?
3. what should be the content of the statement of identification or labelling?
4. what are the methods of detection and verification?

A number of countries, such as EU, Russian Federation, introduced new rules or strengthened old ones regarding requirements to identify or label genetically modified organisms and products. The most interesting examples were summerized in presentation.

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**STRUCTURE-TOXICITY RELATIONSHIP
FOR NEONICOTINOIDES**

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The experimental study of acute toxicity effects of new chemicals compound is a time-consuming process. Moreover it is a very expensive procedure. The increasing quantities of chemical compound with pesticide activity needs to improve the principles and methods of prognosing of pesticide toxicity.

Structure-activity relationship (SAR) provide a useful tool for defining a mathematical relationship between chemical structure and toxicity. QSAR have been evaluated for predicting acute (LD₅₀) and chronic toxicity

(NOEL_{chr}) of new insecticide class-neonicotinoides. The initial toxicological data for rats (LD₅₀, NOEL_{chr}) have been taken from accessible literature. As an independent variables in regression procedure we used parameter's describing lipophilicity, quato-chemical characteristics and geometric peculiarity of selected molecules.

We have received new data about relationship between toxicity of neonicotinoides and parameter's what may influence on the toxicodynamic and toxicokinetic process. Acute and chronic toxicities indices (LD₅₀, NOEL_{chr}) correlated with molecular mass, shape and volume of molecules and lipophilicity.

Obtained relationship may be useful for more accurate selection of dose level in acute and chronic experiment in studies toxicity of new neonicotinoides.

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THE CHEMICAL AND ANALYTICAL ASPECTS OF POLYCHLORINATED DIBENZODIOXINS AND OTHERS PERSISTENTS ORGANIC POLLUTANTS

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In Stockholm Convention on Persistent Organic Pollutants (POPs) by a term the «matter» is marked both individual compound and group of similar compounds. Therefore the concept “dirty dozen”, to which it is often operate at denotation of the POPs number, included in Stockholm convention, not correct. The common number POPs, being the object of Stockholm Convention, makes 36 compounds at least (8 pesticides, 7 polychlorinated dibenzodioxins (PCDDs), 10 polychlorinated dibenzofurans (PCDFs) and 11 polychlorinated biphenyls (PCBs).

Lately in scientific literature at the discussion of different problems related to POPs, the concept of “dioxin and dioxin-like compounds” is widely used. This by a conception unite PCDDs, PCDFs and PCBs. Consideration of structure of the PCDDs, PCDFs and PCBs molecules allows to do a conclusion, what only in regard to PCDDs and PCDFs can be spoken about some structural similarity, as in formation of these tricyclic compounds,

along with identical structural elements (by benzol rings) participate oxygen containing heterocycles: six-article heterocycl 1,4-dioxin containing two atoms of oxygen (PCDDs), and five-article heterocycl furan, containing one atom of oxygen (PCDFs). Presence of exactly these structural elements (atoms of oxygen, connecting chlorine substituted benzol rings), and results in extreme toxic of these compounds and above all things to extreme toxic PCDDs. PCBs in a difference from PCDDs and PCDFs are bicyclic chlorine substituted aromatic hydrocarbons two benzol rings of which are connected by simple carbon-carbon bond, in this connection the structure of their molecules very substantially differs from the structure of the PCDDs and PCDFs molecules.

In the lecture the methods analysis of the PCDDs, PCDFs, PCBs and others POPs are examined and possibilities of organization of monitoring of dioxins and other POPs in Ukraine are discussed.

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EFFECT OF IMIDAKLOPRID ON ANIMAL BEHAVIOR REACTIONS

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Imidakloprid is a widely used insectoacarycide in crops farming. The main mechanism of its technical action is damage to nerve system.

An aim of the study was characterizing of Imidakloprid (96,5%) effects on behaviour reactions of rats at oral admission (90 mg/kg by weight, 2 months). The study was made on Wistar male rats. The control group contained intact rats (without Imidakloprid affect). Animal behavior was evaluated in Halls “open field”. Studied characteristics: latent period of the start of animal moving (sec), amount of crossed squares (conventional units), emotional reactivity (defecation, washing) and “hole” reflex (the amount of peeping in “holes” during 3 minutes). We have used the automatic device “Labyrinth” for the evaluation of rat behavior on the following characteristics: vertical activity (VA), total horizontal activity (THA), directed horizontal activity (DHA) and integral activity index

(IAI). We found an increase of latent period (56,2 %), decrease of amount of crossed squares (54,85%) and tendency to decrease VA (34%), DHA (55.3) and IAI (44%). Study of "hole" reflex found decrease of amount of peeping in "holes" (37,9%). Other parameters deviation was insignificant.

The data show that Imidakloprid cause weak inhibition of nerve system reactivity at these experimental conditions (90 mg/kg by weight, 2 months).

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METHODICAL APPROACHES TO THE ESTIMATION OF HARMFUL ACTION OF CHEMICAL SUBSTANCES ON THE NERVOUS SYSTEM

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It is known that many pesticides, widely used in agriculture (organophosphor and organochlorine, synthetic pyrethroids, neonicotinoids, etc.), render the toxic effect on the central and peripheral nervous system of organism. It is shown that in a number of cases, indexes of the state of the nervous system are most criteria at the estimation of their toxic action. Presently for the estimation of harmful action of chemical, including pesticides, the enormous arsenal of methods of researches is used. However, in connection with the intensive work and protracted preparation of experiments on the study of functional activity of the nervous system, some authors are limited to only the separate indexes, that do not give the complete picture of its state and does not allow objectively estimate the xenobiotics danger for man. In this connection, it is actual to perfect approaches to the estimation of harmful action of xenobiotics on the nervous system on the stage of their toxicological and hygienic regulation. Long-term experience of pesticides researches on indicated issue allows to formulate some general and local provisions which must be taken into account in a toxicological experiment. For the toxicological and hygienic estimation of chemical substances an especially important value is a study of behavioral reactions of animals, because a behavior is not only the indicator of specific sensory

and motor reactions of organism but also integral index of the functional state of the central and peripheral nervous system. Behavioral reactions allow, from one side, to find out the neurophysiological mechanisms of toxic action of xenobiotics, from other, are criteria at the estimation of levels of thresholds of chemical substances, that is very important during their hygienic regulation in the objects of environment. In a toxicological experiment large set of methods of animals behavior studies is used, basis of which are food, defensive, orientational researching and sexual reflexes. Important, that the chosen methods were highly sensitive, adequate, and the explored indexes could be measured quantify. The method of the «opened field» conforms to these requirements from the simplest methods, developed C.S.Hall, and also the modified method of determination of reference reaction on outside court (Boissier J.R. with coauthors) – "mink" reflex of rodents. Along with these methods, other ones which are based on motive-defensive reflexes are recommended: T-shaped labyrinth with an electro-skin reinforcement, shuttle chamber, etc. For the estimation of influencing of matters on forming of track of memory it is recommended to use a method, based on the conditional reaction of passive avoidance (blow by an electric current - 50-60 Volt). Important advantage of this method is a quickness of making of reflex. For the estimation of the state of the peripheral nervous system and muscular capacity the plenty of tests is developed – retaining on a pole and rotation on a bar, running in tretbane, swimming, etc. Most informing is duration of swimming of rodents (mice, rats) and running in tretbane. To beginning of experiment, it is necessarily necessary to conduct the selection of animals and form homogeneous groups on initial indexes (background). Tests are carried out in the isolated room, in absence of extraneous persons, desirably by the same researcher. In every case, it is necessary to use complex of methods, allowing to estimate the different sides of activity of the nervous system (unconditioned and conditioned reflexes reactions, elementary rational activity, orientational researching forms of behavior, etc.).

EFFECT OF CARBOXYNE ON HAEMATO-LOGICAL PARAMETERS OF RATS

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The aim of this work was studying of subchronic effect of Carboxyne technical, 98% on morphological composition of peripheral blood of rats.

Materials and methods. Investigation was performed on male and female rats Wistar using unified clinical-laboratory methods. Carboxyne was administration into the stomach of rats at doses of 1, 10 and 100 mg/kg body weight during 3 months. The studies were conducted after 1, 2 and 3 months of treatment. We determined the hemoglobin level, red and white blood cells, MCH, reticulocytes, platelets and hemogram with the analysis of qualitative changes in cells morphology.

Results and discussion. Carboxyne at dose of 100 mg/kg body weight day in male rats' red blood caused decreasing of hemoglobin level during all periods of experiment. After 4 and 9 weeks were determined decreasing of MCH, after 13 weeks – reticulocytosis, poikilocytosis and weak hypochromia of red blood cells, increasing of platelets and neutrophilic leukocytosis. At female rats after 4 weeks were determined reticulocytopenia, after 9 weeks - decreasing of hemoglobin and MCH, weak hypochromia, after 13 weeks – poikilocytosis of red blood cells. Amount of red blood cells remained without the change. Administration of test material at dose of 10 mg/kg body weight caused analogical changes of parameters of peripheral blood of rats in a lesser degree with recovery in 13 weeks. Carboxyne at dose of 1 mg/kg body weight did not cause changes of the explored parameters of red and white blood cells. Thus, hematological researches showed that Carboxyne at 100 and 10 mg/kg body weight caused anemia with deranged of hemoglobin formation. Changes of parameters of white blood and of platelets had compensative character in reply to anemia.

THE ROLE OF EPIGENETICS IN INITIAL CARCINOGENICITY ASSESSMENT

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The rapid identification and appropriate regulation of human carcinogens before their dissemination into society are of prime importance for the primary prevention of neoplasia in humans. Two-year long-term *in vivo* carcinogenic test using rodents is generally considered as the most reliable method for the evaluation of carcinogenic potential in humans. However, advances in industrial technology have led to a surge in the number of new chemicals developed for a variety of purposes. Given that there are between 70,000 and 100,000 chemicals in commerce today, it is evidently impossible to apply such comprehensive *in vivo* carcinogenicity testing to the large number of compounds introduced into our environment. This clearly shows a crucial need for the development of new alternative assay for carcinogenicity testing, at least for the initial screening of variety of agents for carcinogenic potential. At present time cancer is recognized as a genetic and epigenetic disease. Furthermore, it is becoming evident that epigenetic changes play a crucial role in the origin of cancer. It has been hypothesized that alterations in epigenetic status induced by carcinogenic exposure and sustained by continuing replication in the cellular genome resulting in the emergence of epigenetically reprogrammed cells are indispensable preliminary events in carcinogenesis. These epigenetically reprogrammed cells are characterized by global demethylation of the genome, activation of DNA repeats, hypomethylation of proto-oncogenes associated with persistent proliferative activity, hypermethylation of tumor-suppressor genes involved in the cell-cycle arrest, and inactivation of DNA-repair genes. In other words, these cell populations display epigenetic changes similar to those observed in cancer cells, and detection of these epigenetic alterations may be used as early biomarkers for carcinogenicity. In the present study, by utilizing two well-established models of hepatocarcinogenesis representing genotoxic (tamoxifen-induced hepatocarcinogenesis) and non-genotoxic (hepatocarcinogenesis induced by methyl-deficiency) mechanisms of carcinogenesis, we showed that both models are characterized by early prominent epigenetic changes in liver

cells. These changes include: global loss of cytosine DNA methylation, hypomethylation of LINE-1 repetitive sequences associated with increased expression of LINE-1 elements, global loss of histone H3 lysine 9 and histone H4 lysine 20 trimethylation, hypomethylation and activation of *c-Myc* proto-oncogene, increased proliferative activity, and inactivation of DNA repair genes. Furthermore, these epigenetic alterations are analogous to those observed in liver tumors. The similarity between epigenetic changes and the timetable of their appearance with two different models of hepatocarcinogenesis strongly suggest the leading role of epigenetic alterations in genotoxic and non-genotoxic models of hepatocarcinogenesis. Based on these observations, we speculate that these epigenetic alterations are not specific to hepatocarcinogenesis only. Indeed, we recently showed the similar epigenetic alterations on different models of carcinogenesis. These results strongly suggest that in addition to traditional testing paradigms, evaluation of epigenetic changes may be used as alternative approach to identify potential carcinogenicity, especially as an accelerated bioassay, and should be taken into account for any carcinogenic risk assessment analysis.

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**MORPHOLOGICAL CHANGES OF RAT
NASAL CAVITY INDUCED BY
ACETOCHLOR**

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Acetochlor (ACHI) is one of the widely used herbicide and by the chemical structure it belongs to the group of chloracetanilides. It is known that such compounds may initiate the nasal tumours in rats. The numerous bioassays from different laboratories showed big structure-functional variety of different parts of olfactory analysator in conditions of the administration by the various factors such as a toxic influence of microorganisms, damages of parasympatic innervations, atmospheric pollutants and so on. And intact rat demonstrates different morphological changes in nasal structure as the result of spontaneous inflammatory lesions, for example.

Carcinogenicity, Teratogenicity and
Toxicology of reproductive function

Laboratory of our Institute has carried out 2-year carcinogenicity studies of ACHI by gavages in a dose of 0, 1, 10, 100 mg/kg of body weight. These studies used male and female Wistar rats. To detect in particular the development of changes in respiratory and olfactory epithelium of nasal cavity, by the end of ACHI-treatment all rat's heads after necropsy were fixed in 10 % neutral buffered formalin. Thereafter the nasal cavity was decalcified by formic acid-formalin solution, and trimmed in three frontal sections. The nasal sections were stained with hematoxylin and eosin and examined microscopically.

Histopathological examination of sections all treated animals showed the biggest number of influences and neoplasm arising from the nasal cavity with respect to control. Microscopically, chronic rhinitis in alternative-accusative phase was seen in the nasal cavity of ACHI-treatment rats in the levels of minimum and medial dose. The degeneration and desquamation of the superficial lining epithelium, in which the number, sizes and activity of mucus cells increased. Hypersecretion of the nasal gland observed in these cases. Somewhere the removing of high cylindrical ciliated cells by the squamous multi-lining epithelium was observed. In some cases we observed the absence of cilia in ciliated epithelium, atrophy of mucous cells in respiratory epithelium, squamous metaplasia. The examinations on the animals exposed to ACHI for 24 months at 10 mg/kg/day, and especially in dose 100 mg/kg/day were shown the expressive destruction changes and visible blood vascular spaces, the pictures of hypertrophy changes. The fragmentary desquamation and metaplasia of the respiratory epithelium, the occurrence of papillary structures, hypertrophy of submucosal glands in the olfactory region in which cystic cavities arises and decreasing the number of the mucosal cells have been found. Our observation indicates the focal hyperplasia and cellular atypia in respiratory epithelium and somewhere the gland epithelial hyperplasia in medial and back nasoturbinates.

The occurrences of adenomas from epithelium submucosal glands or from the respiratory nasal cavity epithelium and in part of nasal septum apical and medial nasoturbinates have been diagnosed. Summarising obtained results we have

concludes that our investigations supported the specific action of chloracetanilides and shown, that in un-treated animals and in rats from low dose in nasal cavity developing the alterative changes priority. The increasing dose causes proliferation and arising neoplastic processes, such as hyperplasia and papillomas.

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TO THE PROBLEM OF HYGIENIC ASSESSMENT OF CLOTHES AND FOOTWEAR

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As it is known when conducting state sanitary and epidemiological examination of clothes and footwear average daily threshold permissible concentrations for the atmospheric air in accordance with DSP 201-97 and threshold limit values for water reservoirs for household and drinking purposes and for cultural and domestic purposes in accordance with DSN 383-96 are used as hygienic standards with which the degree of migration of chemicals from the examined samples are compared. In our opinion such approach is not quite adequate because clothes and footwear contact mainly with the human skin. So, chemical substances that can migrate into contacting medium from clothes and footwear can cause irritating and allergic effect onto the skin and penetrate through the undamaged skin. The conducted analysis shows that among chemicals that can migrate from synthetic and polymer materials each third substance can cause unfavourable effect on the skin, namely 19% substances relate to obligatory irritants and to substances with expressed resorptive properties, 9% are allergens and 2% can cause cancer effect when applied on the skin.

It is known that in contrast to the inhalation way, when the entry of chemicals ceases at once after the exposure is finished, even after a single skin application a chemical can cause its effect on the body for a prolonged time and very slowly, as it can penetrate into different structural skin elements. The first place among many factors, which can cause toxic effects when a chemical is applied on the skin, is a

degree of its toxicity. Such most prevalent chemicals as formaldehyde and phenol that can migrate from clothes and footwear are highly toxic (II class of hazard according to GSOT 12.1.007-76), penetrate through the undamaged skin, cause the expressed local skin lesions and are referred to substances that can cause mutagenic and teratogenic effects. The second important factor that can promote developing a toxic effect after application of chemicals on the skin is a contact area in the human body. It is quite obvious that the larger is a contact area the more is the probability of developing a toxic effect. This factor can be of a particular importance in respect of clothes of the first layer, when the contact area can make up to 80-90%. The occlusion (compressor effect) that change hydration and skin temperature is also an important factor, because such physical factors cause changes in the skin reactivity. The occlusion effect can be get by the clothes from synthetic materials, pampers, articles used for medicinal purposes. Aiming to prevent unfavorable effect of chemicals on the skin in occupational health such hygienic regulations have been adopted as threshold limit value (TLM) for skin contamination. Taking into account this value it would be possible to ground rates of migration of the most prevalent chemicals from cloth. Thus, Russian hygienists proposed TLV equal to 5 mg/dm² when rating formaldehyde migration from cloth into water solutions using a ten-fold safety coefficient because of carcinogenic and allergic effects of formaldehyde.

For general principles of hygienic rating of chemicals that can migrate from clothes and footwear sanitary standards of chemical co-complexes should be prevailed. Such standards should be developed not for each specific material, but for the whole class of materials developed by one principle. In view of the above methodical approaches and criteria for assessing safety of clothes and footwear require, in our opinion, new understanding and revision.

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TOXICITY OF POLYMERIC MATERIALS CONTAINED IN LUBRICATING MATERIALS

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One of directions in developing safe lubricating materials (LM) – lubricating fluids (LF), technological oils (TO), other oils, from the point of view of their effect on the environment, is inclusion of various synthetic and polymeric materials into their composition. The use of one ton of lubricating means containing synthetic and polymeric materials allows to free several tons of mineral oils that is of great ecological significance because machine engineering takes the forth place in contamination of the hydrosphere.

Various polymeric materials are included into compositions of lubricants, however the most often these are hydrocarbon polymers, ethylene-propylene co-polymers, epoxide and polyisobutylene compounds, phenolformaldehyde resins, vinyl co-polymers, surfactants, sulphonates, ethanolamine.

This result in emission of vapor-gaseous-aerosol mixtures of harmful substances of the non-constant composition in the working zone air developed in the process of thermal oxidative destruction of lubricating fluids formed on the base of synthetic and polymeric materials. These are various chemical components such as phenols, formaldehyde and organic spirits, monoetholamine, hydrochloric acid, sulfuric and sulfurous anhydrides, etc. The qualitative composition of mixtures is characterized by the component content of LF, that of quantitative one – by technological peculiarities of their use – temperature, developing in the zone of the processing, by the processed metal, the quickness of delivery of FL into the zone of cutting, etc. LF, containing synthetic and polymeric materials, can cause carcinogenic danger as a result of cumulation of nitrosodiethylamine and nitrodimethylamine in them. The value of the oncogenic risk for nitrosodiethylamine, calculated with the use of UPA method (USA), makes from $3,2 \times 10^{-5}$ to $4,0 \times 10^{-5}$ thus showing that the risk can be regulated. In working conditions LM cause regularly skin contamination in workers. The direct relation of occurrence of occupational skin damages on the level of its contamination has been established. The character of the diseases depends on the component content of LF, on technological

oils and other oils. The oiled LF cause mainly oil follicles, whereas FL containing synthetic and polymeric components cause mainly allergic dermatitis. The highest degree of the damaging effect is caused by compositions containing mono-, di- and triethinolamine, sulphates and fulphonates, polyalkylenglycols and alcanolamines. Under the influence of LF containing synthetic and polymeric materials the imunological reactivity of workers also changes which is manifested as sensitizing and allergic action. Reconstruction of imunological reactivity is taken place within the first years of work and increases with the increase of the length of employment. Parallel to formation of allergic disorders autoimmune reactions are developing. In women there was observed such significant cumulation of autohemnolysins that we can speak on the tendency to developing pre-morbid states. The disorder in immunologic reactivity in workers was accompanied by weakening of the natural body resistance. The intensity of phagocytosis was lowering and the bacterial activity of serum was decreased. The stability of the prepared compositions, constancy of their composition, following requirements to operation, keeping to means of personal hygiene, scientifically grounded professional selection, control over the state of the skin and immunological reactivity should be priority preventive measures at work with LM containing synthetic and polymeric materials.

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**SOME PROBLEMS THAT REQUIRE
SOLVING WHEN ASSESSING NEW
MATERIALS CONTACTING FOOD
PRODUCTS**

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It is necessary to implement new methodical approaches to the expert's estimation of polymeric materials contacting food products because the latest relative regulating documents have been elaborated more than 20 years ago. Within this period the range of polymeric materials, used for packing food products, has been greatly changed. As a rule these are new multi-layer materials that lately practically

substitute such packing materials as, for instance, paper, glass and metal. Among more than 100 polymeric materials contacting food products that have been examined over the last years only 9% are films made of polypropylene. The same quantity of films was made of propylene with pictures on the outer side. All other referred to complex multi-layer films, namely metallized – 35,7%, combined paper- and parchment-based – 21,4%, films of polyethylene and polyamide – 7%, from polystyrol-polyethylteraphtalate – 7%. Multi-layer materials have a number of technological advantages, such as mechanical stability, gas and water impermeability. At the same time inclusion of polymer materials, being different by their chemical composition, to the number of multi-layer materials can result in occurrence of chemicals with larger spectrum of action to the contacting medium. Heat-saving and welding films require a particular attention, because as a result of package sealing that, in most cases, are made by welding in high temperature, products of thermal oxidating film destruction can enter both inside the package and into the working zone air. Recently, new stabilizers and antioxidants are used for the composition of polymeric materials, particularly of foreign production. So, it is necessary to solve the problem which of these substances requires sanitary and chemical control and in the composition of what specific polymeric materials. The results obtained during state sanitary and epidemiological examination of polymeric materials, intended for the contact with food products, show that when assessing materials made of polyolefines (polypropylene, polyethylene, etc.) migration rates of heavy metals and such solvents as heptane, hexane, ethylacetate, do not practically exceed permissible levels. In view of the future entering of Ukraine into World Trade Organization it is necessary to harmonize our regulations with requirements of EC Directives. One of requirements of European Directives is the availability of the relative information on a specific polymeric material that will contact with food products. This information should show that for manufacturing a definite material such monomers should be used that are listed in relative Directives. The number of media that are used as models

for investigation of polymeric materials, contacting with food products, should be revised. Directives of the European Community provide the use of only four model media – distilled water, 3% acetic acid, 15% ethanol, purified olive oil or sunflower oil of corresponding characteristics. The great importance is given in the European Directives to organoleptic studies conducted with the use of relative sensor tests; main water and products for which the tested materials will be used are taken as models.

These are, in our opinion, main problems that require their solving when developing new regulations where requirements to polymeric materials contacting food products will be included.

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MUTAGENICITY STUDIES OF METHSULFORON METHYL

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Now in the pest control agricultures is attached large significance to chemical facilities of defense of plants, as the use of pesticides together with the agro-technical receptions allows saving considerable part of harvest.

We investigated preparations which using in agriculture as herbicide on the base of methsulforon methyl (MSM) technical 98,0 % and MSM technical 96,0%. In accordance with "Guidance on short-term tests for the exposure of mutagenicity and carcinogenic chemical matters" it was necessary to conduct the primary mutagenicity of MSM, which will allow setting the class of danger and will help to develop prophylactic methods for safe application of this preparation. The cytogenetical activity of MSM in concentrations of a 40, 200, 1000 and 5000 µg/ml cultural medium was explored in two parallel variants of experiment – without the metabolic activation and with activating by the microsomal activation mixture of S-9 mix.

The mutagenicity of MSM was explored on white nonlinear mice, males, weighting 20–22 g. MSM was entered singly per os for 0,4 ml solutions in the defended plumbing water, in doses 70, 350 and 1700 mg/kg of weight of body. The results of experiments

showed that the reliable increasing of level of MSM mutagenicity was established only in the test on induction of chromosomes aberrations in the culture of human peripheral blood lymphocytes in vitro without the metabolic activation. Mutagenicity of MSM was not shown in the test on induction of chromosomes aberrations in the culture of human peripheral blood lymphocytes with the metabolic activation and in the test on induction of chromosomes aberrations in the cells of mice bone marrow in vivo. It can be related with its rapid disintegration, formation of genetically non-active metabolites, and also with the short period of existence active intermediates which does not enter to the cells and induce the mutagenic effect.

But consideration must be given to MSM 96 % showed greater level of mutagenicity than MSM 98 %.

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IN VITRO GENOTOXICITY OF PAH MIXTURES AND ORGANIC EXTRACT FROM URBAN AIR PARTICLES.

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Two principle aims of this study were to find relevant human derived cell line to investigate the genotoxicity of PAH containing complex mixtures and to analyze DNA adduct forming activity of organic compounds bound on PM10 particles collected in Prague (Czech Republic), Kosice (Slovak Republic) and Sofia (Bulgaria) by high volume air samplers during summer and winter periods. The genotoxicity of extractable organic matters (EOMs) was compared with that of individual carcinogenic polycyclic aromatic hydrocarbons (c-PAHs) and their artificial mixtures. For this purpose we used human hepatoma cell line HepG2, human diploid lung fibroblasts HEL and human monocytic leukaemia cell line THP-1. DNA adducts

were analyzed by ³²P-postlabelling. HepG2 cells gave linear dose-response relationship for most of individual PAHs and their artificial mixtures and were highly responsive to real EOMs. HEL cells were more sensitive to detect adducts at lower individual PAHs concentrations, but strong inhibition occurred when artificial PAH mixtures and real EOMs were employed. THP-1 cells were unable to detect most of the c-PAH induced adducts. Correspondingly to the variability in c-PAH concentration in EOMs, we found seasonal variability of total DNA adduct levels stronger than differences in genotoxic potential of extracts among 3 localities studied. Highest DNA adduct levels were induced by EOM collected in Prague in winter period followed by Sofia and Kosice. In contrast, in summer sampling period the order was quite opposite: Kosice>Sofia>Prague. Considering the EOM content per m³ of air, to compare real exposures of humans to genotoxic compounds in all 3 localities, extracts from respirable dust particles collected in Sofia exhibited highest genotoxicity regardless of sampling period. The results suggest that most of DNA adducts detected in samples incubated with EOMs have origin in the presence in extracts of low concentrations of c-PAHs forming 0.03-0.17 % of their total mass. Finally, our results suggest that HepG2 cells, among the three cell lines tested in this study, represent the best in vitro model to test genotoxic potential of complex mixtures containing PAHs. Supported by EC grant QLK4-CT-2000-00091 and Czech Ministry of Environment grant VaV/740/5/03.

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STUDY OF THE QUALITY OF FOOD-PRODUCTS AND THE STATE OF HEALTH OF THE POPULATION OF THE ISYKKOL REGION, KYRGYZSTAN

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The nutrition factor plays an important role in the health of the population. Children are more sensitive to adverse environmental influences due to their different body mass and metabolic features. This study was supported by the State Agency for Intellectual Property under the Government of the Kyrgyz Republic and the Swiss SCOPES Programme 2000-2003. The aim of this work was to investigate contamination of food products by biologic toxins and their effect on the health status of certain population groups. Study area: Isykkol Region of the Kyrgyz Republic. The quality of foods of vegetable and animal origin (cereals and cereal foods: wheat, flour, macaroni products, groats, milk, cream) was assessed. Mycologic and mycotoxicologic (aflatoxins M₁ and B₁) studies were done using thin-layer chromatography. Population health indices were studied for the period 1999-2002 according to ICD X Revision. Our studies found that food products in the study region were intensively contaminated by microscopic fungi of g. Aspergillus genus: Flavus, Niger, Candidus and g. Penicillium: Citrinum, Cyclopium, Rubrum, Expansum and g. Mucor and aflatoxins. Aflatoxin B₁ occurred most frequently in cereals especially maize groats, aflatoxin M₁ in curd. Data on the morbidity of the population indicated a high prevalence of diseases of the endocrine system, and malnutrition which was increased by 13.3-fold in children (3428 per 100000 population in 2002 versus 258 in 1999), by 2.8-fold in adolescents and adults. Health risk assessment of the children of the Isykkol Region was made based on consideration of environmental conditions.

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PROTEOMIC AND PATTERNS OF ENDOTOXEMIA MANIFESTATIONS

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The object of the work – to define the mechanism of development of toxemia in the cases of different diseases and to systematize their dependence on the etiological factor and on the stage of illness

(exacerbation, remission), on the general system-organ target of lesion.

Materials and methods of explorations.

The analysis of clinic observations and laboratorial researches was conducted among 1645 patients with different diseases, which were accompanied by the development of the endogenous intoxication syndrome of the various stages. The patients' age varied from 1 month to 65 years.

Researches of cytotoxicity parameters and of autoimmune activity of autoaggressive matters (AM), which were accumulated in the bloodstream in the process of development and course of illness, were conducted among all patients with use of the complex toxicometry. To define cyto- and AM autoimmune activity autologous biological targets were used – leucocytes, lymphocytes, erythrocytes. By means of membrane technologies of biological medium division AM were systematized due to the size of molecules (elements). In the results of that researches the next parameters were obtained: the main mechanism of lesion of biological target by endotoxins – straight (cytotoxic) or mediate – is autoimmune, the toxicity of the integral plasma and toxinbearing fractions, sizes of AM molecules (elements) accumulated in the bloodstream, their disturbing potential and others. Besides, analogical toxicometry researches of blood plasma were conducted among donors. The results were systematized to the groups according to the etiological agent of disease (which was defined through the traditional methods), leading clinical syndrome, general system-organ target of lesion, the stage of disease development. In accordance with the ascertained potentials of AM cyto- and autoimmune activity, were created the toxemia “graphics”, which are typical for each systematized group. Thus, the library of toxemia graphics was created, which appears in cases of various etiological agents, various leading clinical syndromes, various general system-organ targets of lesion, at various stages of disease development.

Results of explorations. In the results of conducted researches and systematization of data file, the parameters of toxemia accompanies healthy person (donor) and develops in the course of illness got into the

toxemia graphics library. Toxemia graphics were systematized in accordance with the types of etiological causes – bacteriological, viral-parasitic, traumatic and others (8 types in total), with 13 system-organ targets of lesion, and also with the stages of disease development (exacerbation, remission). During the exploration of filtrates contained AM with various amount of molecules (elements), albuminous fragments were found with the different concentration among donors and patients. Theoretically supposing the correlation between endotoxiosis, toxicogenomics, toxicoproteomics and also relying on the results of toxemia graphics systematization the expert system of diagnostic was worked out, which allows to recognize etiological agent, the stage of disease, and system-organs distraction of AM among patients. The main point of functioning of the system is to conduct complex toxicometrical researches, to create toxemia graphic and to compare the last with the similar one from the library. By the numerous quantity of authentic ($p < 0.05$) coincidences it is possible to make a number of important for the therapeutic approach conclusions about the origin and parameters of toxemia. The results of clinical approbation allow to continue and deep works in this direction.

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'PROTECTIVE' FOODS FOR REDUCTION OF WATER AND FOOD PRODUCTS RADIONUCLIDE TOXICITY

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Presently the threat comes from technogenic radionuclides that got in the environment after nuclear weapons tests, nuclear power plants failures, and production activity using artificial radionuclides.

Extremely dangerous are ^{137}Cs ($T_{1/2}=30.2$ years) which actively competes with potassium and accumulates in depots and muscle tissues of the man, and ^{90}Sr ($T_{1/2}=28.8$ years) which competes with calcium and accumulates in bone tissues. Of no less danger are short-living (^{89}Sr , ^{141}Ce , ^{144}Ce , ^{103}Ru , ^{106}Ru , ^{134}Cs , ^{131}I , ^{140}Ba , ^{91}Y , etc.) and long-living (^{238}Pu , ^{239}Pu , ^{240}Pu ,

^{241}Am , etc.) radionuclides. Accumulating in the upper part of the plants radioisotopes come to animal bodies and milk posing a threat to the man. Anti-radiation protection of the population should include dosimetry, desactivation of products contaminated by radionuclides as well as application of 'protective' foods – radioprotectors, decorporants and enterosorbents.

Biological radioprotectors of plant and animal origin can be produced by the domestic industry and perform the functions of antioxidants, immune- and hemostimulants, vitamin complexes, adaptogens, and antidepressants. These are the products made of mussel and carotene-containing plants and berries.

Decorporants are the substances that accelerate excretion of radionuclides by the body. Of special importance is algetic acid and its salts (4 to 6 grams per day) extracted out of brown sea weeds and used for production of bread, canned food, and various emulsifiers.

Due to high incidence of thyroid pathology special attention should be paid to an adequate consumption of stable 'organic' iodine to prevent and treat this pathology. The diet should include oceanic fish and weeds, tinctures of green (unripe) walnuts, and special iodine sour dairy products.

The Ukrainian industry has developed highly effective enterosorbents like granulated activated charcoal, extra-refined cellulose, apple and beetroot pectines, pectine-vitamine formulas, alginate-based sorbents, ferrocine.

A method to measure antioxidant activity of biological objects developed and patented by I. Shevchenko and N. Ye. Kalinichenko allowed selecting the most active formulas for detoxication of free radicals in the irradiated water and water solutions.

High activity detoxicants have been obtained through fermentative treatment of mussel, sea-weeds and some kinds of fruit and berries in the Azov and Black sea basin (A.G. Gubanova, O. Ye. Bitutskaya).

Value of 'protective' food products is in the fact that due to their long-lasting effect they can and must be used for treatment of diseases caused by chronic irradiation of humans unlike chemical radioprotectors which are highly toxic and have been studied mainly in experiments of acute radiation exposure.

**TOXICOLOGICAL EVALUATION OF
HAZARD LIMIT FOR ORGANISM ACUTE
INTOXICATION BY CARBON MONOXIDE**

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Carbon monoxide (CO) is a one of main constituent of gas forming in firing carbon compounds at reduced access of air oxygen. Almost all types of fire are accompanied by definitive making of certain CO concentrations.

Increasing number of chemical accidents, fires and other emergencies are often accompanied by short yet high concentrations of carbon monoxide in air that extremely exceed its safety levels. In such situations using of hygiene standards of safety such as Maximum Permissible Concentration (MPC) for work area of functioning plant or MPC for air control of populated areas is inadequate. There has been appeared the complex problem of toxicological statement for hazard limit in the case of people's short stay within area polluted by CO that amounts to 30 minutes in average, by long-term observations. This time is enough for person to leave or be evacuated from the hazardous area. For solution of this problem it was necessary to prove the concentrations of CO in polluted air either produced no pathological shifts in an organism or accompanied by small and reversible functional reactions. The mandatory condition for such disorders should be the ability of suffered person to leave the hazardous area within 20-30 minutes. Concerning toxicological evaluation of hazard limit for organism' acute intoxication by CO, for the first time it is proposed the permissible doses (concentrations) of action for emergency situations (PDA_E) as a toxicological index. Upon validation of these concentrations we tried to use only direct experimental data obtained at CO action to people within fully prescribed concentrations and upon fixed time of expositions. Additionally we took into account the correlation between the level of

external inhaled dose of CO, level of carboxyhaemoglobin formation in blood and functional shifts in organism. As a result, for 30-minute exposition the PDA_E level of 1 mg/l is proved and it is recommended for calculations of sanitary losses in carbon monoxide' contaminated area and for estimation of respiratory protection efficacy.

**ECOLOGICAL PROBLEMS OF
CHEMICAL DEMILITARIZATION IN
RUSSIA**

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Due to beginning of implementation of workload on destruction and neutralization of former chemical objects for manufacturing chemical weapon (CW) agents in Russia territory, ecology and human health care as well as monitoring of personnel health working upon destruction of CW is now crucial and actual problem of international importance.

Recently there have been scientific publications concerning the ability of some physiologically active substances (including CW agents) to induce pathological shifts in human organism and other biological objects at certain micro concentrations. This ability may not be interpreted in terms of usual dependence of 'dose-effect' and it is characterized by so called 'silence' areas ranged within three orders of magnitude.

It is of principal importance that such 'ultra-low' doses of these substances appear to be lower by many orders of magnitude than their maximal permissible concentrations (MPC). Thus, the need of principally new approach to developing more adequate monitoring is emerged that would be based upon direct biotesting of their super-low action or presence of CW in a living organism, rather than 'indirect' analytical measuring of CW concentrations in the environment. For these purpose, new methods of physiological, biochemical, morphological and crystallographic research

are experimentally well founded and proposed in SRI OCT. These methods have not been used before to prove harmless levels of CW at manufacturing conditions and they are superior to modern methods of chemical analysis by their sensitivity. This concept stipulates the objective recording of the degree for specific biodamaging action of CW on the effect in-between 'norm-pathology' in dynamically observed persons. This degree is estimated by reference data obtained on model animals exposed by the same CW within the range of all possible doses including their action combined with working area factors (noise, electromagnetic field and others), use of individual protections and other unexplored factors capable to additionally increase pathological shifts in an organism. Thus, proposed prophylactic monitoring may be successfully used not only on objects of CW chemical destruction but also on other harmful chemical plants.

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ABUNDANT VAPOR-PHASE PAHS AND THEIR BIOMARKERS AS SURROGATE MEASURES OF TOTAL POLYCYCLIC AROMATIC HYDROCARBON EXPOSURE

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Polycyclic aromatic hydrocarbons (PAH) are a large class of chemicals composed of hydrogen and carbon atoms in a structure of two or more fused aromatic rings. These chemicals are of significant interest due to their carcinogenic potency and their ubiquitous and abundant production in occupational and environmental settings. PAHs exist at varying levels in both vapor and particulate phases, thus making routine sampling of many individual species both complicated and costly. Whereas the greatest carcinogenic potency exists with larger particle-bound PAHs, the gaseous species are typically more abundant. Here we consider using naphthalene and phenanthrene and their biomarkers as surrogates for total PAH exposure. Since these are smaller PAHs and exist predominantly in the gaseous form, they are easily measured without the sensitivity

limitations that may influence larger particle-bound PAHs. Naphthalene, a two-ring PAH, has been shown to be carcinogenic in animal bioassays, producing malignant tumors in the respiratory tracts of rats and mice. Although phenanthrene is unclassifiable as to its carcinogenicity in humans, it is the simplest PAH to contain a bay region, a feature closely associated with carcinogenicity in several larger PAHs. Noting the abundance and significance of these compounds, we used data from published sources to show that log-transformed levels of naphthalene and phenanthrene are highly correlated with those of total PAHs in several industries. Considering the adequacy of using air measurements of naphthalene and phenanthrene as surrogates for total PAH exposure, we are currently investigating the utility of using urinary biomarkers of these compounds to assess exposures. When compared to more traditional air measurements, these urinary measurements may represent a more accurate estimation of internal PAH dose, accounting for various exposure routes and the use of respiratory protection. Specifically, head space-solid phase microextraction (HS-SPME) coupled with gas chromatography-mass spectrometry (GC-MS) are being used to measure naphthalene and phenanthrene in the urine of steel workers and control subjects. The limits of detection for naphthalene and phenanthrene using this method are 0.01 µg/L and 0.005 µg/L, respectively. Such analytical sensitivity allows the detection of these PAHs in samples collected after both occupational and environmental exposures. Results of this study will be presented. In future investigations, these urinary measurements can be used in concert with air measurements to determine contributions of airborne PAHs to total body burden, and can potentially be used to investigate the uptake and metabolism of PAHs in humans.

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SYSTEMIC PRINCIPLE OF REGULATION IN A MODEL XENOBIOTIC – ENVIRONMENT – HUMAN

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In 60th instead of accepted in the world isolated setting of norms of pesticides in the objects of environment L.I. Medved and his followers developed and inculcated the complex toxicological and hygienic setting of norms in food products, water, air and soil. Integral criterion of ADI is base of this regulation. Systemic principle taking into account toxicological and hygienic data, side and delayed effects is used for determination of ADI. Classification of pesticides by hazard by ADI criterion is introduced. Pesticides with ADI less than 0.001 mg/kg are in the first class, from 0.001 to 0.005 mg/kg – in the second class, from 0.006 to 0.03 mg/kg – in the third class, more than 0.03 mg/kg – in the fourth class. The calculations show, that the most hazardous pesticides are in the first class. Some of them are forbidden or severely regulated in the world (aldicarb, aldrin, dieldrin, heptachlor, DDT, 2,4-D, 2,4,5-T, toxaphene, mercury containing formulations, etc.). ADI is the base for constructing complex system of management in the aim of minimization of pesticides harmful action. On the ADI base dozen thousands of pesticides limits are approved. In 60-70th it is forbidden or severely limited application of number of pesticides, which are known as POPs. Principle and standards in soil for the hundreds of pesticides are developed taking into account migration on soil-water-air and food chains. Systemic principle is applied at development of now operating pesticides classification by hazard.

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**BIOMARKERS OF URBAN AIR
ASSOCIATED GENOTOXICITY**

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Biomonitoring of the genotoxic potential of environmental factors and their biological effects in man is essential for ensuring primary prevention of human cancers and damage of genetic material. During the last 10 years in environmental exposure studies were used biomarkers: DNA adducts by ³²P-postlabeling, protein adducts, single cell gel electrophoresis, urinary PAH metabolites,

urinary mutagenicity, proteins p53 and 21, chromosomal aberrations by conventional method and FISH (whole chromosome painting, fluorescence in situ hybridization), SCE (sister chromatid exchanges), genetic polymorphisms of genes CYP1A1, GSTM1, GSTP1, GSTT1, EPHX1, MS, MTHFR, NAT2, XRCC1, XPD6, XPD23, hOGG1, vitamins A, C, E, folate. Recent results from Scandinavia, Italy and the Czech Republic show that an increased level of chromosome breaks appears to be a relevant biomarker of future cancer risk. The Czech Republic was probably the first country in Europe, where biomarkers of exposure and effect were used for preventive measures to decrease the exposure to carcinogens. The capital city of Prague becomes one of the most polluted localities of the Czech Republic. Therefore, the effect of exposure to carcinogenic polycyclic aromatic hydrocarbons (carc-PAHs) adsorbed onto respirable air particles (PM_{2.5}, <2.5 μm) on DNA adducts and chromosomal aberrations was studied in a group of policemen (males, aged 22-50 years) working in the downtown area of Prague and spending >8 h outdoors. The matched healthy volunteers spending >90% daily time indoors were chosen as controls). Ambient air particles (PM₁₀, PM_{2.5}) and (carc-PAHs) were monitored using VAPS sampler, personal exposure was evaluated using personal samplers during working shift. DNA adducts were analysed in lymphocytes by ³²P-postlabeling assay, chromosomal aberrations by conventional cytogenetic analysis and fluorescent in situ hybridization (FISH), cotinine in urine to control for exposure to tobacco smoke by radioimmunoassay, plasma levels of vitamins A, E and C by HPLC, folic acid by ELISA, cholesterol and triglycerids using commercial kits. Polymorphisms of metabolic genotypes (GSTM1, GSTP1, GSTT1, EPHX1, CYP1A1-MspI) and DNA repair genotypes (XRCC1 and XPD) were determined by PCR-based RFLP assays. The level of "like" B[a]P-derived DNA adduct was higher in exposed group (0.122±0.036 vs. 0.099±0.035 adducts/10⁸ nucleotides, P=0.003). DNA adduct levels were modified by XPD repair gene in exon 23 and EPHX1 gene. Using FISH technique and probes for chromosomes 1 and 4 (Cambio, UK) the genomic frequency of translocations calculated as F_G/100 was 1.72 and 1.24 for

EXP and CON ($P < 0.05$), respectively. Obtained results were confirmed in a new study, where city policemen were subsequently sampled in January, March, June, and September.

It was for the first time when was observed the relationship between DNA adducts (biomarker of exposure) and chromosomal aberrations by FISH (biomarker of effect). These results indicate that carcinogenic PAHs exposure during winter is on the level inducing genetic damage.

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**ASSESSMENT OF THE LEVEL OF
MIGRATION OF ORGANOCHLORINE
PESTICIDES FROM THE PROHIBITED
AND OBSOLETE PESTICIDES STORAGE
PLACES INTO THE GROUND WATERS**

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One of the priority directions in the assessment of the pesticides-related risk for the environment and human health is the assessment of the level of pesticides entrance in the organism not only during their production and utilization, but also along with the consumption of food and water that contain their residues. In the spring of 2005, the investigations on the estimation of residues of organochlorine pesticides (OCP) in 14 samples of drinking water from the wells and artesian pores, placed on the distance of 500 m or less from the non-functioning depots with obsolete pesticides (including 5 wells that are on the territory of an locality), were carried out. 4 samples of the surface waters, which are at 1.5 km distance from the mentioned depots, were also investigated. At the same time, the surface and arable soil layers within the radius of 100 m from the depot were collected and analyzed in order to reveal the content of OCP residues. The investigations of the water and soil samples (144 and 890 respectively) were carried out using the methods of thin-layer and gas chromatography. It was estimated that almost 50% of water samples contain residues of OCP in the limits of 0.0002 – 0.011 mg/dm³. The presence of significant

quantities of DDT residues in soil does not lead to the accumulation of this pesticide in water. According to the frequency of disclosure and the level of RQ content, isomers HCH (β -56,0, γ -33,6, α -21,8 % of samples) are on the first place. Heptachlor and dicofol were detected in 38 and respectively 29.2% of samples. DDT was revealed in 28.6, DDD-14.3, DDE- 4% of positive samples. As the data from the table shows, the average quantities of pesticides were at the level of thousandth and tenthousandth fractions of mg/dm³, which is significantly lower than its MAC in water. There was only one sample of well water where the residues of HCH (the sum of all the isomers) exceeded MAC (0.0116 mg/dm³).

The place of sample collect.	Soil	The well on the depot territory	500 m from the depot territory	Surface water	MAC in water
Pesticide	mg/kg	Min.-Max. mg/dm ³	Min.-Max. mg/dm ³	Min.-Max. mg/dm ³	mg/dm ³
DDT	1,18	0,0002-0,0003	0,0002-0,001	< 0,0002	0,002
DDE	0,069	<0,0002	0,0002-0,0007	< 0,0002	0,002
DDD	1,37	0,0002-0,0007	0,0002-0,0006	< 0,0002	0,002
α -HCH	0,009	0,0002-0,0006	0,0002-0,0009	0,00008-0,0003	0,002
β -HCH	0,108	0,0007-0,0012	0,0005-0,011	0,0006-0,003	0,002
γ -HCH	0,008	0,0002-0,0009	0,00008-0,0002	0,00008-0,0003	0,002
Heptachlor	0,043	0,0002-0,0007	0,0003-0,0006	0,00008-0,0004	0,001
Dicofol	0,33	0,0002-0,0004	0,0002-0,001	0,0002-0,0003	0,02

According to the data received, the farther the well from the depot is, the higher level of residues of the investigated pesticides in water becomes. If the norm of daily consumption of water in drinking purposes is considered 3 l per day, than the presumable summary entrance of the HCH isomers into the organism is 10 times lower than that of ADI for adults and 5 times lower than the normative for the children (0.01 and 0.005 mg/kg b.w./day). The same can be said about the presumable level of DDT and dicofol receipt (0.005 and respectively 0.002 mg/kg b.w. /day). At the same time, the average quantity of heptachlor that can enter the human organism together with drinking water, equal with 0.00045, practically reaches ADI – 0.0005 mg/kg

b.w./day. The obtained data thus show that the inhabitants of the localities in the nearest neighborhood of the depots with obsolete toxic chemicals are exposed to the risk of toxic influence of OCP that enter their organism with drinking water.

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DETERMINATION OF THE FUNCTIONAL PROPERTIES OF THE BIOLOGICALLY ACTIVE DETOXICANT MAGNESIUM-PECTIN COMPLEX (IN VITRO) ON ALTERNATIVE MODELS

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The study of the functional properties of the biologically active magnesium-pectin complex was carried out to diversify its application at the manufacture of makeup preparations, dermatologic protective shampoos, creams, gels, face packs, lotions and special detergents. The research was carried out in some directions: determination of the magnesium-pectin complex detergency and emulsify ability; the study of the magnesium-pectin complex' influence on the skin transepidermal water loss (TEWL) *in vitro*; combined magnesium-pectin complex and different additions action on the TEWL value of liquid-crystal gel; the diminution of the negative surfactants influence with the magnesium-pectin complex.

The gravity measurements of the magnesium-pectin and appropriate compositions detergency showed the essential increase of this parameter for magnesium-pectin-surfactant mixtures. Thus the washing power of magnesium-pectin-surfactant solutions with concentration 0,1% was 90%. Similar detergency of magnesium -surfactant mixtures was reached for 1% solutions only. The emulsifying ability of magnesium-pectin-surfactant mixtures was estimated by measurements of the phase immiscibility time for standard "oil in water" emulsion. The measurements of emulsion particles size were carried out too. The data obtained showed the essential increase of phase immiscibility time with the increase of magnesium-pectin complex content. Some decrease in average particles size of standard emulsion was also registered. The

emulsify ability of other magnesium containing preparations was at least twice worse.

Here the TEWL-value measurements showed that the components of magnesium-pectin-surfactant mixtures salutary potentize each other and provide the effective preservation of acidic mantle of the skin. Besides, the additions of the magnesium-pectin complex to the cosmetic cream compositions results in the effective coverlet moistening. Also, the addition of the magnesium-pectin complex provides the decrease of the negative surfactants effect on the skin health. The TWL parameter value is less by half, the water balance of the skin is normalized and the wrinkled skin becomes smoothed out and velvety.

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EXPRESS-METHOD OF THE DETERMINATION OF COMPLEXING ABILITY OF AMIDOPECTIN - DETOXICANT.

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During a last time the ecological situation becomes worse and pectin is more often used as structure formation agent and detoxicante of the ionic - exchange action in the production of dermatological protective shampoos, Tooth-pastes of ionic - exchange in particular when it is necessary to bring into the person organism the calcium ions and to bring out the ions of heavy and radioactive metals. Amidopectins are characterized by the especially high complexing ability.

Express-method of the determination of amidopectin complexing ability with the respect to the calcium ions has been developed with the aim of market protection from falsified and unqualitative products.

Essence of a method is concluded in following: the definite sample weight of amidopectin was dissolved at 25 ml of distilled water and well mixed. Then the aliquot part was placed into the centrifugal test tube, which already contained the solution of calcium salt with known titre (pH 7,5-8). When the calcium pectat was formed the solution was centrifuged, then by the flame photometric method the content of

calcium ions in the solution under precipitate has been determined. The amount of calcium ions which entered in the reaction of complexing has been calculated on the difference between introduced amount of calcium ions and amount of calcium ions in the solution under precipitate.

The usage of offered method of the determination of amidopectin complexing ability with the respect to the calcium ions in contrast to the traditional gravimetric method ensures the following advantages:

- reduction of the time of the analysis of pectin quality approximately in 8 times;
- increasing of sensitivity and accuracy of method at the expense of using the flame photometric method of analysis.

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**SUPERFUND BASIC RESEARCH
PROGRAM: BASIC SCIENCE TO RISK
ASSESSMENT-IMPACTING HUMAN
HEALTH AND THE ENVIRONMENT**

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Environmental threats in Central and Eastern Europe comprise a significant global public health challenge. Environmental threats are widespread, increasing as nations in the region undergo industrial and economic development. Chemical toxicants in the environment, poverty, and little or no access to health care are all factors contributing to life-threatening diseases. Risks for almost all human diseases result from the interactions between inherited gene variants and environmental factors, resulting in dramatic changes in patterns of illness in the last century, and will continue to change in this century. A conceptual framework that has guided the NIEHS Superfund Basic Research Program (SBRP) is one that encompasses a holistic approach to environmental health sciences and basic research: The long-term improvement of public health requires an interdisciplinary approach that integrates biomedical, geochemical and engineering sciences. Decisions that are needed to protect human health, ecosystems and the environment

must be based on mechanistic knowledge gained from the integration of data from all relevant research disciplines. For example, it is important to understand the consequences of exposure to environmental agents on human health and the relationship between exposure and disease outcome, as well as the effect of exposures on ecosystem dynamics. From a scientific perspective, a holistic approach involves contributions from all research disciplines: Identifying chemical contaminants; assessing properties that may affect transport and bioavailability of contaminants; and determining the critical pathways that result in exposures to human populations or ecosystems requires incorporating tools and approaches utilized by engineering, geochemical, biomedical and ecologic domains. The risk assessment process helps to define exposures of concern and potential threats. The more robust the risk assessment, the better one is able to contribute to cost-effective and yet protective choices. The synthesis of environmental health knowledge resulting from research, ultimately, should contribute to the robustness of the risk assessment process. Scientific inquiry that supports a paradigm whereby knowledge gained through understanding disease processes resulting from environmental exposures would furthers our understanding of potential human health effects; provide a creative, holistic approach to integrate seemingly separate biological systems, ecological and human health risk assessments into more comprehensive model. However, to fully realize the benefits from such conducted research a new generation of risk assessment models is required. While each region of the world faces unique public health challenges, Central and Eastern Europe presents unique public health challenges. It is vital to develop and implement interdisciplinary research programs to bridge research gaps and meet the needs of affected communities, improving the overall public health of all.

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**ADDRESSING THE ISSUE OF
ESTIMATION OF THE LEVEL OF
HAZARD OF THE NEW INSECTICIDAL**

MEANS USED IN MEDICAL EXTERMINATION OF INSECTS

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Synanthropic insects (tongs, fleas, flies, gnats, cockroaches, mole, red ants, etc.) have sanitary-epidemiological meaning, since they are the carriers of the agents of infectious diseases and have a negative effect on the health and hygiene state of living quarters and social institutions. To dealing with them, the insecticidal means are widely applied, which are the complex compositions, which are consistent of the active ingredient and the auxiliary components - solvents, the fillers, the synergists, the odorants, the dyes, propellants, etc. The active substances of insecticidal means in its majority relate to the same chemical groups, as the acting substances of the insecticidal means, used in the agricultural sector. At the time, the application of insecticidal means of everyday usage has its specific character, which must be considered along with their use. Thus, from the standpoint of effectiveness, the means must:

- to possess selective action on the arthropods at all stages of the development of insects;
 - to be effective within minimum doses in short range usage;
 - to have residual action on the surface;
 - not to damage of daily life appliances - furniture, coatings of different types, cloths, etc
- from the standpoint of the safety
- to be less toxic and less dangerous for the health of population in comparison with the used substances of the same purpose in the agriculture and in the area of medical extermination of insects;
 - not to be accumulated in the objects of the environment (be able to decompose easily with water and soaping detergents);
 - not to cause acute and chronic poisonings if used in accordance with the developed recommendations
 - not to possess the distant effects;
 - not to possess the irritating action on the skins and the mucous membranes of eyes;
 - not to possess skin-resorbitive properties;

- not to possess the sensitizing action.
- Should be also considered the fact that the insecticidal means against the synanthropic insects will be used in the socially significant objects (in the closed, badly ventilated installations), where the people of different ages with different health status are located for the considerable amount of time (they live, work, etc). Therefore, at the estimation of the hazard level and the development of the regulations of the safe use of insecticidal means in the area of medical extermination of insects it is absolutely necessary to consider not only the results of toxicological studies regarding their specific effectiveness, but also the results of chemical and hygiene tests, which are important for the hygienic estimation of the regimes of the application of means as for the persons, conducting the application of these means within institution, as well as for those, who will live in them later. Alongside, hygienic regulation will enable to provide the objective evaluation of the conditions of means application in accordance with the targeted purpose and to develop the substantiated measures for prevention of unwanted influence on human health.

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HAZARDOUS WASTE SITE CHEMICALS: POTENTIAL ROLE OF OXIDATIVE STRESS IN TOXICITY AND CARCINOGENICITY

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Oxidative stress is a common state in pathophysiology where the number of reactive oxygen species (ROS) being formed exceeds those being detoxified. It is thought to play an important role in many diseases including cancer, neurodegeneration and ageing. Many environmental chemicals or their metabolites that are classified as nongenotoxic are known to induce ROS through redox cycling. Reactive oxygen

species interact with many cellular constituents, including lipids and DNA. In addition, ROS is involved in signaling pathways associated with cell death and cell proliferation. DNA damage induced by ROS and cell proliferation are thought to be two of the primary modes of action for carcinogenesis by nongenotoxic environmental chemicals, but they may also be important modes of action for genotoxic chemicals. Nongenotoxic carcinogens present major problems for risk assessment, since the shape of their dose-response curves at low exposures is not known. We have developed a battery of highly sensitive assays for DNA damage arising from a variety of ROS-induced responses including direct oxidation of DNA, the formation of abasic sites in DNA, lipid peroxidation products and deoxyribose damage leading to base propenal and 3-phospho-glycoaldehyde (PGA). The different types of DNA damage are repaired by a variety of pathways, so chemical exposures may have different dose responses in cells and tissues. One of the simplest ROS species is H₂O₂, yet it has one of the most complex dose-responses identified, having a steep initial slope, followed by reduced DNA damage and finally a lower slope increase with increasing exposure. This same dose response is evident for AP sites and 8-OHdG. In contrast, M1G was found to have a supralinear dose response following exposure to PCBs and pentachlorophenol, where the steepest slope was at low exposures. Vinyl chloride represents yet another type of response, as exocyclic etheno DNA adducts are formed by its ultimate metabolite, chloroethylene oxide, but also form endogenously from PGA. We were able to demonstrate the relationship between those adducts induced by VC and those arising from endogenous sources using exposures to [¹³C₂]-VC. Carcinogenicity was associated with molecular exposures 30-40 fold higher than present endogenously. Current research is focusing on demonstrating detailed dose-responses for ROS-induced DNA damage in the TEF carcinogenicity studies on PCBs, dibenzo(a,l)pyrene and environmental exposures to mixtures of PAHs and PCBs. The ultimate goal of this research is to utilize cutting edge science to improve the accuracy of hazardous chemical risk

assessments, rather than relying on default assumptions

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**GENETIC VARIATION DETERMINES
RESPONSE TO ALKYLATING AGENT
EXPOSURE AS MODELED BY
AZOXYMETHANE**

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The azoxymethane (AOM) model has been used extensively in mice to model damage associated with DNA alkylation. The primary site of response is the colon, where tumors arise in a genetic background-dependent manner. However, we have also noted significant liver damage that is also genetic background dependent. Using AOM, we show how mice can be used to model the variation present within human populations in response to environmental exposures. Using a wide variety of mouse strains, we further show that not only is there population variation in disease response, as demonstrated by the development of colorectal tumors after AOM exposure, but also significant variation in the types of tumors marked by unique histopathologies and perturbed signaling pathways. Similar variation is observed in liver responses, corresponding to the site of AOM metabolism. Using new genome sequence and SNP data, we have genetically characterized the responses to AOM exposure in order to identify genomic intervals harboring genes that are responsible for determining whether an individual will have a pathological response. These data demonstrate the power of looking at exposures from an experimental population level rather than within individuals and frequently out of context as is historically done for mechanistic studies. These results are easily extendable to other types of environmental exposures.

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**REDOX-REGULATED MECHANISMS OF
ORTHO-CHLORINATED PCB-INDUCED
TRANSENDOTHELIAL MIGRATION OF
TUMOR CELLS**

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Polychlorinated biphenyls (PCBs), a group of worldwide, persistent environmental contaminants, are known to cause carcinogenesis and tumor promotion and also may affect the development of cancer metastases. Because vascular endothelial cells create a selective barrier to the passage of cancer cells, we hypothesize that specific PCB congeners can disrupt endothelial integrity and increase the transendothelial migration of tumor cells. To examine this hypothesis, we elucidated the effects of 2,2',4,6,6'-pentachlorobiphenyl (PCB 104), a representative of highly *ortho*-substituted non-coplanar PCB congeners, on transendothelial migration of the MDA-MB-231 breast cancer cells. Exposure of human endothelial cells to PCB 104 induced cellular oxidative stress, metalloproteinase (MMP)-3 expression, endothelial hyperpermeability and transendothelial migration of the MDA-MB-231 cells. PCB-induced MMP overexpression was regulated by the interplay between redox-regulated Janus kinase 3 (JAK3), epidermal growth factor receptor (EGFR) and MAP kinases, such as JNK, ERK1/2, and p38. In addition, PCB-induced endothelial permeability was associated with overexpression of vascular endothelial growth factor (VEGF). PCB 104-mediated elevation of VEGF expression was induced by phosphatidylinositol 3-kinase (PI3K). In addition, the PI3K-dependent pathway was involved in PCB 104-induced activation of AP-1, a transcription factor implicated in regulation of the VEGF gene expression. The VEGF receptor (KDR/Fik-1) antagonist, SU1498, and the PI3K inhibitor, LY294002, inhibited PCB 104-induced hyperpermeability. Another prominent factor that modulates endothelial cell proliferation, migration, and angiogenesis is interleukin-8/CXCL8 (IL-8). Treatment of human endothelial cells with PCB 104 dose-dependently increased levels of IL-8 mRNA and secreted protein. IL-8-neutralizing antibody inhibited migration of endothelial cells stimulated by

conditioned media derived from PCB 104-treated cells. Site-directed mutagenesis of the IL-8 promoter and DNA binding assays revealed that AP-1 and NF- κ B sites are required for PCB 104-induced IL-8 transcription. Most importantly, pharmacological inhibition of Src kinase activity or overexpression of dominant negative c-Src in human endothelial cells resulted in a significant decrease in IL-8 expression and promoter activity. In contrast, ectopic expression of activated c-Src markedly increased promoter activity of IL-8. These stimulatory effects of dominant-positive c-Src were abrogated by mutagenesis of AP-1 and NF- κ B binding sites in the IL-8 promoter. Thus, c-Src may regulate crucial downstream signaling pathways leading to activation of NF- κ B and AP-1, followed by overexpression of IL-8 in PCB 104-treated endothelial cells. Our results provide strong evidence that *ortho*-substituted PCBs may contribute to tumor metastasis by inducing alterations of cellular redox status and stimulation of redox-responsive pathways leading to overexpression of VEGF, MMP-3 and IL-8. Supported by NIH/NIEHS (P42 ES 07380).

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THE HYGIENIC PROBLEMS OF USING THE INTENSIVE SWEETENERS IN HUMAN CONSUMPTION

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Sweeteners is a group of food additives, another than sugar. They are used in sweet food products manufacturing. They have sweetening coefficient much higher than sugar – from 30 to 300.

A lot of authors say that daily sugar consumption in the 20th century is more than 80-100g. This fact is considered as not positive for human health. Sugar in organism needs insulin and large amounts of sugar consumption need large amounts of insulin, which leads to pancreas tension. High sugar consumption causes tooth caries, dysbalance of hydrocarbon and lipid metabolism and may be one of factors of atherosclerotic changes in organism and one of etiological factors of fatness. But the

question if sucrose is the main factor of these diseases remains disputable.

In Europe there is a tendency to control sugar consumption. This fact is important for persons that have body weight excess and who care of tooth health in general.

Today we can see high interest to intensive sweeteners in sweet products manufacturing. They are assimilated in organism in another way than sugar, without insulin participation and are considered as dietary sweeteners. These are acesulfam-K, aspartame, cyclam acid and its salts, saccharin, which are much sweeter than sugar and practically have no calories.

Today in the countries of European Community we can see a wide assortment of food products which are manufactured with intensive sweeteners. But philosophy of intensive sweeteners is simple: according to Ukrainian sanitary legislation intensive sweeteners may be used in foods which have special diet status. We must remember that at first sweeteners were searched as alternative to sugar substance for persons that have the disturbance of carbohydrate tolerance. By chemical natures intensive sweeteners are the outside substances for human organism. We can use them only after investigation of each of them and determining them as safe for organism, taking into account possible distant influence on organism.

In Ukraine the list of intensive sweeteners which have legal status for using in food product manufacturing is the following: acesulfam-K E 950, aspartame E 951, cyclam acid and its sodium and potassium salts E 952, isomalt E953, Saccharin E 954, maltol E 965, xylitol E967, otyzon (has analogy to acesulfam-K), sacharol. In Europe and Russia the list of intensive sweeteners approved by legislation is wider: besides the above-mentioned sweeteners, they can use taumatine E957, neohesperidine E959, Erythrite E966, Stevioside E960, Sucralose E955.

If we consider intensive sweeteners in detail, we can see that each of them has such characteristics as ADI. This ADI has value from "0" to a determined one, for example to "15" mg/kg of body weight. From hygienic positions this means that if we have possibility to reach a desirable effect in other ways the sweetener shouldn't be used at all.

Besides, ADI of some intensive sweeteners has temporary status. This means that investigations of these sweeteners are under process at the moment.

That's why intensive sweeteners must be used strictly in the framework of existing Legislation.

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TO THE ESTIMATION OF DANGER OF AEROSOL INSECTICIDES AGAINST SYNANTHROPIC INSECTS

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Among the complex of prophylactic measures aiming at prevention and reduction of infectious diseases, spread only by blood-sucking insects, insecticides have significant specific weight. To eliminate synanthropic arthropoda (flies, mosquitoes, cockroaches, fleas etc.) there is number of aerosol preparations, whose active agents are combinations, relating to different classes according to their chemical structure. Analysis of "List of pesticides and agro-chemicals allowed for use in Ukraine" shows that synthetic pyrethroid is of the widest use among household insecticides. Aerosol insecticides are multi-component preparations containing not only active agent but also dissolver, rust inhibitors, propellant, perfume. It's worth stating that to increase biologic effect several pyrethroids and piperonyl butoxid – their synergist – are introduced to aerosol insecticides. Analysis of literary information shows those synthetic pyrethroids are dangerous compositions when influencing the organism through respiratory organs and gastrointestinal tract. That is why research of toxicological peculiarities of new agents recommended for household use is relevant.

Data about pyrethroid-based insecticides' toxicity level testify that they are less dangerous as compared with their active agent. Results of research show that these aerosols are of no resorptive-toxic and local irritating action. They are slightly or moderately harmful during inhalation. Specific sensitivity of laboratory animals for toxic action of the aerosol insecticides was not discovered.

During hygienic estimation of conditions of household use of such products,

information, testifying that content of active agents (synthetic pyrethroids) in all analyzed air samples are less than hygienic standards, was obtained. It was established that content of active agents in the air of working zone depends on type of disinsection. After ventilation, analytic methods of research showed no insecticides in the air. During disinsection, the insignificant amount of aerosol is accumulated on the surface of floors and furniture. The content of pyrethroids in all researched objects was approximately on the same level, depending on height of surface.

The results of researching toxicological-hygienic features of pyrethroid-based aerosol insecticides were grounds of standards for safe use of preparations, the observance of which excluded possibility of their negative influence on human organism.

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**TOXICOLOGICAL-HYGIENIC
CHARACTERISTICS OF A NUMBER
OF RODENTICIDE AGENTS**

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Rich agricultural crops and preservation of grain reserves depend on protection from mouse-like rodents to a great extent. Rodents do significant harm to agricultural crops, grain reserves, which demands measures to eliminate pest. Along with above-said, deratization is integral part of a complex of sanitary-epidemiologic measures aiming at prevention and liquidation of a number of infectious diseases, caused by agents carried by rodents. The list of rodenticide agents allowed for use in Ukraine includes substances from various classes of chemical combinations. Rodenticides, whose active agents are derivatives of coumarin, hydroxycoumarin and zinc phosphide, are widely used in agriculture.

Analysis of literature testifies that derivatives of coumarin and hydroxycoumarin have very dangerous influence on organism and selective organotoxic action. They have strong cumulative properties; the intoxication is characterized with slow evolution, prolonged

lethality, which is not inherent with rodenticide agents based on zinc phosphide. Rodenticide agents based on zinc phosphide relate to "acute action". There is no tolerance to these agents, as distinct from derivatives of coumarin and hydroxycoumarin. If zinc phosphide gets to the stomach, it decomposes under the influence of gastric juice, forming phosphorous hydrogen, which determines toxicological features of a rodenticide. Phosphorous hydrogen mainly influences nervous system, respiratory organs, blood vessels, liver and kidneys. Taking the above-stated into account, the research of new rodenticide agents toxicological features is relevant. Information about the toxicity level of rodenticides means based on derivatives of coumarin, hydroxycoumarin and zinc phosphide testifies that they are less harmful at peroral influence, than their active agents. Specific sensitivity of laboratory animals for toxic action of the preparation was discovered. The results of toxicity research show that these agents are of no resorptive-toxic and local irritating action. They are slightly harmful during inhalation. Rodenticides means, whose active agents are derivatives of coumarin, hydroxycoumarin and zinc phosphide, have not sensitization potential

It is important to mention that active agents of these preparations (brodifacum, zoocoumarine, coumatetralyl, bromodialon, difetialon, difenacum, difenacin, flocoumafen, zinc phosphide) are supplied by various foreign companies in the form of raw materials. Rodenticides baits in the form of paraffin briquettes, pellets, dough-like grain baits etc. are produced in Ukraine on the basis of different medical-supervision companies. During current sanitary inspection of the state of air in the working zone (hazardous production factor) at the enterprise during production of rodenticide baits, contents of above-mentioned compositions are controlled. It's worth stating that there are approved maximum allowable cocentration of zinc phosphide, difenacin, coumatetralyl in the air of working zone. Taking into consideration that further development of measures for safe production and use of rodenticides is relevant, hygiene standards for brodifacum, bromodialon, difenacum, difetialon, zoocoumarine, flocoumafen should be validated.

**INFLUENCE OF SOME MEDICINES ON
THE DYNAMICS OF ACTG AND CYCLIC
NUCLEATIDES CHANGES UNDER
ACUTE TOXIC LIVER DISEASE**

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Experiments were carried out on the white rat-males line Wistar weight 150-190 g. Toxic acute liver disease was reached by the way of one time 4-hour inhalation dynamic influence by the flying compounds of epoxide resin ED-20 (ER) in concentration of $1/3 LC_{50}$ (120-140 mg/m³) by epichlorhydrine. Some rats received flavinate (F) intramuscular in dose 4 mg/kg (ED₅₀), lipine (L) – intraperitoneal 0,8 mmol/kg (ED₃₀), omeprazole (O) – intraperitoneal 50 mg/kg according to the treat-preventing scheme, in compliance in 1; 0,5 and 0,5 h after the beginning of intoxication and in 5 min after ending. Samples of blood and liver for radioimmunitive research took after 6, 24 and 72 h after the last medicine injection.

Find out that toxic disease of liver by ER followed the essential increasing of ACTG concentration in blood and only in 24 h after finishing of inhalation in average on 117%. Changes of ACTG level in 6 and 72 h were not essential and weren't higher then 10%. Reliable increasing (in 2 times) of cAMP level was earlier, on the 6-th hour of experiment. Later the concentration of this substance sharply decreased and reached at 24 h the level of intact rats, and on 72 h was lower, as to this substance in 3,5 times. Contention of cGMP in liver cells in 6 and 24 h decreased as cAMP concentration, accordingly on 73 and 54% and increased on 97% in 72 h.

Using in the condition of acute toxic liver breach by ER, F and L followed the essential decreasing of ACTG concentration in blood on 24 h of experiment in compliance on 42 and 34%. And the effect of F also characterized by decreasing cAMP level comparably with intact rats on 196 and 65% in first two terms after intoxication and decreasing in 27% - in third term. At the same time the efficacy of medicines as to poisoned rats (control group) was in compliance 45, 71 and 159%. In 24 h after

injection of L the level of researching substance in poisoned animals was higher then in healthy ones on 24% and in 72 h was lower - on 27%. Comparably to the control group we registered increasing of cAMP concentration on 29 and 160%. Injection O for poisoned rats made grow up cAMP level in liver in 6 and 24 h on 285 and 95% accordingly, and its efficacy was 88 and 102%. Under the influence of F we had only tendencies to normalization of cGMP level in liver in all terms of experiment and essential increasing correlation cAMP/cGMP.

Summing it up, the influence of ER flying compounds on organism caused phase changes in system cAMP/cGMP and ACTG. At the first period after poisoning cAMP level in liver increased, and then decreased with concerning predomination cGMP-depend processes. Under O influence, less under F and L, which were used according to the treat-preventing scheme before and after poisoning by ER, was long lasting increasing of cAMP level in liver and decreasing of ACTG concentration in blood. F, which showed moderate influence on cGMP concentration in liver, made essentially increased cAMP/cGMP correlation.

**SERUM ALBUMIN ADDUCTS OF
BENZENE OXIDE AND 1,4-
BENZOQUINONE AS BIOMARKERS
OF EXPOSURE TO BENZENE**

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Benzene causes hematotoxicity and leukemia in humans. The complex metabolism of benzene yields several reactive metabolites, including benzene oxide (BO) and 1,4-benzoquinone (1,4-BQ)

that can form adducts with macromolecules such as DNA and proteins. We have measured adducts of BO and 1,4-BQ with serum albumin (Alb), designated as BO-Alb and 1,4-BQ-Alb, respectively, in 360 benzene-exposed workers and 211 local controls from Shanghai and Tianjin, China. Based upon the individual geometric mean exposure in the month preceding phlebotomy, the median benzene exposure level was 2.31 ppm (interquartile range: 1.35-6.11 ppm; range: 0.074-328 ppm). After extracting Alb from serum or plasma, adducts were removed from the protein by reacting with methanesulfonic acid and trifluoroacetic anhydride and their volatile derivatives were extracted and measured by GC-MS. Both BO-Alb and 1,4-BQ-Alb were detected in all subjects. The median levels of BO-Alb and BQ-Alb in control subjects were 150 pmol/g (range 44-544 pmol/g) and 1420 pmol/g (range 420-12,625 pmol/g), respectively. The median levels of BO-Alb and BQ-Alb in exposed subjects were 252 pmol/g (range 54-7,465 pmol/g) and 2,291 pmol/g (range 265-15,950 pmol/g), respectively. Since the average adduct levels of both BO-Alb and 1,4-BQ-Alb in controls differed across studies, each exposed subject's adduct level was expressed as a fold increase above the control value from the corresponding study. Plots of the individual relative adduct levels versus benzene exposure shows nonlinear production of adducts over the indicated range pointing to saturable metabolism of benzene in humans.

A number of chemicals that are classified as non-genotoxic carcinogens are known to activate nuclear receptors. Peroxisome proliferators (PPs) are a class of such compounds whose risk to human health has been in question for several decades. Because there is a high potential for exposure to these compounds, which are ubiquitous in the environment, understanding the mechanism of hepatocarcinogenesis in rodents and the relevance of this mechanism in humans is critical. Nuclear receptor, peroxisome proliferator activated receptor (PPAR) α mediates several responses to these compounds and is required for liver carcinogenesis in mice. Many early effects of peroxisome proliferators, as determined by both *in vivo* and *in vitro* studies, are mediated by Kupffer cells in a PPAR α -independent manner. In this study, we investigate the role of Kupffer cells in mediating long-term effects of peroxisome proliferators using NADPH oxidase - deficient mice (p47^{phox}-null), in parallel with PPAR α -null mice. The findings demonstrate that PPAR α is required for sustained oxidant production, cell proliferation and oxidative DNA damage, all of which are important modes of action in non-genotoxic carcinogenesis. Kupffer cell mediated events on the other hand, appear to be short-lived. Overall, these results suggest that nuclear-receptor independent pathways are not imperative for chronic responses to peroxisome proliferators (Supported by ES11391, ES11660, ES12686 and ES13342).

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**ROLE OF NUCLEAR-RECEPTOR
INDEPENDENT MECHANISMS IN LONG-
TERM EFFECTS OF NON-GENOTOXIC
HEPATOGENOTOXIC CARCINOGENS**

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**FEATURES OF CLINIC AND
PATHOGENESIS OF TMTD CHRONIC
INTOXICATION**

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In the mechanism of TMTD toxic action substantial part is acted by the decline of oxidative and reductive processes in an organism, because of depressing of activity of metal-containing enzymes, that is related to helative properties of xenobiotic, and also features of his metabolism in organism - formation of carbon bisulfide, tetramethylthiourea, etc. (M.V. Korablev,

1971; Y.A. Antonovich, 1973; S.I. Tabagari, 1999).

The aim was to study features of clinic and pathogenesis of TMTD chronic intoxications. We investigate health status of 475 workers, having a professional contact with fungicide in the conditions of centralized corn and sugar beet seed dressing in ambulatory and in hospital. At majority of inspected (60%), experience of work with TMTD exceeded 3 years. The results of research of persons, contacting with TMTD, were compared to such at the persons of control group which 183 men entered in the complement of age, sex, conditions of work and working experience in seed-dressing factories, but not undergoing in the process of work influence of toxic substances.

Pathology of the nervous system at 64.4% of workers with TMTD showed up as vegetative-vascular and asthenic disorders (compare with 35.2% in control).

Hypothalamic syndrome, flowing with vegetative-vascular, mainly sympatho-adrenalic paroxysms, was diagnosed in 7.8% cases. The origin of these pathological states can be related to violation of exchange of biogenic amines, because at inspected the increase of excretion of adrenalin and noradrenalin was exposed with urine, maintenances of serotonin in blood, the decline of excretion of 5-oxiindolacetic acid – last metabolite of serotonin is set also. Change of exchange of biogenic amines, presumably, are a result, both violation of the hypothalamic hypophisar influencing of regulators and direct influence of TMTD on adrenal glands with the decline of activity of copper containing enzyme monoaminoxidaze, participating in oxidizing dezaminating of biogenic amines.

Disorders of peripheral department of the nervous system as a vegetative form of polyneuropathy are found out at 7.4% of inspected. At a long and intensive contact with TMTD the development of encephalopathy (2.1%) and encephalomyelopolyneuropathy is possible (0,6%).

Pathology of the endocrine system is reflected by hyper- or hypomenstrual syndrome. It manifests in disorder of function of thyroid gland, mainly toward its decline, by the diffuse increase of thyroid gland, rarer by the nodose goiter. On

occasion there were thyreotoxicosis, mixedema and cancer of thyroid. Hematological changes were characterized by the moderately expressed hypocromic anemia, rethyculocytosis, by a tendency to leucopenia with neutropenia, relative lymphocytosis and monocytosis. At 32.8% of inspected there was pathology of the hepatobiliar system (as compared to 13.6% in control): diskinetik and inflammatory changes of gall-bladder, rarer chronic hepatitis and hepatoholecystitis. In biochemical blood tests more, than at a half of inspected the decline of activity of ceruloplasmine and alkaline phosphates was marked. Thus these changes prevailed at persons with hepatitis and hepatoholecystitis. The decline of activity of the indicated enzymes is explained both by toxic influence of TMTD on a liver, where these enzymes are synthesized and his helatoforming properties. As is generally known, ceruloplasmin contains in catalytic center ions of copper, and alkaline phosphataze is activated by the ions of zinc and magnesium.

Thus, TMTD possesses a polytrophic action. In pathogenesis of intoxications an important value has depressing of enzymes of oxidate-reductive process. As a result there is tissue hypoxia, to which the nervous system, thyroid gland, adrenals, blood forming tissue are most sensible. Appeared disorders of the hepatobiliar system are aggravated by the displays of intoxication and strengthen hypoxia. Substantial in the mechanism of intoxications of TMTD also there is disorder of exchange of biogenic amines.

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NA⁺,K⁺-ATPASE ACTIVITY OF THE RAT HEPATOCYTE PLASMA MEMBRANE AFTER SUBCHRONIC INTRAGASTRIC INTRODUCING OF HERBICIDE 2,4-DICHLOROPHENOXYACETIC ACID, PLANT GROWTH REGULATORS IVIN AND POTATIN

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At a cell level lipid matrix of plasma membrane (PM) and its enzymes, Na⁺,K⁺-ATPase in particular which provides the

supporting of cell ionic homeostasis are the first to be exposed to negative effects of pesticides. Herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) is widely used in the world and in Ukraine, and it may display a number of toxic effects. Plant growth regulators are used to increase the harvest of cultivated plants. Ivin (N-oxide-2,6-dimethyl-pyridine) and its molecular complex with succinate – potatin belong to the compounds of this class. Ivin in some forms of application reduces a toxic effect of numerous pesticides on plants and soil microorganisms. The aim of this work is the study of hepatocyte PM Na⁺,K⁺-ATPase activity under the subchronic influence of 2,4-D, ivin, potatin and sodium succinate and their combined use with herbicide.

Subchronic effects of the substances were investigated on Wistar male rats. Compounds were injected by intragastric way in dose: 2,4-D – 10 mg/kg of weight, ivin – 50 mg/kg of weight, potatin – 50 mg/kg of weight, and sodium succinate – 5 mg/kg of weight in 1 ml volume daily within four weeks. In case of combined use each substance was injected together in these doses in 1 ml total volume. Hepatocyte PM fraction was isolated by centrifugation method in sucrose gradient.

Na⁺,K⁺-ATPase activity is 25,9±1,9 nmole Pi/(min4mg protein) in liver cell PM of intact rats. The increase of enzymatic activity (for 46% according to control) under the subchronic influence of 2,4-D was observed. It may depends on interaction of negatively changed 2,4-D molecules with enzymes molecules.

Under the influence of ivin, potatin and its combined use with 2,4-D PM Na⁺,K⁺-ATPase activity was decreased: 30% decreasing enzyme activity was produced by ivin, 33% – by combination of ivin and 2,4-D, 24% – by potatin and 34% – by combination of ivin and 2,4-D according to control. Evidently, such effect was produced by ivin present in all these studied groups. Ivin has membranotropic properties and incorporates in hydrophobic membrane core decreasing membrane fluidity. Na⁺,K⁺-ATPase binds cations in each side of membrane and increasing fluidity of lipid matrix in the presence of ivin leads to enzyme inhibition. Besides similar effect of ivin and potatin on hepatocyte PM Na⁺,K⁺-ATPase activity these substances

completely inhibit activating influence of herbicide 2,4-D on enzyme activity.

Subchronic influence of sodium succinate and its combined using with 2,4-D leads to the increasing hepatocyte PM Na⁺,K⁺-ATPase activity according to the control (29% and 27%, respectively). Firstly, it may be caused by direct interaction of negatively changed succinate molecules with extramembrane enzymes domains of Na⁺,K⁺-ATPase protein, it may be a reason of enzyme activation. Secondly, Na⁺,K⁺-ATPase activity may increase as a result of intensification of energoproducing process in liver cells after subchronic injection of succinate – metabolite of Krebs circle.

Therefore, Na⁺,K⁺-ATPase activity is sensitive to different xenobiotics and in case of its combined use the effects of toxic herbicide 2,4-D was modified.

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DIRECT-ACTING OXIDATIVE MUTAGENS IN PAH-CONTAMINATED SOIL FROM A HAZARDOUS WASTE SITE

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Soils at hazardous waste sites contain complex mixtures of chemicals and are often difficult to characterize in terms of risk to human and ecological health. Over time, biogeochemical processes can decrease the apparent concentrations of pollutants, but can also lead to accumulation of new products whose toxicity and behavior in the environment are often not considered. Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental contaminants and are frequently present in soils contaminated with fossil fuels and petrochemicals. Bacterial and fungal metabolism of PAHs often produces oxidized PAH products such as catechols and quinones. Such products can be resistant to further breakdown and are known to cause DNA and protein modification through covalent bonding and the production of reactive oxygen species. We report the presence of direct-acting oxidative mutagens in aged PAH-contaminated soil collected from a former

manufactured gas plant site in North Carolina. The soil was extracted with dichloromethane in a soxhlet apparatus and separated into fractions by normal-phase chromatography. Mutagenicity of the fractions was evaluated using a reversion assay with *E. coli* WP2 *uvrA*/pKM101 (IC188) and *E. coli* WP2 *uvrA oxyR*/pKM101 (IC203) without metabolic activation. Both *E. coli* strains are able detect mutations resulting from base substitutions such as those caused by oxidative mutagens. The $\Delta oxyR30$ mutation in strain IC203 prevents the expression of several important anti-oxidant proteins in response to increased oxidative stress. Fractions of soil extracts expected to contain semi-polar substances, such as oxidized PAHs, caused an increased reversion rate in the oxidative stress-susceptible strain IC203. Increased reversion was not observed when cells were treated with un-fractionated extract due to toxicity of the mixture to the test organisms, indicating that the concentration of oxidative mutagens was too low in the whole extract relative to the concentration of non-specific toxicants. Antagonistic effects which are often present in complex mixtures may also be partially responsible for the decrease in mutagenicity. Reduction of the chemical complexity of the extract by fractionation seems essential for evaluating mutagenicity and is also expected to aid in the eventual identification of specific mutagens.

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INFLUENCE OF TETRAN ON GROWTH OF INFUSORIANS POPULATION TETRAHYMENA PYRIFORMIS W

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The influence of plant growth regulator Tetran (bis-N-oxide-2-methylpyridin-Zn(II)chloride) on growth of an infusorians population *Tetrahymena pyriformis* W in the concentrations range 10^{-2} — 10^{-28} M per different phases of their development (lag phase – 24 hours, logarithmic phase – 48 hours, steady state – 72-96 hours) is investigated.

It's established, that concentration 1×10^{-2} M of Tetran in all growth phase causes a significant decrease (78,4-93,3 %) of the

number of population *Tetrahymena pyriformis* W.

In lag phase under the influence of concentrations 1×10^{-4} , 1×10^{-6} , 1×10^{-10} , 1×10^{-14} , 1×10^{-16} and 1×10^{-18} M a meaningful increase in the number of infusorians is shown on 84,6%, 92,3%, 107,7%, 76,9%, 84,6% and 107,7%, accordingly. In 48 hours Tetran make mainly inhibition effect on infusorians growth on the all investigated concentrations. The most signified effect was in concentrations 1×10^{-12} M (20,5%) and 1×10^{-22} M (14,1%). In steady state (72-96 hours) depending on concentration of Tetran the different-directional effect is observed. In 72 hours the most significant inhibition of infusorian growth is observed in concentrations 1×10^{-2} M (92,3%), 1×10^{-8} M (48,7%), 1×10^{-16} M (42,3%) and the insignificant increase in the number of infusorian - in concentrations 1×10^{-12} M (20,5%) and 1×10^{-22} M (14,1%). In 96 hours the significant increase in the number of infusorian is found in concentrations 1×10^{-4} M (40,7%), 1×10^{-14} M (36%), 1×10^{-24} M (23,3%) and the most signified decrease – in concentration 1×10^{-2} M (86%), 1×10^{-6} M (25,6%), 1×10^{-8} M (30,2%), 1×10^{-16} M (33,7%).

Thus, depending on concentration and time of influence of Tetran the different-directional effect (increase or decrease in the number) on growth and the number of infusorians population *Tetrahymena pyriformis* W is found. The exact dependence "concentration-time-effect" is not found.

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COMPARATIVE ESTIMATION OF ALLERGEN ACTION OF PREPARATIONS ON METHSULFURON-METHYL BASIS

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Study and estimation of possible allergen action is the one of requirements during registration of new pesticides. We studied sensitizing behavior of set of preparations Saracen, Metas, Mezo, Exit and AS-4M on methsulfuron-methyl basis. The study of allergen action of herbicides (Saracen, Metas, Mezo, Exit and AS-4M) was conducted on albinos guinea-pigs by sensitizing complex (intracutaneously and

cutaneous) by the method of Alekseevoy-Petkevich. While testing on animals skin tests, changes of mast cells degranulation (CMCD) and specific lysis of leucocytes (SLL) were taken into account. It is determined that preparations of Mezo, Exit and AS-4M do not possess an allergen action and in accordance with Hygienical classification (1998) are related to 4-th class of danger. While testing skin reaction preparations Saracen and Metas 25 percents of experimental animals are marked positive while spotting increase of CMCD on 12 percents. Changes of SLL was not revealed. Achieved results show that Saracen and Metas possess weak sensitizing behavior and as allergen related to 3-rd class of danger. Taking into account that technical methsulfuron-methyl does not possess allergen reaction it is possible to assume that sensitizing action of Saracen and Metas is conditioned due to auxiliary substances that included in preparative forms. Analysis of composition of mentioned preparative forms of herbicides let us assume that substances, which stipulate for its sensitizing behavior, are sodium of naphthalen-sulfonate and condensate of dialkyl-naphthalen-sulfonate formaldehyde because formaldehyde is a strong allergen. For some structural analogues of naphthalen-sulfonate weak sensitizing is also typical. Avhieved results show that during development of new preparative forms of pesticides it is necessary to take into account sensitizing behavior of auxiliary components and not to include them in the complement of preparations if possible.

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**THE HEMOCARBOPERFUSION AS
PREVENTION OF THE DELAYED
NEUROPATHY, CAUSED BY
ORGANOPHOSPHOROUS COMPOUNDS**

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The aim of the research was to learn the possibility of the use of the hemocarboperfusion for the correction of the immune derangements of the hard forms of neuropathy by the example of the organophosphorous neurotoxicant aphos. The research was made on the Leggorn

hen. The animals were given aphos single dosing orally in the dose of 200 mg/kg. The hemocarboperfusion was done with the help of activated carbon SCN-2k single on the 10-12 day after the introduction of aphos. Earlier it was shown that aphos in the preparalytic period (7-14 day) of the delayed neuropathy in the dose of 200 mg/kg caused the accumulation of small dispersion circulating immune complexes (CIC) in blood serum, increased the titers of autoantibodies to tissue antigens from the hens' brain, and decreased considerably the functional activity of the neutrophils and T-lymphocytes, number of NK-cells and T_s. Separate animals had the ratio of small dispersion to macro dispersion CIC -1,5 – 2,7, titers of the autoantibodies to tissue antigens of the hens' brain increased to 1: 512.

During the modelling of the delayed neurotoxic effects (DNE) with the help of aphos in the dose of 200 mg/kg for hens which were intended for hemocarboperfusion, during the preparalytic period the clinic of the development of the delayed neurotoxic effects and immunological shifts in organism were similar. After the realization of hemocarboperfusion, the clinical picture of the delayed neurotoxic effects was not intensified, paralysis did not develop. Comparing the received experimental data it can be marked that after hemocarboperfusion, the changes of the quantitative composition of immunocompetent cells and their functional activity, which were under review, were directed on the normalization of the functional activity of the immune system. The most important consequence of hemocarboperfusion is the removal of small dispersion CIC, the increase of metabolic activity of neutrophils, normalization of the ratio of T_h and T_s due to the decrease of the number of T_h. The correction with the help of hemocarboperfusion of the most important indices of the immune system of the hens which are responsible for the autoimmunological process in organism allows to reduce the course of the delayed neurotoxic effects and prevent paresis and paralysis. The positive effect of hemocarboperfusion testifies about the fact that in the pathogeny of the DNE the immune system plays the important part. Thus on the example of aphos, the high

effectiveness of hemocarboperfusion was shown as the method of prophylaxis of the delayed neurotoxic neuropathies caused by neuroparalytic organophosphorous substances. Hemocarboperfusion promotes the elimination of pathogenic CIC out of blood, autoantibodies to neural tissue, normalization of T- and B- systems of immunity, which allows preventing the complications such as paresis and paralysis. In conclusion, it can be marked that the offered method of prophylaxis of paresis and paralysis can be recommended in the complex therapy of the delayed neurotoxic effects caused by the organophosphorous substances poisoning.