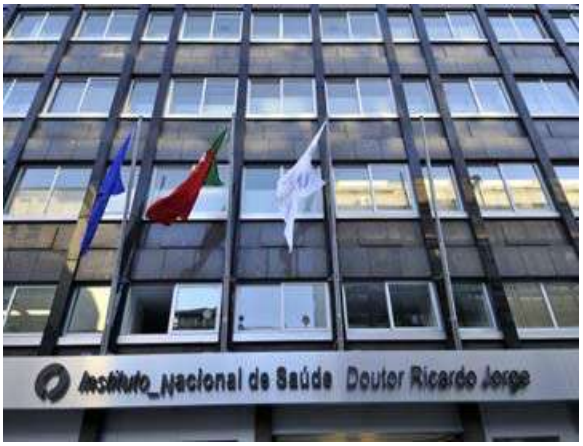

Abstracts

Conference proceedings

WG projects presented at 3rd International
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Sea Porto Hotel in Matosinhos–Porto, Portugal

National Institute of Health, Environmental Health Department, Air and Occupational Health Unit, Porto, Portugal and EPIUnit - Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal

Presented by:

Multicenter EU COST Action, CA 15129 DiMoPEx (Diagnosis, Monitoring and Prevention of Exposure-related Non-communicable Diseases)
http://dimopex.eu/meetings-events/

Knowledge development and dissemination about environment-health interaction within the DiMoPEx COST Action

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The World Health Organization has ranked environmental exposures among the top risk factors of chronic disease mortality. Worldwide, about 70% of human deaths is attributable to non-communicable diseases (NCD), mainly cardiovascular diseases, cancer, diabetes and chronic respiratory diseases. The Diagnosis, Monitoring and Prevention of Exposure Related Non-Communicable Diseases (DiMoPEx) COST Action aims at developing new concepts for a better understanding of health-environment (including gene-environment) interactions in the etiology of NCDs by facilitating a joint effort of European scientists, coordinating information transfer, dissemination and implementation of new knowledge. DiMoPEx organizes workshops, conferences, short-term scientific missions and training schools to foster capacity-building and cooperation of partners resulting in the development of new ideas for research, joint applications, projects and publications. The collaborative work of DiMoPEx partners focuses on evidence-based exposure data, low dose cumulative exposures, animal models reflecting total human life-span and biomarkers of early response that help to bridge the knowledge gap between risk factors in the environment and human health.

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DNA-methylation of cancer-related genes is associated with occupational exposure to polycyclic aromatic hydrocarbons

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Some polycyclic aromatic hydrocarbons (PAH) are known carcinogens and workplace PAH exposure may increase the risk of cancer. Monitoring early cancer-related changes can indicate whether the exposure is carcinogenic. Here, we enrolled 151 chimney sweeps, 152 controls and 19 creosote-exposed male workers from Sweden. We measured urinary PAH metabolites using LC/MS/MS, the cancer-related markers telomere length (TL) and mitochondrial DNA copy number (mtDNAcn) using qPCR, and DNA methylation of lung cancer-related genes F2RL3 and AHRR using pyrosequencing. The median 1-hydroxypyrene (PAH metabolite) concentrations were highest in creosote-exposed workers followed by chimney sweeps and controls. TL and mtDNAcn did not differ between study groups. Chimney sweeps and creosote-exposed workers had significantly lower methylation of AHRR than controls. Creosote-exposed workers, but not chimney sweeps had lower methylation of F2RL3 than controls. These cancer-related markers were not associated with urinary concentrations of PAH metabolites. In conclusion, although we found no associations with PAH metabolites in urine (short-term exposure), our results suggest dose–response relationship between PAH exposure and DNA hypomethylation of lung cancer-related loci. These findings indicate that further

protective measures should be taken to reduce PAH exposure. Preliminary data on changes in protein profile of cancer-related proteins among chimney sweeps will be presented as well.

Functional and quantitative determination of inherent DNA repair capacity as a novel biomarker for personalized risk assessment, disease prevention and intervention, and precision medicine.

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DNA repair is a critical mechanism to determine health effects and response to therapy. Therefore, we have developed the Challenge-comet assay to characterize individual's DNA repair capacity both functionally and quantitatively, especially on base-excision and nucleotide-excision DNA repair capacity. Studies have shown that exposure to mutagenic substances compromised DNA repair capacity and further increased individual's risk for health effects. In addition, breast cancer patients had significantly lower DNA repair capacity than matched normal controls. Among these patients, those with lower repair capacity had poorer prognosis, e.g. metastasis. Together with other data, our results show that this approach can significantly change the risk assessment process from the population to the individual levels. Precise identification of molecular defects can also be used for better understanding of cancer causation and of response to therapeutic interventions, as well as for development of molecular-target-specific therapy.

Reference: Kaina, Au, Inherent and toxicant-provoked reduction in DNA repair capacity: a key mechanism for personalized risk assessment, cancer prevention and intervention, and response to therapy. Int J Hygiene Env Health, in press, 2018.

From pollen to fungal spore allergy: *Alternaria* spores under differing environmental regimes in Bavaria, Germany. A need for an electronic, real-time spore information network in Europe?

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Background: Airborne pollen and fungal spores are major causes of respiratory allergy worldwide. Although pollen has been extensively studied, still little is known about fungi. What are the environmental factors affecting fungal abundance? Is there a 'safe' place or time-period that we can 'switch off' fungal exposure and allergies? To answer these, we investigated the spatiotemporal abundance of airborne *Alternaria* spores in a variety of climatic and pollution regimes, in both field and laboratory conditions.

Methods: *Alternaria* is the most allergenic and one of the most representative in the atmosphere across the globe. The abundance of airborne *Alternaria* spores has been examined in 24 sites in Bavaria, Germany, in 2015. Monitoring took place using Hirst-type volumetric traps and counts were performed on a 2-hourly basis. Differences among bioclimatic zones across Bavaria were investigated. Airborne *Alternaria* spores

were also monitored in Augsburg (in 2017) using a portable Hirst-type volumetric trap. Sampling was conducted 3-4 times a week and twice per day, early in the morning and evening, in four different sites across the city varying in vegetation, urbanisation levels and temperature. Finally, *A. alternata* was experimentally grown under a variety of temperatures and different
nutrient availability. Spore production was examined in variable climatic scenarios, along with an IPCC climate change scenario for 2100.

Results: Fungal spores of *Alternaria* seem to be more abundant when temperature is lower, both in field measurements and experimental conditions. Spores showed their peak concentrations mostly in the evening and at night. This pattern was consistent regardless of the bioclimatic zone, air pollution or urbanisation level involved. This was more intense in extreme locations like the Alpine region. In laboratory conditions, *A. alternata* produced more spores with increased nutrient availability but less with elevated temperature.

Conclusion: *Alternaria* spores are inversely correlated with temperature. This might be good news as lower spore production means less exposure and fewer fungal allergies. However, we have to keep in mind that *Alternaria* is an endophytic fungus, thus being influenced by the plants hosting it. So, it is also suggested that *Alternaria* exhibits a delayed response to environmental stress, which would mean abrupt changes in the future. Unpredictable *Alternaria* spore abundance highlights the need for a spore information network to warn of high-risk exposure.

HEASP - Health, Environment And Susceptible Populations

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Some studies suggest that individuals respond to environmental exposures in different ways according to sociodemographic characteristics and preexisting clinical conditions (1, 2). Health effects might be exacerbated in susceptible subgroups exposed to the same levels of exposure as the whole population.

The aim of the project is to identify individual factors that modify the association between mortality and environmental exposures (3, 4). To this aim, the associations

are assessed according to individual medical conditions (diabetes, cardiac diseases).

For this purpose, national administrative databases are linked (mortality, medication sales and interventions databases) as well as environmental data (based on air pollution, temperature measurements). The study population includes the people living in the nine biggest Belgian cities, and who died between 2010 and 2015.

Assessing the individual and medical effect modifiers of the association between environmental exposures and mortality will allow the identification of specific populations at risk.

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CELLULAR AND MOLECULAR EFFECTS OF IRON OXIDE NANOPARTICLES ON NERVOUS SYSTEM CELLS

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Nanotechnology industry has rapidly grown in the last decades accompanied by significant economic and scientific impacts. The small size of nanomaterials (less than 100nm) is comparable to many cellular structures, making possible the interaction with cells and tissues with possible harmful effects. Iron oxide nanoparticles (ION) are nanomaterials especially suitable for biomedical applications, including diagnosis and drug delivery, particularly those focused on nervous system. However, and despite being considered generally safe and biocompatible, the possible accumulation and effects of ION on nervous system cells still needs to be comprehensively clarified. Besides, little is known on how the different ION coatings and surface modifications may influence their interaction with biological structures. On this basis, we propose to determine their possible toxicity in nervous system cells, at the cellular and molecular level. After a complete physicochemical characterization of two differently coated ION, including also the analysis of iron ions released from the nanoparticles and their cellular uptake, a complete set of assays will be applied to determine cytotoxicity, genotoxicity and effects on DNA repair mechanisms induced by exposure of neuronal and glial cells to ION. Experimental conditions will comprise short- and long-term incubations, a dose range, and presence/absence of protein-rich serum in the cell culture media, in order to elucidate the influence of a protein corona on ION toxicity profile. Results obtained in this work will contribute to increase the knowledge on the impact of ION on nervous system cells, which will help to define conditions to use these nanomaterials under minimal reasonable risks for human health, thus guaranteeing manufacturers' and consumers' safety.

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HBM parameters of exposure and effects to/by diisocyanates

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Background

Diisocyanates (DIC) are reactive chemicals, which are used in a wide range of products, particularly in the production of polyurethane. They are classed as sensitizers and a prominent cause of occupational asthma. Some of the aromatic DIC are suspected carcinogens. Studies on the association between exposure and effect deserve a consideration on the validity of the appropriate HBM parameters.

Metabolism of diisocyanates

The hydrolysis to the diamines is the major metabolic route of DIC. DIC react also spontaneously with nucleophilic sites of proteins. These adducts at the N-terminal valine of (haemo)globin can be analysed after thermal degradation. The diamines are eliminated via urine mainly. However, they can also form protein adducts after oxidative activation via nitroso arylamines. After acidic or alkaline hydrolysis of the protein the diamines are released again.

Characteristics of HBM parameters of exposure and effect

The determination of the corresponding diamine in urine represents the most established HBM parameter of DIC exposure. However, the parameter can't distinguish between DIC and diamine exposure. This limitation applies also to protein adducts of diamines. In contrast, adducts, which are generated by the direct reaction of DIC and protein, are very specific for DIC exposure. Additional HBM markers are presented by the specific IgG and IgE antibodies to DIC. Specific IgE antibodies to DIC display very specific effect markers for sensitisation, but the diagnostic reliability is questionable. In contrast, specific IgG antibodies to DIC do not play a relevant role in the sensitisation process and may be useful as exposure markers. The carcinogenic effects of aromatic DIC may be taken into account too, but there is a lack of DIC-specific parameters

Conclusion

The exploration of association between DIC exposure and allergic effects shall consider the use of DIC-specific HBM parameters. HBM parameters of diamine exposure are more relevant for studies on the carcinogenic effects of aromatic DIC.

Human biomonitoring tools for the exposure assessment of organic and inorganic contaminants

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Background

Human biomonitoring (HBM) is the most powerful approach for an accurate assessment of the individual exposure to a chemical. It can ever be applied if an appropriate biomarker in an ethical acceptable taken biological material is defined. For hundreds of chemicals HBM parameter are developed. Since five decades the Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine of the University of Erlangen-Nuremberg (IPASUM) explores appropriate HBM parameters, develops and establishes efficient HBM methods and offers these tools for applications from medical practice as well as research studies worldwide.

Methods

The presentation covers the spectrum of HBM parameters which are served by IPASUM as tools for the assessment of the chemical exposure. The parameters were divided by their inorganic and organic identity, by the industrial and consumer use of the parent compound, by the analytical procedure and by their assessment in a joint analytical procedure. They are evaluated by their specificity and their sensitivity.

Results

IPASUM provides biomonitoring parameters for about 30 metals and metalloids using urine, blood, plasma and the erythrocyte fraction by AAS, ICP-MS and ICP-MS coupled with chromatography. Moreover it provides biomonitoring of about 160 pesticides and biocides, 100 organic solvents, 50 polymer monomers and additives, 40 polychlorinated biphenyls, 25 aromatic amines and nitro-compounds, 20 alkylating agents and many other chemicals. Here, urine, blood, plasma and erythrocyte fraction are used too. Analyses are performed by HRGC coupled with mass spectrometry, HPLC coupled with UV absorption, fluorescence and mass spectrometry detection. Most analytical procedures enable the quantification of the HBM parameters in the occupational as well as environmental exposure range.

Conclusion

IPASUM provides HBM for several hundreds of contaminants. The spectrum covers HBM parameters for inorganic and organic compounds from all prominent application areas. Most analytical procedures enable HBM for workplace settings and environmental exposure scenarios.

LIQUID AND VOLATILE BIOPSIES IN PERSONALIZED MOLECULAR DIAGNOSIS AND BIOMONITORING OF LUNG CANCER

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Aim: Determination of genetic mutations via “Liquid” (from plasma) and “Volatile” (from Exhaled Breath Condensate-EBC) biopsy samples by next generation sequencing(NGS) method for lung cancer patients. **Method:** Cell free DNA(cfDNA) was extracted by using Invitrogen PureLink™Genomic DNA Kit(Qiagen). To detect hotspot mutations Ion Ampliseq Colon and Lung Cancer gene panel v2 were used. **Results:** Patients C001,C008,C010 had *PIK3CA* mutation(c.3141T>A) and PatientC002 had *EGFR* mutation(c.2361G>A)in their plasma samples. In PatientC007, a new variation in *FGFR2* and another mutation in *TP53* (c.729C>A) isolated from EBC DNA. Liquid and Volatile Biopsy results were compatible in only one patient at the moment(C001). **Conclusion:** In this present ongoing study, hotspot mutations were able to be determined via Volatile and Liquid Biopsy samples from patients with lung cancer along with standard tissue samples. Concordance among mutations of cfDNA got obtained from EBC, plasma and tissue samples is still under investigation with more number of patients’ samples.

LINKS BETWEEN IMMUNOLOGICAL BIOMARKERS AND FRAILTY IN THE ELDERLY

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Over the last decade, the concept of frailty has been established in geriatrics and gerontology fields as a progressive physiologic decline in multiple body systems, characterized by loss of function, loss of physiologic reserve, and increased vulnerability to external stressors. Frailty is related to increased risk of illness, falls, disability, institutionalization, and death. Chronic immune system activation and inflammation are processes related to ageing, neurodegenerative disorders, and age-related syndromes. These processes have been proposed to contribute also to the development of frailty.

On this basis, the main objective of the present work was to evaluate the possible relationship between immunological biomarkers and frailty status in the older people. To this aim, the levels of several immune activation molecules – neopterin, tryptophan, kynurenine – and inflammatory mediators – interleukin 6 (IL6), C reactive protein (CRP), tumor necrosis factor alfa (TNF) and soluble TNFα receptor II (sTNF-RII) – were analysed in a population of Spanish older adults (aged ≥65) classified according their frailty status.

Serum concentrations of neopterin, kynurenine/tryptophan ratio, and all inflammatory mediators were significantly higher in frail individuals as compared with non-frail subjects. Moreover, significantly lower tryptophan concentrations were also observed in the frail group.

Significant correlations were found between immune biomarkers, suggesting the parallel activation of several immunobiochemical pathways. These results agree with previous studies reporting alterations of the immune response in frail older adults. Still, further investigation is required to demonstrate the consistency and reproducibility of these findings as well as to evaluate the possible association of psychological, sociological, and clinical features with immunological alterations in frailty.

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Detection of chronic obstructive disease, COPD, from deposition of inhaled nanoparticles

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COPD is the third leading cause of death globally. Two major phenotypes of COPD are predominantly bronchial disease with narrowing of the conducting airways, and emphysema, which is damage and enlargement of the terminal airways including the

alveoli. A precise diagnosis is important for treatment, but currently there is a lack of cheap and specific methods to diagnose COPD – especially in the form of emphysema. A new technique, named Airspace Dimension Assessment (AiDA), derives dimensions of the peripheral airspaces from the half-life time of airborne nanoparticles. Enlarged airspaces result in a decreased deposition and hence a longer half-life. The objective of this study was to investigate if AiDA can provide information about emphysema.

AiDA measurements were carried out on 66 subjects: 25 healthy, 23 smokers with COPD and 18 subjects with alpha-1 antitrypsin deficiency (AATD). AATD is a genetic disorder that greatly increases the risk to develop emphysema. This group differs from smokers with COPD, which are likely to have both bronchial disease and emphysema. AiDA data were aggregated into two numbers: an airspace dimension calculated from the nanoparticle half-life and a parameter named intercept, which is related to particle losses in the conducting airways. A comprehensive investigation of lung function was also carried out for all subjects, including spirometry, diffusion capacity of the lung for carbon monoxide ($D_{L,CO}$) and forced oscillation technique (FOT).

In a first analysis of the data, the peripheral airspace dimensions derived from AiDA were 0.27±0.03 mm, 0.37±0.07 mm and 0.34±0.08 mm for healthy, smokers and AATD subjects, respectively. Both groups with disease differed significantly from the healthy subjects ($p<0.001$), which indicate presence of emphysema. The AiDA intercept was 0.50±0.18, 0.33±0.18 and 0.50±0.22, for the three groups: healthy, smokers and AATD. Thus, the AATD group had almost identical intercept as the healthy subjects, while the smokers deviated significantly ($p<0.01$), which imply that the smokers, but not the AATD group, had changes in the conducting airways compared to the healthy subjects. AiDA data correlated significantly with measures of emphysema from $D_{L,CO}$ and CT.

In conclusion, this study shows that AiDA has potential as a new method for detection and phenotyping of lung disease. The method is less expensive than CT and does not involve radiation. It is more specific to lung geometry than $D_{L,CO}$ and is

in no need of pressurized CO. Thus, it has ability to be more widely available in healthcare, which would facilitate early discovery of COPD.

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Occupational Bladder cancer in painters' population with focus on shipyard.

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Cases report:

Two shipyard painters, 45 and 48 years old, smokers, with diagnosis of bladder papillary urothelial carcinoma. They have been exposed to coating paints for 21 and 18 years.

Occupational cancer was recognized for the youngest man.

For those two cases, excepted tobacco, no other etiologies (medics, family history..) was found.

Background:

Blader Cancer risk factors are tobacco, arsenic, medics (phenacetine, Cyclophosphamide, Chlornaphazyne), aristolochia fangchi, aspartame?; occupational (aromatic amines, arsenic, PAHs, nitrosamines).(1)

In france, 13 000 cases of bladder cancer were diagnosed in France in 2017 with about 10% attributable to occupational factors. (2)

Working as Painter is classified by IARC carcinogenic to humans C1 (vol 98). (3)

Painters have occupational exposure to PAHs, solvents (dichloromethane (CAS. 75-09-2), ethylbenzene (CAS 100-41-4), trichloroethylene (CAS. 79-01-6), toluene (CAS. 108-88-3) , xylene (CAS 1330-20-7)).

In naval and civil ship building and repairing, PAHs like coal tar, high level of copper, Zinc are noted and also biocides like dichlofluanid (CAS: 1085-98-9), Irgarol (CAS 28159-98-0), Chlorothanolil (CAS 1897-45-6)are noted in coating paints composition.

In a Metanalysis on bladder cancer in painters included 41 studies (11 cohort and 30 cases-control study) results are 1.25 (95% CI 1.16 to 1.34; 41 studies) overall and 1.28 (95% CI 1.15 to 1.43; 27 studies) when including only smoking adjusted risk estimates

The conclusion is Although there was not enough information in the studies provided to assess the association of bladder cancer with specific chemical agents encountered in painting. (4)

More recently, Myong published cases in a population of shipyard workers (5)

Questions:

is working as a shipyard painter is a risk factor for bladder cancer?

Because of PAHs levels, metals like copper, Zinc, biocides or mixtures?

Project :

First step: inclusion of all painters (building, shipyard, car) more than 40 years old from our land. With clinical examination and urinary cytology. Comparaison in painter's population

Second step: Case-control study of all cases of bladder cancer in Brittany in 2016 and 2017 with phone interview (more than 600 cases). + research in national database of cancer and national database of occupational diseases center.

Third step: Medical follow-up of painters population. test in laboratory? Depending on the results of first and second steps

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Interlaboratory evaluation of the genotoxic properties of pencycuron, a commonly used phenylurea fungicide

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Pencycuron is used in agriculture for inhibiting fungi growth. Pencycuron residues were found in various samples, indicating the possibility of human exposure. However, data on its genotoxic and carcinogenic potential are lacking. This study was performed in collaboration of two laboratories (University of Debrecen and Ospedale Policlinico San Martino) to investigate pencycuron genotoxicity in *in vitro* cultures of human mononuclear white blood cells (MWBCs) and human hepatocytes (HepG2) by cytokinesis-block micronucleus assay and comet assay. The combined results of the identically performed micronucleus test in the two laboratories showed a dose-dependent DNA damage that reached significance at 100 µg/ml in hepatocytes. Significant genotoxic effect was also observed in comet assay from 50 µg/ml in MWBCs and 100 µg/ml in hepatocytes in one lab. Nevertheless, this finding was not confirmed by the other lab, where different study protocol was used. The

results indicate that pencycuron may have DNA-damaging potential as well as point out inter-laboratory variability of the comet assay.

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NanoOffice – nanoparticles in new and renovated office buildings

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Background/Aim

More and more people work in offices with complicated ventilation and heating systems, where they often feel uncomfortable. One of the possible reasons could be exposure to nanoparticles that can be penetrated from outdoors or emitted by heating and ventilation systems, by office equipment and from used materials, and chemicals.

The NanoOffice study aims to determine nanoparticle, temperature, humidity and CO_2 levels in indoor environments, establish potential links between indoor, and outdoor particle levels and characteristics of the buildings, and investigate any associations with air quality and self-reported health symptoms, and well-being.

Methods

The measurements of nanoparticles for one week have been conducted using Scanning Mobility Particle Sizer Spectrometers indoors and outdoors with DiscMini. Health and wellbeing will be assessed using the self-administrated questionnaire. The relationships between air quality, building characteristics and health will be analysed using multiple regression analysis.

Results and conclusions

Currently twelve offices have been studied showing great variety in indoor nanoparticle concentrations, being higher during winter period and closer to the busy streets and bus terminal. The effect of ventilations systems have been seen as well,

but it is seems to be somewhat smaller compared to infiltration from outdoor air. The further analyses are in progress.

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THE COMPARISON BETWEEN THE HEALTH RISK ASSESSMENTS OF PAHS IN NOVI SAD, SERBIA

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The atmospheric samples are the most homogenous gas systems, due to number of components and efficient mixing of air. On the other hand, the atmospheric samples are the most variable in time due to the fast response of atmosphere to any changes in point and diffusive sources. The quantitative detection of polycyclic aromatic hydrocarbons (PAHs) in ambient air associated with health risk assessment is of remarkable importance for Novi Sad since Novi Sad is the second largest city in Serbia, with a significant industrial and traffic contamination and without properly waste management practice. Furthermore, Novi Sad was one of the cities which industrial zone was damaged during the Balkan conflicts in the late 1990s [1]. The aim of this study was to compare the results of health risk assessments of PAHs obtained within studies conducted in 2004, 2012/2013 and 2014.

The gaseous phase of ambient air, in the study from July 2004, on 3 representative sites (oil refinery, kindergarten in the vicinity of oil refinery and landfill site and the city centre) was sampled by high-volume air samplers which were deployed for 3x24 hours, in one sampling campaign. The second investigation was performed from June 2012 until April 2013 on the landfill site in Novi Sad which is in operative status from early 1980s and represents potential significant source of pollution. The third study was conducted on background locality, Fruška gora, in the vicinity of Novi Sad.

For the purpose of ambient air sampling in 2012/2013 and 2014 campaigns, the passive air samplers (PAS) were applied. PAS as cheap and versatile alternative to the high volume air sampling were exposed “continuously” during one year sampling campaign. Sixteen PAHs on the priority pollutant list by the United States

Environmental Protection Agency (US EPA) were analysed. The cumulative cancer risk is calculated for each sampling site, as a sum of individual risks for 16 PAHs, according to US EPA methodology [2, 3, 4].

The cumulative cancer risks obtained within the study in 2004 were 2.92E-08, 3.67E-08 and 3.91E-08, for the city centre, oil refinery and kindergarten, respectively. The cumulative cancer risk obtained from landfill site, in 2012/2013, was 2.48E-07 indicated the significant contribution of landfill site to the overall emission of PAHs in ambient air of Novi Sad. The higher results from landfill site could be a consequence of frequent accidental events of uncontrolled solid waste combustion, improperly waste management operations and historic pollution. In addition, the vicinity of the highway and households with individual furnaces contribute to the PAHs emission on this location. The total cancer risk obtained within the study conducted in 2014 was of the same order of magnitude (1.91E-07) as the result obtained on landfill site indicating the prominence of passive air samplers for obtaining representative concentration levels of PAHs in ambient air.

The calculated total risk values for PAHs were less than the limit value defined by EPA (1E-6) [5]. One of the reasons for insignificant total risk values is that passive samplers collect only free gaseous molecules of PAHs and it is known that PAHs were predominantly sorbed to the particle phase. Even though, the calculated total risk values for PAHs cannot be assessed as significant for the human population it is important to emphasize that the long-term passive air monitoring programs could be used as an adequate tool in preliminary health risk assessment studies.

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Risk assessment of environmental exposure – linking environmental factors and human health

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A lot of efforts has been made to identify and develop biomarkers for different types of diseases and for different clinical questions, which can ideally be integrated in minimal-invasive diagnostic assays. In addition, considerable progress has been made in linking genetic factors with predespositions for certain diseases. However, due to the complexity of environmental factors and their effect on the human body, there is still a great need to link the influence of human environmental exposures with disease, to define biomarkers for risk assessment and to understand the (molecular) pathological mechanisms behind the impact of environmental factors on human health.

AIT can include a variety of aspects to investigate the interplay between environmental exposures and diseases:

a) **Mobility data collection and analysis**
b) **Environmental pathogen detection**
c) **in vitro models for biological barriers**
d) **Genomic , epigenetic (DNA methylation, miRNA), transcriptomic , and proteomic biomarker development and validation**
e) **Bioinformatics**
f) **Diagnostics Biosensors, Systems Integration and Point of Care Devices**

(a)With **MODE**, a software solution for smartphone-based travel mode and route identification, it is possible to link environmental data (e.g. nitric oxides, pollen) with movement data. That allows investigations between the individual's different omics-layers and environmental exposure. This can be expanded by detection of environmental pathogens (b). Pathogens in the environment can cause severe damage to human health and it would be of great interest to investigate the causation to non-communicable diseases. Therefore, we suggest including maps of pathogen pollution to the MODE software. This would allow the analysis of chemical as well as biological exposures and, in combination with longitudinal omics-profiling, their impact on different diseases.

Alterations of biological barriers and the different omic-layers (e.g. epigenomics, transcriptomics) caused by exposure to different chemical and biological compounds can be investigated by in vitro models (c) and analyzed by our screening and validation platforms for nucleic acids and proteins (d). Those platforms are based on high throughput technologies, allowing a high level of multiplexing, which reduces on the one hand the amount of biological material needed and on the other hand increases the numbers of targets, which can be investigated. Big data solutions as well as statistical evaluation and interpretation of the data are offered by AIT's own group of bioinformaticians (e), who have a special focus on NGS data interpretation and biostatistics.

Finally, AIT can provide know how in developing biosensors and Point of Care (PoC) devices to monitor chemical and biological compounds for self-monitoring and lifestyle optimization (f).

DEP- lipophilic components trigger endothelial cell inflammatory responses involving the AHR non-genomic pathway

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Diesel exhaust particles (DEP) form a fraction of the combustion particulate pollution that has been associated with adverse health outcomes in the population. These particles have been classified as carcinogenic, but are involved in other diseases, in particular cardiovascular diseases. If the responses can be attributed mainly to the particles themselves or to the adsorbed soluble components is still under investigation. Here we present some results of studies that focus on the importance of soluble components for inflammatory responses and attempt to disentangle through which signalling pathways these responses might be elicited. The results indicate that lipophilic and semi-lipophilic chemicals seemed to detach from DEP, translocate through alveolar epithelial cells and trigger pro-inflammatory reactions in endothelial cells at exposure-relevant concentrations. These effects appeared to be triggered by AhR agonists, and involve PAR-2 signaling. One of these compounds, pyrene, binds to AhR, acts as an antagonist of the canonical genomic AhR/Arnt/CYP1-pathway, reduces ordered membrane lipid domains, and activates AhR nongenomic Ca^{2+}-signaling from intracellular stores.

SERUM ADIPONECTIN AS A MARKER OF EXACERBATIONS IN PATIENTS WITH COPD

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COPD is a chronic inflammatory lung disease associated with different co-morbidities including metabolic disorders. Systemic inflammation may be a major factor linking COPD to metabolic disorders. Recently has been discovered that adipose tissue produces variety of adipokines, which influence systemic inflammation. Adiponectin is a 30 kDa multifunctional adipokine with a large spectrum of metabolic and anti-inflammatory effects. So far, the association between the levels of adiponectin and the risk for COPD or severity of the disease remains undetermined.

The aim of the current study was to explore the role of serum adiponectin in COPD.

We assessed the serum levels of adiponectin in 58 patents with COPD and 22controls, by applying commercial ELISA kit.

Results: The levels of adponectin tended to be lower in COPD patients compared to the controls (58.98±7.75 (SE) vs. 76.90±16.40 ng/ml, p=0.097). In patients the adiponectin levels correlated negatively with BMI (r = -0.293, p=0.025), as the levels were higher in patient with normal weight (111.86±17.53 ng/ml) than those with overweight (77.70±10.74 ng/ml, p=0.085) and especially that obese patients (73.87±13.06 ng/ml, p=0.065).

Leptin levels were significantly higher in those with 2 or more exacerbations during the last year than non-exacerbators (107.79±27.95 vs. 51.25±6.57 ng/ml,

p=0.030). Similarly, obese patients which had at least one hospitalization during the last year had significantly higher serum adiponectin levels that those without hospitalization (126.12±39.03 vs. 56.44±8.76 ng/ml, p=0.016).

The results of our study suggest that the serum adiponectin levels cannot determine reliably COPD, but are associated with exacerbations and hospitalization, especially in obese patients.

Key words: COPD, adiponectin, serum, ELISA

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GENETIC PREDISPOSITION IN DEVELOPMENT OF COPD - MATRIX METALLOPROTEINASES

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Chronic obstructive pulmonary disease (COPD) is characterized by abnormal chronic inflammation in the airways, development of extensive tissue remodeling and local and systemic oxidative stress. COPD is multifactorial disease which is influenced by genetic factors, environmental agents, and gene-environmental interactions. Considering the main processes and pathways implicated in pathogenesis of COPD, several genes grouped into 4 main panels, have been proposed and investigated as candidate genes for COPD: i) genes encoding xenobiotic-metabolizing and antioxidant enzymes; ii) genes encoding proteases and antiproteases; iii) inflammatory mediators and iv) genes encoding proteins involved in airway hyperreactivity.

A growing body of evidence indicates that matrix metalloproteinases (MMPs) play a pivotal role in remodeling of the small airways and particularly of the terminal bronchioles in lungs of COPD patients.

In the current report we aim to present our results concerning the possible role of several functional SNPs in promoter regions of MMPs (*MMP-1607 1G>2G, [rs1799750], MMP2–1306C>T [rs243865], MMP3-1171 5A>6A, [rs3025058], MMP7-181A>G [rs11568818], and MMP12-82A>G [rs2276109])* in development of COPD in Bulgarian population from the central region of the country.

The performed case-control studies showed that *MMP2–1306 C>T, MMP7-181A>G* and *MMP12-82 A>G* may affect the risk for COPD, while the other promoter SNPs did not have any associations with COPD. The old carriers (≥65 years) of minor T allele genotypes (CT+TT) had higher risk than CC carriers (OR=4.54, 95%

CI:1.20-17.24, adjusted for gender and age, p=0.026). Concerning *MMP7-181A>G* SNP, we observed that the minor G allele genotypes (AG+GG) were more frequent in COPD than AA carriers among the younger individuals (OR=2.30, 95%CI:1.00-5.27, adjusted for gender and age, p=0.050). Moreover, patients with minor G allele genotypes developed COPD significantly early that those with AA genotype (61.01±10.11 vs. 64.87±9.00 years, p=0.032). The minor G allele of *MMP12-82 A>G* SNP appeared to be a protective factor for COPD as the carriers of G allele genotypes had about 2-fold lower risk for the disease (OR=0.446, 95%CI:0.25-0.80, adjusted for gender and age, p=0.007).

KEY WORDS: COPD, MMPs, polymorphisms, risk factors

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