AUSTRIAN SOCIETY OF TOXICOLOGY (ASTOX)

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OBJECTIVES / ASSIGNMENTS

ASTOX was launched in January 1991, currently the society amounts to more than 130 members. The objective of the society is to advocate scientific and applied interests of Toxicology in Austria. The duties of the society comprise:

- ASTOX takes care of the advancement of Toxicology in Austria.
- Organization of scientific meetings.
- Education and professional development.
- Is responsible for registration of toxicologists and their official recognition by EUROTOX.
- Taking professional procurements and competent advice in matters of public health.
- Holds contacts with societies of toxicology in other countries and international societies.

INFORMATION

Conferences

ASTOX organizes annual scientific meetings. Emphasis is placed on addressing current scientific and applied issues in toxicology at any one time (e.g. the sixth symposium in 2010 was focussed on "REACH: experience of two years after implementation"). ASTOX sponsors prices for poster and oral communications to encourage young scientists to actively participate.

Experts in Toxicology

ASTOX members include experienced scientists at universities, private research institutions, industry and consultants. A list of ERTs available in Austria is published at http://www.**astox**.at enabling the public to directly contact an expert in case of questions or concerns.

EDUCATION / CAREER

University Course in Toxicology for postgraduates at the Medical University of Vienna (http://www.meduniwien.ac.at/toxicology).

ASTOX supports the Toxicology Course Vienna which provides education and training in all relevant subjects. Successful attendants are qualified to identify and characterize adverse effects of chemical compounds, to elucidate mechanisms of action at the cellular, biochemical and molecular level, to review and assess safety data generated for a specific chemical, to estimate the probability of the occurrence of adverse effects (risk assessment), to contribute responsibly to risk-benefit evaluation, risk management and risk communication, to develop approaches for prevention, diagnosis and treatment of adverse effects. Duration of course: 3 years; Certificate: "Master of Sciences (Toxicology). The sixth course started in June 2010.

European Registered Toxicologist (ERT)

Toxicologists wishing to be included in the register should apply at the Austrian Register of Toxicologists (AR-TOX), a body in the frame of ASTOX and linked to the EUROTOX Register. The objectives of the AR-TOX are to recognize experienced scientists who are actively engaged in the multi-disciplinary field of toxicology, to ensure that Registered Toxicologists observe and maintain high standards of professional competence and ethical conduct and to ensure the description "Registered Toxicologist" or the use of initials or letters having a similar meaning to be confined to persons who have satisfied the registration committee of their professional competence and experience.

CZECH SOCIETY FOR EXPERIMENTAL AND CLINICAL PHARMACOLOGY AND TOXICOLOGY
A branch of the Czech Medical Association J. Ev. Purkyne

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THE PAST AND PRESENT OF SCIENTIFIC TOXICOLOGICAL OFFICIAL ORGANIZATION IN THE CZECH REPUBLIC

Within the framework of EUROTOX and IUTOX, Czech toxicologists are represented by the Toxicological Section, which is a unit of the Czech Society for Experimental and Clinical Pharmacology and Toxicology of the J. E. Purkyně Czech Medical Society. In the Czech territory, the association of toxicology as a branch of science with pharmacology is rooted in history. When in the mid-1960s, soon after the thalidomide malformation case, the European Society for Drug Toxicology (the predecessor of the present EUROTOX) was being established, the then Czechoslovak Pharmacological Society was one of the initiators, the Czech representative and spokesperson being the pharmacologist Prof. Helena Rašková. Some of the first European toxicological conferences thus took place in Bohemia, in Prague in 1967 and in Karlovy Vary in 1974, and later again in Prague in 1995. At the national level, toxicological conferences have been organized since the 1970s. Their programmes were interdisciplinary and variable. Topical toxicological areas were purposefully selected (e.g. experimental toxicological models, questions of data transfer from experimental systems to humans, hepatotoxicology, ontogenetical aspects in toxicology, cellular toxicology, experimental immunotoxicity, teratogenicity, Good Laboratory Practice in toxicology). Since the separation of Czechoslovakia into the Czech and Slovak Republics, these annual toxicological conferences have been alternatively held under the auspices of the two national toxicological associations. The first one of these joint Czech-Slovak or Slovak-Czech conferences was held in Piešťany in Slovakia in 1996. This year's (2010) toxicological conference in Stará Lesná is thus the fifteenth one. Besides, the Czech Toxicological Section has participated in the organization of monothematic toxicological symposia, e.g. repeatedly in Pilsen, "Chelating Agents in Pharmacology, Toxicology and Therapeutics", in Prague, "Alternative Toxicological Methods" and regularly in Hradec Králové "Round Table Discussions on Pharmacological and Toxicokinetical Topics".

In the period when the principles for toxicological methodologies (above all those concerning medicaments) were being formulated at the national level, the Toxicological Section was one of the units consulted. At present it possesses no other competence than organizing professional meetings and discussions. Within their framework, the topical effort is to cover the widest possible spectrum of toxicological research fields, both in the university and hygienic spheres, and the toxicological units of chemical industrial plants.

ISSN: 1337-6853 *(print version)* | 1337-9569 *(electronic version)*

THE POLISH SOCIETY OF TOXICOLOGY

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The Toxicology Section of the Polish Pharmacological Society, established in 1966, was the first organization of Polish toxicologists. In 1968 the Toxicological Section organized the first Polish Toxicological Symposium.

In March 1978 the Polish Society of Toxicology was formally founded as an interdisciplinary scientific society acting under the auspices of the Polish Academy of Science. The aims of the Society comprise organization and promotion of scientific research in the field of toxicology;

- dissemination of research results in toxicology and related fields;
- informing the public about current toxicological issues;
- representation of Polish toxicology in Poland and abroad.

The Polish Society of Toxicology operates nationwide. There are 11 regional branches in Białystok, Gdansk, Krakow, Lublin, Lodz, Poznan, Silesia, Szczecin, Warsaw, Wrocław, Warmia and Masuria. Altogether, the Society gathers over 370 members. At present, Prof. Wojciech Wasowicz is acting as the President of the Society and its seat is located in Lodz. The board of directors of the Polish Society of Toxicology co-ordinates the activities of its regional branches and fulfils its duties through established commissions and sections. They include: the Charter Commission, the Commission for Education, the Commission for the Registration of Toxicologists, the Commission for International Cooperation, the Editorial Commission and the Environmental Toxicology Section.

The Society became a member of EUROTOX in 1991, and IUTOX in 1999. Training of toxicologists in Poland under the auspices of the Polish Society of Toxicology was formally included in the postgraduate education programs as early as 1983. Since the very beginning of its existence the Society has acted as an advisory body and provides scientific consultation in toxicology. The Commission for the Registration of Toxicologists appoints experts who are recognized internationally. In 1994, the Editorial Commission compiled and published the "Dictionary of Toxicological Terms" (2nd ed. published in 2008).

Scientific congresses organized by the Society provide the largest forum for the presentation of the research results in all areas of toxicology and stimulate further advances in this field and Polish toxicologists largely contribute to the development of the Polish and world science. The Polish Society of Toxicology, in cooperation with the Nofer Institute of Occupational Medicine was also the organizer of the 42nd Congress of The European Societies of Toxicology (EUROTOX) held in Cracow, Poland, on 11–14 September 2005. The Travel Grant for EUROTOX has been founded by the Polish Society of Toxicology and it is awarded to Polish young toxicologists each year.

The Society is very proud of having organized nine national scientific congresses. At those congresses, the most innovative doctoral dissertations and habilitation theses are granted rewards. Two recent annual meetings of the Society (RICH in toxicology, 2009; Food toxicology, 2010) were held under the name of "New trends in Toxicology".

The scientific activity encompasses all areas of toxicology, including environmental, industrial, clinical, forensic and veterinary toxicology, toxicological biochemistry, immunotoxicology, toxicological analysis, regulatory toxicology and others.

SLOVAK TOXICOLOGY SOCIETY SETOX

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The Slovak Toxicology Society (further only SETOX) is a body corporate and civil association, associating professionals in the field of toxicology. SETOX was established in 2006 by splitting from the Slovak Medical Society.

MAIN ACTIVITIES OF THE SOCIETY

- supporting the development of toxicology in Slovakia
- organizing scientific events (seminars, conferences)
- education in toxicology (professional courses, cooperation and support in PhD. study and post-doctoral fellowship)
- publication activities (editing of monographs, conference proceedings, textbooks)
- cooperation with state authorities, other societies in fields related to toxicology at national and international level
- support development and implementation of in vitro methods into toxicology praxis
- dissemination of information for members

DIVISIONS

Experimental Toxicology
One of the scopes of this division is experimental modeling of adverse effects during intrauterine development and study of the effect of diverse agents on structural as well as functional integrity using modern in vivo as well as in vitro methods. Another topic of this division is to study of carcinogenity, mutagenity and teratogenity mechanisms.

Clinical Toxicology
This division focuses mainly on common intoxications present in the population and cooperates with experienced physicians to elucidate and solve problems of toxic exposure in humans.

The problem of hypoxia during gravidity and labor is another big issue of this division. Renowned pediatricians and obstetricians, members of SETOX, are focusing on the early detection and treatment of these conditions.

Industrial Toxicology
Industrial toxicology and ecotoxicology is the main focus of the third division of SETOX.A great deal of work concerns occupational hazards and possible toxic exposure during the work process.

In Vitro Toxicology
This fourth and youngest division of SETOX brings together scientists interested in in vitro methodologies and assessment of toxicity by means of alternative/in vitro methods.

The mission of IVT section is to:

- promote in vitro toxicology and its practical applications,
- support development and implementation of in vitro methods into toxicology praxis,
- stimulate, support and promote use in vitro tests in the field of education,
- serve as an information channel between national and international groups interested in toxicology in vitro,
- arrange scientific seminars with the subject of in vitro methods.

One of the goals of our society is also spreading information about toxicological research by issuing books and proceedings from the conferences. Over the past years the society disseminated and published several presentations from the conferences in international peer-reviewed journals. In 2008 new toxicological peer-review journal *Interdisciplinary Toxicology* was established and in 2010 was accepted for full-text indexing in the PubMed Central.

ISSN: 1337-6853 *(print version)* | 1337-9569 *(electronic version)*

STUDY OF THE APC GENE FUNCTION IN MOUSE *APC*$^{+}$/*APC*^{1638N} MODEL

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Familial adenomatous polyposis (FAP) is an autosomal dominant disease characterized by the presence of hundreds to thousands of benign polyps in the colon, which if not removed prophylactically in an almost 100% penentrance represent risk of developing malignant cancer. FAP is induced by germline mutation in the *APC* gene. Tumorigenesis launched a second somatic mutation of *APC* gene allele, leading to synthesis of non-functional APC protein.

One of the possibilities of cancer prevention could be an alternative gene therapy using bacteria as vectors for delivery of therapeutic protein molecules. The first step of this work was cloning of complete *APC* gene into vector for expression in bacterial cells. For this purpose vector pET24a+ was used and expression was performed in *Escherichia coli* BL21(DE3) and BL21(DE3) pLysS. After each transformation, accuracy of complete *APC* gene was tested by sequencing. *APC* gene expression was induced by IPTG and APC protein was identify by Western blot analysis using monoclonal antibodies against the APC protein.

Cells of this bacterial strain were per oraly applied into transgene mice *APC*$^{+}$/*APC*^{1638N}, which carry mutated APC gene resulted in production of nonfunctional protein and consequently formation of intestinal tumors. Potential reduction of intestinal tumors formation are analysed.

IMPLICATION OF GAP JUNCTION CONNEXIN-43 CHANNELS IN ANTIARRHYTHMIC EFFECTS OF OMEGA-3 FA AND ATORVASTATIN

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We have previously shown that hereditary hypertriglyceridemic (HTG) rats, characterized by moderate hypertension, insulin resistance and myocardial structural remodelling, are prone to malignant arrhythmias. Omega-3 fatty acids (omega-3 FA) and statins exhibit besides others effects also antiarrhythmic ability, while definite mechanisms are not yet elucidated. Our goal was to examine whether these compounds may affect susceptibility of the HTG rat heart to ventricular fibrillation (VF) and whether they affect myocardial cell-to-cell coupling protein connexin-43 (Cx43).

Part of HTG and healthy Wistar rats was fed with omega-3 FA (Vesteralens, Norway, 30mg/100g/day/2mth). Atorvastatin (Zentiva, Slovak Republic, 0.5mg/100g/day/2mth) was orally applied to another part of HTG and Wistar rats. Some functional parameters and susceptibility of the heart to electrically-induced ventricular fibrillation was monitored using Langendorff-perfused isolated heart. Ventricular tissues from treated and untreated HTG and Wistar rat hearts were processed for ultrastructure examination as well as for analysis of myocardial Cx43 distribution and expression using antiCx43 MAB, immunofluorescence and immunoblotting.

1/ Both, omega-3 FA and atorvastatin reduced elevated blood pressure, triglycerides and heart rate in HTG rats. 2/ VF-threshold was significantly increased due to treatment in HTG and healthy rat hearts. 3/ Abnormal localization of myocardial Cx43 was not eliminated, whereas elevated phosphorylated form of Cx43 was suppressed by the treatment in HTG rat hearts. 4/ Subcellular examination revealed an improvement of cardiomyocyte and intercellular junctions integrity.

Results indicate that antiarrhythmic effects of omega-3 FA and atorvastatin are associated with modulation of Cx43 phosphorylation and protection of cell-to-cell junction integrity. As both compounds are ligands for PPAR, a possible modulation of Cx43 gene expression as well as the way of Cx43 phosphorylation should be examined in further studies.

This work was supported by APVV SK-UA 0022-09 and VEGA 2/0049/09 grants.

BIOLOGICAL PROPERTIES OF BIOGLASS SAMPLES IN Li_2O-SiO_2-CaO-P_2O_5-CaF_2 SYSTEM EVALUATED ON FIBROBLAST CELL LINES

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Synthetically prepared biomaterials that are used in clinical practise as alternatives of damaged, diseased or undeveloped parts of skelet as well as missing parts of body for correction of inherited or pathological deformities or for traumatic injuries, are the most often used materials. To improve the surface properties of biomaterials for cell adhesion and colonization, the bioglass with various content of P_2O_5 in oxide system Li_2O-SiO_2-CaO-CaF_2-P_2O_5 was prepared by Kuzielová et al. Inthis worh the biocompatibility and cytotoxicity of bioglass with 0, 10, 12 and 14% content of P_2O_5 were evaluated on human fibroblast cells VH10 and B-HNF-1 and mouse fibroblast NIH-3T3 cells. The biocompatibility of new glass-ceramics was assessed on the base of the cell adherence and the colonization of fibroblast cultures on biomaterial surface by light microscopy. The cytotoxicity was determined by the direct contact test / vital staining – direct counting of adherent – growing

cells, the evaluation of cell viability, cell morphology, the determination of LDH level. The dishes without bioglass presence were used as negative control.

We found that all used cell lines were sensitive to bioglass. All used methods: cell proliferation, morphology and LDH level have indicated slight cytotoxicity. The inhibition of cell proliferation was concentration- and time-dependent and was in the range from 1.4% to 28.4%. The difference was observed among bioglass with various content of P_2O_5 . The microscopic observations shown that control cells grew on the surface of the cultivation flask. The vast majority of them were scattered and exhibited a typical fibroblast morphology with an elongated and polygonal shape. In some areas, cells in mitosis were observed. VH10, B-HNF-1 and NIH-3T3 cells growing on the surface of bioglass were homogeneously distributed on the substrate with good colonization. No significant morphologic changes were found in treated cells, their morphology was completely similar to that of the control cells. The amount of released LDH in cells cultured with bioglass was increased in comparison to the control and was P_2O_5 content- and time-dependent.

On the basis of the obtained results it can be concluded that bioglass with various content of P_2O_5 in oxide system Li_2O-SiO_2-CaO-CaF_2-P_2O_5 showed a slight cytotoxicity and very good biocompatibility.

Supported by the Slovak State Committee for Scientific Research VEGA grant 1/0165/10.

EFFECT OF RADIATION AND STRESS FACTORS ON DNA DAMAGE IN PILOTS

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Epidemiological finding suggest a possible causal relationship between cancer incidence in flight personnel and exposure to cosmic radiation.

In the biomonitoring study of aircrew (all pilots) and ground crews we measured biomarkers of genetic stability and oxidative stress.

A total of 98 subjects were recruited from two airlines, 58 pilots (57 men and 1 woman, average age 37 years), and a reference group of 40 ground crews (all men, average age 32 years), similar in age, nutrition and life style, without a history of frequent airline travel. All study participants signed an informed consent form and the Ethical Committee of the Slovak Medical University in Bratislava approved the study.

Micronuclei (MN) and chromosomal aberrations were measured in the stimulated cultured peripheral lymphocytes, the Comet assay (single-cell gel electrophoresis) was performed on isolated lymphocytes.

For chromosome analysis a total of 200 well-spread metaphases per person were examined. Chromosome damage was expressed as% of aberrant cells (AB.C) and break per cell. We also analysed number of dicentric chromosomes, which are known as sensitive indicator of ionizing radiation exposure.

MN were measured by micronucleus cytokinesis block assay. We analysed 2000 binucleated lymphocytes per person.

The Comet assay we used to detect DNA-strand breaks and alkali-labile lesions as oxidized purines and pyrimidines. Sensitivity of lymphocytes to H_2O_2 challenge was also measured.

We did not find a statistically significant differences between two monitored groups neither in the frequencies of aberrant cells (0.78% AB.C in pilots, 0.87% AB.C in ground crews), in number of dicentric chromosomes (0.027% in pilots, 0.038% in ground crews), in the micronucleus frequencies (0.91 MN/1000 cells in pilots; 0.98 MN/1000 cells in ground crews) nor in Comet assay (sbs, oxidised purines, oxidised pyrimidines, and resistance to H_2O_2).

Both pilots and ground crews have the frequencies of aberrant cells in spontaneous level of standard population.

We found a positive correlation between length of occupation and MN frequency in pilots. We suppose that it this result reflects to the effect of age, as MN frequency is increasing with age.

This work was supported by Slovak Grant Agency of Ministry of Health MZ 2005/42-SZU-20, the EC contract INTARESE, GOCE 018385.

STUDY OF COMBINATION OF PINOSILVIN AND METHOTREXATE IN THE MODEL OF ADJUVANT ARTHRITIS: BENEFITIAL EFFECT ON CLINICAL AND NON – CLINICAL PARAMETERS

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Pinosylvin (PIN) belongs to stilbenoids, which act as natural protective agents in defending the plant against viral and microbial attack, excessive ultraviolet exposure, and disease. The already proved antiinflammatory and antioxidant activities favor this compound as a candidate for rheumatoid arthritis (RA) therapy. In our previous study PIN was found to be the more effective compound of two stilbenoids evaluated in a rat model of RA – adjuvant athritis (AA). As a number of disease-modifying antirheumatic drugs (DMARDs) have often side effects at high doses and/or during long-term administration, increased efficacy without increased toxicity is expected for combination therapies of RA. In this study, the combination of a basic DMARD – methotrexate – with PIN was evaluated by clinical and non-clinical parameters measured in AA. In Lewis male rats, AA was induced by intradermal injection of *Mycobacterium butyricum*. The experiment included healthy control animals, arthritic animals

without treatment and arthritic animals with pinosylvin and methotrexate monotherapies and animal group with combination of MTX + PIN. The basic clinical parameters – hind paw volume (HPV), change of the body weight (CBW) and arthrogram – were evaluated in time profile on experimental days 14, 21 and 28. Of the non-clinical parameters, we analyzed the MCP-1 and TBARS plasmatic levels and GGT activity in tissue homogenates from spleen and joint. The combination therapy was shown to improve the effect of MTX on the main clinical parameter, HPV. This improvement was significant on experimental days 14 and 21 – namely in the acute phase of arthritis. This finding was further supported by a more pronounced decrease of TBARS levels, as compared to MTX monotherapy. MCP-1 levels as well as GGT activity, reaching the control levels of healthy animals, were not significantly different on comparing the combination MTX+PIN with MTX alone. This study proved that PIN could be a suitable compound for combination therapy in arthritis.

Supported by the grant VEGA 2/0090/08 and APVV-0315-07.

COMPARISON OF HUMAN PATCH TEST AND 3D HUMAN SKIN MODEL RESULTS WITH CLASSIFICATION OF CHEMICALS BASED ON RABBIT DRAIZE TEST

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Efforts to replace the *in vivo* rabbit Draize test for skin irritation have been underway for many years and various *in vitro* protocols have been assessed. However, one key difficulty in determining the validity of any particular protocol/prediction model is that the *in vivo* rabbit data are both scarce and often of limited utility for the prediction of the biological effect in man.

In the current study, using the 4h human skin irritation patch test, we examined 15 irritants and 10 non irritants. The outcome of human patch test was compared with results obtained with reconstructed epidermis model EpiDerm using two *in vitro* skin irritation protocols. Of the 15 tested chemicals reported to be irritating in the rabbit, only 5 substances were found to be significantly irritating in human skin to merit the R38 classification. Using the Epiderm test protocol evaluated in the ECVAM skin irritation validation study (15 min exposure), 7 out of 15 rabbit irritants were identified as R38 with one false negative prediction compared to human data. With the modified protocol (60 min exposure), 10 of 15 rabbit irritants were classified as R38, without the false negative outcome compared to 4h human patch test results.

Consequently, when approaching validation of alternative methods, existing human data should be taken into consideration, as only those may provide a final judgment about the predictive ability of a new alternative method. The *in vitro* models derived from human skin cells, if used in appropriate test designs and optimized by reference to human hazard data, may prove to be more useful than the animal tests for the prediction of human hazard from previously untested substances.

The study was supported by ZEBET at the BfR, Germany, and a grant project of the Ministry of Health of the Czech Republic (No. NS9648-4/2008). The commercially non-available samples from the ECVAM Skin Irritation Validation Study were provided by CORRELATE at JRC, Italy.

TIME- AND DOSE-DEPENDENT MODULATION OF NITRIC OXIDE PRODUCTION IN RATS WITH ELEVATED BLOOD PRESSURE

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Nitric oxide synthase (NOS) inhibitor N^G-Nitro-L-arginine methyl ester (L-NAME) induces hypertension in rats when it is administered in the dose more than 5 mg/kg/day. However, administration of a low dose of L-NAME (1.5 mg/kg/day) activated NO production in the cardiovascular system of Wistar rats (1). These findings led to the hypothesis that NO production can be modulated *in vivo* in order to reduce blood pressure (BP) in rats with elevated BP. To test this hypothesis adult borderline hypertensive rats (BHR) were treated with L-NAME 1 mg/kg/day, in drinking water, for 4 or 10 weeks, respectively. Spontaneously hypertensive rats (SHR) were treated with 0.1 mg/kg/day L-NAME for 10 weeks. BP and heart rate were determined non-invasively by tail-cuff method. NOS activity was determined by conversion of [^{3}H]-L-arginine in the hypothalamus, aorta, left ventricle (LV), liver and kidney. In BHR, four-week L-NAME administration significantly reduced NOS activity in the hypothalamus and aorta, without changed in the LV. Ten-week treatment led to activation of NOS in the aorta without improvement of NO production in both hypothalamus and LV. In the liver and kidney, NOS activity was rather reduced after 4 weeks and it was significantly increased after 10 weeks of L-NAME treatment *vs.* control. In SHR, 10-week L-NAME administration resulted in reduction of NO production in the hypothalamus and elevation of NO production in the LV, liver and kidney. No effect was observed in the aorta. Interestingly, reduced oxidative stress (determined as the level of conjugated dienes) was observed in the LV, liver and kidney of SHR after low-dose L-NAME treatment. However, L-NAME significantly elevated average BP and reduced average heart rate in both BHR and SHR after 4 or 10 weeks of treatment in both doses investigated. In conclusion, results suggest that NO production can be increased in BHR and SHR rats in the given peripheral tissues by 10-week L-NAME treatment in the dose of 1 and 0.1 mg/kg/day, respectively. However, this mechanism

failed to reduce BP, supposedly due to reduced central NO production.

Supported by grants No. APVT-51-018004 and VEGA 2/0084/10.

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EFFICACY AND SAFETY OF SMe1EC2 AND ATORVASTATIN IN HEREDITARY HYPERTRIGLYCERIDEMIC RATS

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The major risk factors for atherosclerosis and coronary heart disease are an elevated plasma total cholesterol (TC), triglycerides (TRG) and low density lipoprotein cholesterol (LDL-C). Thus, hereditary hypertriglyceridemic rats (hHTG) were developed as an inbred model for studying the relationships between blood pressure and lipid metabolic abnormalities. The purpose of this work was to evaluate the efficacy and safety of long-term oral administration of the novel pyridoindol derivative SMe1EC2, compared to the clinical drug atorvastatin, in an hHTG model of hereditary dislipidemia.

Male hHTG rats were fed either control or high-cholesterol diet (hCholD; 1% cholesterol and 7.5% lard fat). Moreover, the hHTG groups fed hCholD were administered SMe1EC2 (30 mg/kg/day p.o.) or atorvastatin (50 mg/kg/day p.o.) for consecutive 4 weeks. Lipid profiles of experimental animals were characterized by serum levels of TC, TRG, LDL-C and high density lipoprotein cholesterol (HDL-C). To investigate whether inflammatory parameters might play a role in the pathogenesis of hypercholesterolemia, pro-inflammatory cytokines TNF-α, IL-1 and IL-6 in serum were determined. Safety parameters providing an index of lipid peroxidation and of oxidative stress involvement were also evaluated in serum and the kidney (thiobarbituric acid reactive substances; lysosomal enzyme N-acetyl-β-D-glucosaminidase). To characterize the effect of drugs tested on the generation of reactive oxygen metabolites in whole blood, chemiluminescence was used.

Feeding the animals hCholD resulted in hypercholesterolemia and increased the serum level of TC, TRG and LDL-C. SMe1EC2, affected selected parameters in hHTG rats, especially those related to the lipid profile: decreased serum levels of TC and TRG in hHTG rats, either on control or hCholD diet. In conclusion, the results showed that SMe1EC2 was able to safely lower the levels of lipid parameters, similarly as did atorvastatin, the standard hypolipidemic drug.

This research was supported by the Grant agency Ministry of Education VEGA 02/0086/08, VEGA 02/0083/08, VEGA 02/0056/09, VEGA 02/003/10.

ANTIMUTAGENIC POTENTIAL OF BERBERINE EVALUATED BY AMES TEST, *HGPRT* GENE-MUTATION ASSAY AND COMETT ASSAY

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Berberine represents one of the most studied among the naturally-occurring protoberberine alkaloids. Several reports on the biological properties of berberine have proposed its extensive use for biomedical research. From the literature it is known that this alkaloid is not a potent genotoxic and mutagenic agent. In our previously experiments, we found antiproliferative, cytotoxic and non-genotoxic effect of berberine on several cancer and non-cancer cell lines.

In this work, we examined antimutagenic potential of berberine after 3 h incubation. N-methyl-N´-nitro-N-nitrosoquanidine (MNNG) was used as positive mutagen. Genotoxicity was assessed by single-cell gel electrophoresis (comet assay) and mutagenicity was evaluated by the *hgprt* gene-mutation assay and by bacterial mutagenicity – Ames test. Chinese hamster V79 cells and bacterial histidine-auxotroph strains of *Salmonella typhimurium* TA98, *TA100*, *TA 102* were used as the test models.

We found out that berberine decreased revertant number of bacterial strains of *Salmonella typhimurium* TA98, *TA100* and, *TA 102* in comparison with MNNG. Similarly, in comparison with MNNG, the decrease in the number of *hgprt* gene-mutants of V79 cells treated with berberine was observed. Comet assay showed that berberine in comparison with MNNG decreased DNA damage in V79 cells.

On the basis of the obtained results it can be concluded that berberine has a potent antimutagenic activity which probably results from DNA topoisomerase I inhibition.

Supported by the Technology Assistance Agency under contract No. APVV- 0055-07.

FISH BILE AS A TOOL FOR POLLUTION ASSESSMENT ON BÍLINA RIVER, CZECH REPUBLIC

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Polycyclic aromatic hydrocarbons (PAH) are group of hydrophobic organic contaminants that are ubiquitous pollutants derived from pyrogenic and petrogenic sources. The major sources of PAH in the aquatic environment include urban runoff, wastewater effluents, industrial output, atmospheric deposition, and spills and leaks during the transport and production of fossil

fuels. PAH are rapidly transformed into more hydrophilic metabolites that are excreted, thus fish exposed to these compounds show only trace amounts of PAH in their tissues. PAH metabolites are usually determined in fish bile, where they are concentrated and stored prior to excretion.

The aim of the present study was the assessment of the Bílina River (Czech Republic) by PAH using their metabolite concentrations in fish bile as a biomarker. Bílina River rises on the slopes of Ore Mountains, north of Chomutov and flows through the most industrial region of the Czech Republic (opencast coal mining, chemical industry, power plants, high polutation density). Fish bile samples were obtained from fish caught on the nine locations in the Bílina River (Březenec – control locality; Jirkov – below the waste water treatment plant (WWTP); downstream and upstream of Jiřetín; Záluží; Želenice, Bílina – below the WWTP; Rtyně nad Bílinou and Ústí nad Labem). Selected PAH metabolites were determined in bile samples from four fish species, chub (Leuciscus cephalus), bream (Abramis brama), roach (Rutilus rutilus) and trout (Salmo trutta m. fario). Levels of PAH metabolites were determined by reverse phase HPLC with fluorescence detection. For valid assessment of bile accumulation levels, the PAH metabolites concentrations were normalized to the biliary protein content. Of the monitored PAH metabolites, 1-hydroxypyrene was the major metabolite in all fish species. The contents of PAH metabolites were correlated with the PAH content in passive samples (semi-permeable membrane device).

This research was supported by MSM Project No. 6215712402 and IGA 89/2010/FVHE.

NEONATAL FORM OF MOLYBDENUM COFACTOR DEFICIENCY – A CASE REPORT

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Molybdenum is an essential element required to form molybdopterin, a cofactor essential for the function of sulfite oxidase (SO), xanthine dehydrogenase (XD) and aldehyde oxidase (AO). Deficiency of molybdenum cofactor is a serious and fatal disease.

The aim of this study was to present a case of term newborn with a rapid progression of symptoms of neurodegenerative disease.

In a case of term newborn with a numerous dysmorphic features with seizure activity from the 3rd day of life, hypertonia and serious changes on brain parenchyma. Diagnosis of molybdenum cofactor deficiency was confirmed by the decreased level of uric acid 31 µmol/l in serum, increased excretion of thiosulfate and S-sulfocysteine in urine, taurine (1 729.3 µmol/mmol crea; normal range 30–300 µmol/mmol crea) and xanthine (276.9 µmol/mmol crea; normal range < 25 µmol/mmol crea) in urine. Sulfite oxidase activity on skin fibroblasts in culture was not detectable. The patient died at the age of 28 days of life.

Deficiency of molybdenum cofactor leads to accumulation of toxic metabolites (levels of sulfite), which causes disturbances of neurotransmitters even before delivery. Therapy is symptomatic, no effective therapy is generally available. Seizures are difficult to suppress. This case report is about the first patient in Slovak republic.

This research was supported by the Ministry of Education, VEGA 2/0083/08.

ETIOLOGY AND OCCURRENCE OF PROFESSIONAL CANCER OF RESPIRATORY TRACT IN SLOVAK REPUBLIC IN A 25-YEAR HORIZON

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European Risk Observatory (ERO) which was founded in 2002 at EU OSHA (European Agency for Safety and Health) pointed out that there are notable differences in acceptance of occupational diseases in national systems of EU. Especially it was stressed that it should be informed more accurately about cancers caused by occupational exposure and about risk factors coming from workplaces which can cause them.

Respiratory system (RS) is the most frequent target organ for carcinogens present at workplace. The goal of present study was to analyse 277 occupational respiratory cancer cases in the Slovak Republic between the years 1984–2008, starting in 1984 when the first case of lung cancer caused by ionising radiation was registered in a miner of ore mines in Banská Hodruša, who had been exposed to radon for many years.

Within the years 1984–2008 there were reported 202 other cases of lung cancer caused by ionising radiation which appears especially in iron-ore mines in the areas of Slovenské Rudohorie, Banská Štiavnica, Hodruša, and Dúbrava.

After registration of the first case of cancer caused by asbestos in 1984, there were in 1984–2008 registered 43 cases of lung cancer and cancer of pleura from asbestos – preferably from a factory producing different asbestos-cement materials prepared from chrysotil and crocidolite. The factory had been in operation since 1912.

Since 2004, when a new entry No.46 „*Cancer disorders based on exposure to evidenced chemical*

carcinogens in working environment of damaged person which are proved in his target organs and which are not present in other parts of the list..." appeared in the List of Professional Disorders in the Slovak Republic, there were till the end of 2008 reported 16 cases of respiratory tract cancer caused by work in working environment where the presence of human chemical carcinogens (compounds of Cr IV, products of combustion, silicium-oxide dust) were evidenced.

Professional cancers of respiratory tract caused by radon were seldomly manifested over the age of 40. Maximum number of cases was at the age above 60. Cancers of respiratory tract according to article 46 of the List of Professional Disorders had their maximum at the age between 55–59.

Percentage of respiratory tract´s cancers was between 1.19% (1999) – 1.44% (2008) within the last decade, with absolute numbers from 5 (2003) to 10 (2006) annually. During this time the number of new cases of occupational diseases was continuously decreasing ranging from 673 (1999) to 417 (2008).

Cancers caused by ionising radiation and by asbestos appeared in former workers and the retired that were exposed in workplaces with very bad conditions.

The number of employees exposed to evidenced human carcinogens and mutagens at workplace has been continuously decreasing. Despite this fact, in 2008 there were 6497 employees exposed to some of them (at risk of asbestos – 829, hard wood dust – 1383, hexavalent chromium – 669, formaldehyde – 669 and other). Based on these observations we can expect that occupational cancers will occur for a long time.

OCCURRENCE OF DEFINED TOXIC METALS IN SILVER CRUCIAN CARP *CARASSIUS AURATUS* L.

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Crucian carp (*Carassius auratus L.)* is a very sturdy fish commonly and abundantly found in bodies of water in the Czech Republic. It is a member of the family Cyprinidae, and it accompanies standard ichthyofauna in bodies of both lentic and running water. It can adapt itself very well to extreme conditions with scarce oxygen, minimum food, and it can also survive in strongly polluted water. It is a schooling fish and capable of pushing other cyprinid species out of its habitat. Its distribution is the result of its ability to propagate by gynogenesis, and its high resistance against external influences.

Water contamination is a problem associated with anthropogenic activities. Fish are known to accumulate considerable quantities of toxic substances in their tissues. The most closely monitored metals include Cd, Pb, Hg and As. Hygienic limits for the assessment of fish meat quality and consumption safety are set forth in the Commission Regulation (EC) 1881/2006 setting maximum levels for certain contaminants in foodstuffs.

In our study, Cd, Pb and Hg concentrations in the liver and muscle tissues of the Crucian carp (*Carassius auratus* L.*)* were investigated. Samples for analysis were obtained during the fishing out of a pond where carp was farmed and where Crucian carp, from the carp-farming point of view, was considered unwanted fish. The samples were first mineralized and then analyzed for the above contaminants by the AAS method and using the AMA analyzer. Toxic metal concentrations in muscle tissues obtained were compared with effective legislation. Mean cadmium concentrations in the liver (0.005 mg/kg) and muscle tissue (0.017 mg/kg) were far below the limits. Lead concentration in muscle tissue samples was below the method detection limit, and mean lead concentration in the liver was 0.031 mg/kg, mean mercury concentration in the liver was 0.021 mg/kg and muscle tissue 0, 241 mg/kg, respectively, which is also below the hygienic limit.

It follows from the above results that the analyzed fish met the criteria laid down by valid legislation for the selected metals in freshwater fish.

*This study received support from the Research Plan No. MSM 6215712402 Veterinary Aspects of Food Safety and Quality***.**

ACUTE PESTICIDES POISONINGS REPORTED TO THE TOXICOLOGICAL INFORMATION CENTRE IN BRATISLAVA

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The National Toxicological Information Centre (NTIC) in Bratislava has frequently been consulted for advice on pesticide exposures. To obtain more information about pesticide poisonings in Slovak Republic, we performed a retrospective analysis of all telephone calls to our Centre. Methods: All telephone inquiries involving pesticide exposures were extracted from our databases for the period 1994–2008. The following data were analysed: age, sex, intent of exposures (accidental or suicidal), substances ingested and clinical severity. All intoxications were classified in accordance with the Poisoning Severity Score.

During the 15-year period 26.547 acute intoxications were reported to the Slovak NTIC, of which 3.156 (11.9%) involved pesticides. Pesticide exposures in male (60.8%) were more prevalent than those involving female (33.4%). Accidental poisonings were more common (82.5%) than suicidal poisonings (15.8%). Almost half of the cases (48.1%) were children. Most exposures were caused by insecticides (46.0%), but rodenticides (23.3%), fungicides (9.3%), herbicides (12.3%) and other pesticides were also involved. Referring to the insecticides, 39.4% were organophosphates, 36.9% pyrethroids and 8.2% carbamates. 81.2% of patients had symptoms. The majority of them developed only mild toxicity (63.8%), moderate symptoms occurred in 12.4% and severe symptoms in 4.2% of all poisonings. 24 cases (0.8%) resulted in death.

Pesticide poisonings are still associated with many fatalities, especially among patients with organophosphate exposures. More efforts, such as legislative control of the availability of pesticides and further innovation in therapeutic measures, are required to reduce the serious impact of pesticide poisonings.

A COMPARISON OF REACTIVATING EFFICACY OF NEWLY SYNTHESIZED OXIMES IN TABUN-POISONED RATS

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The potency of newly developed bispyridinium compound K203 and its fluorinated analogue KR-22836 in reactivating tabun-inhibited brain acetylcholinesterase was compared with commonly used oximes (obidoxime, trimedoxime, the oxime HI-6) using *in vivo* method. The percentage of reactivation of tabun-inhibited brain acetylcholinesterase was determined by histochemical method. Thirty minutes after tabun poisoning, rat brains were removed, frozen and cut to slices of 20 μm. Acetylcholinesterase activity was measured by histochemistry using Karnovsky-Roots method. The data were evaluated and quantified by digital analysis of pictures taken by CCD camera. According to the results, the ability of newly synthesized oximes to reactivate tabun-inhibited brain acetylcholinesterase is not significantly higher compared to the reactivating efficacy of some currently available oximes.

The study was supported by the grant of the Czech Ministry of Education – SV KTOX.

OVERVIEW OF ALTERNATIVE METHODS IN IMMUNOTOXICOLOGY

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At present, assessment of immunotoxic effects relies on different animal models and several assays have been proposed to characterize immunosuppression and sensitization. The use of whole animals, however, presents many secondary issues, such as expense, ethical concerns, and eventual relevance to risk assessment for humans. Furthermore, due to the new policy on chemicals (REACH), in the European Union, *in vitro* methods will play a major role in the near future. In addition, there is still a lack of human cell-based immunotoxicity assays for predicting the toxicity of xenobiotics toward the immune system in a simple, fast, economical and reliable way. Hypersensitivity and immunosuppression, for which animal models have been developed and validated, are considered the primary focus for developing *in vitro* methods in immunotoxicology. Nevertheless, *in vitro* assays, as well as *in vivo* models, to detect immunostimulation and autoimmunity are also needed. Even if no validated alternative *in vitro* tests to assess immunotoxicity exist, in the last decade, much progress has been made toward these assays. Such models can be, at least, used for the pre-screening and hazard identification of unintended immunosuppression and contact hypersensitivity of direct immunotoxicants. The state-of-the-art in the field of *in vitro* immunotoxicity will be presented and discussed.

PULMONARY CYTOTOXICITY OF SECONDARY METABOLITES OF MICROMYCETES *STACHYBOTRYS CHARTARUM*, ASPERGILLI AND *PENICILLIUM* SP.

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Microfungi aspergilli and penicillia are the primary indoor colonizers of mouldy buildings, *Stachybotrys chartarum* (SCH) represents a tertiary one. Their adverse effects on the human health, incl. lung damage, are considered to be the result of action of their toxic metabolites. Aim of this work was to examine the possible cytotoxic effect of endometabolites (crude chloroform extracts of biomass) and exometabolites (extracts of cultivation media) of *Stachybotrys chartarum* (SCH), A*spergillus versicolor* (AV), A. *ustus* (AU) and *Penicillium* sp. (P) on the respiratory tract *in vivo.*

Male Albino Wistar rats (ca. 200 g) were intratracheally instilled by 4 μg of examined metabolites dissolved in 0.2 ml of 0.2% dimethylsulphoxide (DMSO). The control group was given only DMSO. After three-day´s exposure, the animals were exsanguinated in thiopental anaesthesia and the bronchoalveolar lavage (BAL) was performed. Viability and phagocytic activity of alveolar macrophages (AM), activity of lactate dehydrogenase (LDH), acid phosphatase (ACP) and cathepsin D (CATD) in cell-free BAL fluid (cfBALF) as well as activities of ACP and CATD in cells isolated from BALF (BAL cells) were used for assesment of the lung cytotoxicity of these fungal metabolites.

Viability of AM was depressed after exposure to all of tested metabolites. Phagocytic activity of AM was depressed after exposure to endo- and exometabolites of P, after exposure to exometabolites of AV and endometabolites of AU. Significant increase of LDH activity in cfBALF was found after exposure to endometabolites of AU and P.

Exposure to examined metabolites caused increase of CATD activity in cfBALF. The rise of ACP activity in cfBALF was significant after exposure to endometabolites of SCH and endo- and exometabolites of AU and P.

Exposure to metabolites of AV and P reflected also in increase of ACP and CATD activity in BAL cells

Changes of above mentioned parameters after exposure to the most of examined fungal metabolites confirm their cytotoxicity and ability to cause lung injury.

Supported by the grant APVV-0322-07.

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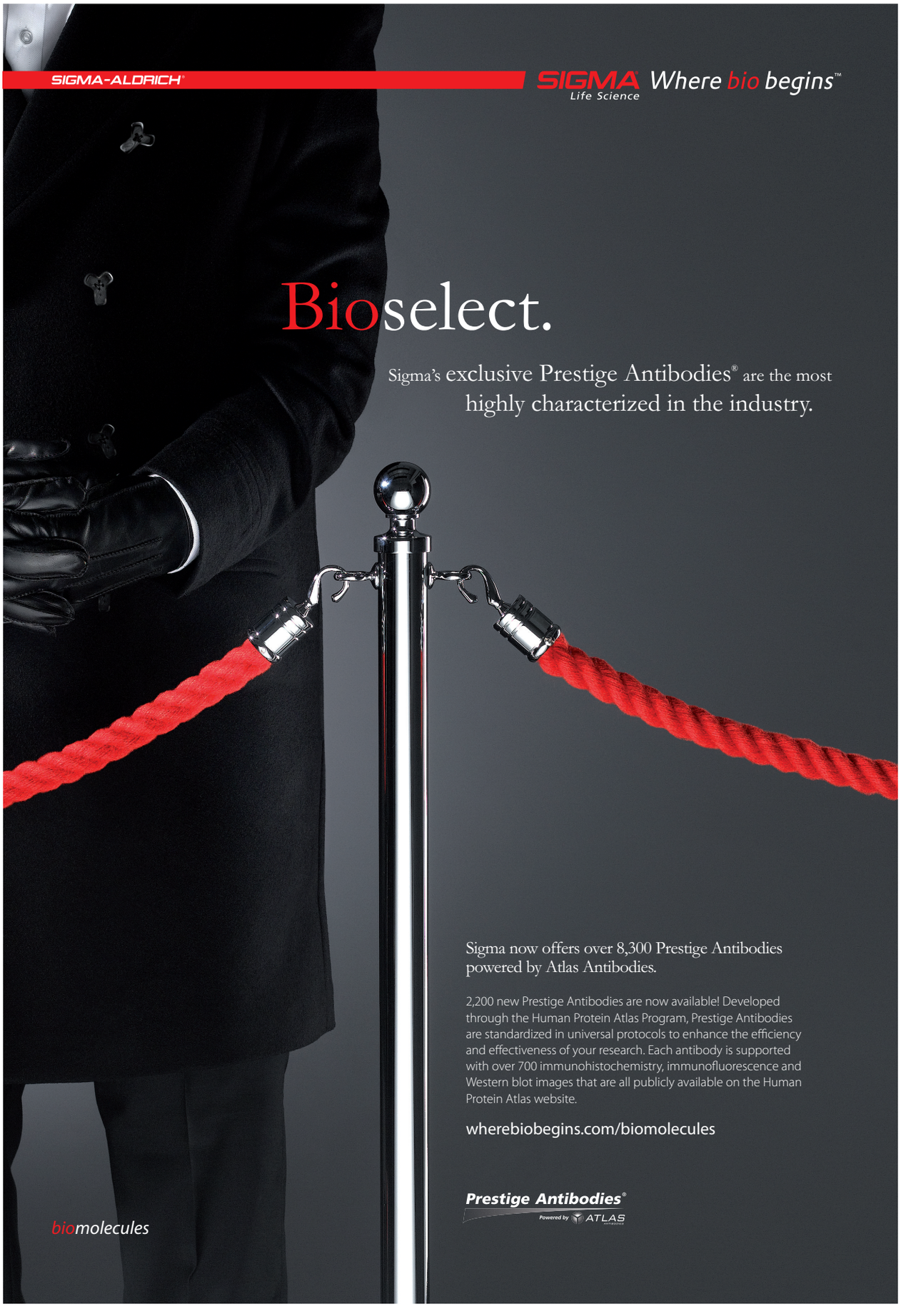
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