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Poster Presentations

GENETIC POLYMORPHISMS

P01

Basal expression of the human catalase gene in HepG2 Cells is mediated by NF-Y

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Catalase is a ubiquitous antioxidant enzyme found in all organisms. The main task for catalase is to catalyze the decomposition of hydrogen peroxide to water and oxygen. Several rare polymorphisms have been found in the catalase gene. Most of them are associated with acatalasemia. A common C>T exchange, –262 bp from the transcription start site, influences promoter activity and blood catalase levels. A C>T exchange at –844 in the promoter has been associated with hypertension in Chinese individuals. The human catalase gene consists of 13 exams and is located on chromosome 11p13. The human catalase promoter lacks a TATA-box but contains 3 GC-boxes and 5 CCAAT-boxes. The GC- and CCAAT- boxes generally work as promoter signals in many eukaryotic cells. The Sp-transcription factor family recognises GC-boxes while the CCAAT-boxes are recognised by transcription factors such as NF-Y. Deletion analysis of the human catalase promoter showed that a region containing 2 GC-boxes and 5 CCAAT-boxes is necessary for basal transcription. Site-directed mutagenesis was used to mutate the GC- and CCAAT elements. Expression studies with reporter constructs showed that mutated GC-boxes give increased promoter activity. Expression studies with reporter constructs containing mutated CCAAT-boxes also influence promoter activity. Mutation of CCAAT-box 92 results in a complete lack of activity. Leading us to conclude that CCAAT-box 92 is necessary for the basal expression of the human catalase gene in HepG2 cells. EMSA analysis showed that transcription factor NF-Y binds to the CCAAT-box. To establish the mechanism of differential promoter activity we are currently investigating whether negative regulation via an upstream GC box is influenced by the 262 C/T promoter polymorphism.

P02

Genetic variants in oxidative stress related genes and their association with diabetic polyneuropathy

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Oxidative stress, a consequence of long-term hyperglycemia, is considered a major cause of diabetic polyneuropathy (DPN). Reactive oxygen species (ROS) may damage neurons by lipid per-

oxidation, the breakdown of mitochondrial DNA and inhibition of the respiratory chain. We proposed that some etiological mutations of the genes, encoding antioxidant scavenging enzymes can be involved in the genetic susceptibility to DPN in patients with type 1 diabetes mellitus (T1D). We studied an association with DPN of some polymorphic markers located in such candidate genes: *Ala(-9)Val* of mitochondrial superoxide dismutase gene (*SOD2*), *Arg213Gly* of extracellular superoxide dismutase gene (*SOD3*), *C1167T* and *T(-262)C* of catalase gene (*CAT*) and *Pro197Leu* of glutathione peroxidase gene (*GPX1*), +/0 of glutation-S-transferase T (*GSTT1*) and glutation-S-transferase M genes (*GSTM1*). The groups (total 180 patients) had no overlapping (polar) phenotypes. Group DPN+ included 86 patients with DPN and diabetic record no more than 5 years. Control group DPN– included patients without DPN and diabetic record of at least 10 years. Using PCR protocols, higher frequencies of *SOD2* allele *Val* and genotype *Val/Val* and of *SOD3* allele *Arg* and genotype *Arg/Arg* were established for group DPN+. In case of polymorphic marker *T(–262)C* of *CAT* gene the carriers of *C* allele had higher risk of DPN development. No association were observed in these groups for other polymorphic markers. In conclusion, the association of antioxidant enzymes with the progression of DPN is evidence for an initial role of oxidative stress in the development of DPN.

P03

Human glutathione S-transferase polymorphisms modify the relation of methylmercury to fish intake

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Introduction: Fish ingestion is the predominant source of the neurotoxin methylmercury. Methylmercury is eliminated through glutathione conjugation, and since glutathione S-transferases (GST) catalyze glutathione conjugation, these enzymes might be involved in methylmercury elimination. GSTs are polymorphic in humans; hence, polymorphisms of these genes could be associated with different elimination rates. *Methodology:* Erythrocyte mercury concentration (EryHg), plasma polyunsaturated fatty acids (PPUFA), and fish intake were measured from 365 Swedish individuals. DNA was collected for genotype analysis. Substitution genotypes in the promoter region of GSTA1 and the coding region of GSTP1 were analyzed using real-time PCR. Deletion genotypes for GSTM1 and GSTT1 were analyzed using multiplex PCR. The study individuals were grouped according to genotype, and a general linear model was used to determine if the genotype affected the slope of the regression of EryHg on PPUFA, and the regression of EryHg on fish intake.
Results: GSTP1 polymorphism is associated with a steeper slope in the regression of EryHg on both PPUFA and fish intake, particularly when the homozygous GSTP1-105 valine/valine genotype occurs in combination with at least one valine allele for GSTP1-114. This is consistent with slower methylmercury elimination in these genotypes. No similar trends were shown for GSTA1, GSTM1 or GSTT1.
Discussion: These results indicate that GSTP1 may play a role in conjugating methylmercury with glutathione, and that the variant genotype group has approximately 2.6-times longer elimination half-life than usual. This is not, however, expected to translate into an increased risk of prenatal effects, since the predicted EryHg at the 97.5th percentile fish intake for this group (13.1 µg/L) remains below the levels associated with the provisional tolerable weekly intake.

P04

Effects of CYP2A6 polymorphism on nicotine metabolism and smoking habit

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We have developed a convenient and specific *CYP2A*6 genotyping method. Among 252 Japanese persons genotyped, 10 were genotyped as homozygous deletion (*CYP2A6*4/*4*). Since experiments with recombinant human cytochrome P450 enzymes in baculoviorus systems had revealed that CYP2A6 had the highest nicotine C-oxidation activities, nicotine metabolism in the *CYP2A6*4/*4* subjects was studied. Urinary cotinine, a principal metabolite of nicotine, was analyzed subsequent to smoking among 11 volunteers. Cumulated urinary cotinine excretion in the *CYP2A6*4/*4* individuals was about one seventh compared to the control group (*CYP2A6*1-positive*).
Cotinine levels in morning spot urine specimens from 190 healthy men were also analyzed by HPLC. The number of cigarettes smoked and *CYP2A6* polymorphism were significantly associated with urinary cotinine levels. In particular, the urinary cotinine levels of smokers who were *CYP2A6*-deleted homozygous were drastically lower than those of the *CYP2A6*1* allele possessed. The relation between *CYP2A6* genotype and smoking behavior was studied among 649 healthy male subjects. The *CYP2A6*4/*4* individuals may have a decreased risk of becoming smokers. They smoke less number of cigarettes and absorb less nicotine. Furthermore, there is evidence that the smokers who lack *CYP2A6* are difficult to stop smoking.

P05

Association between *XRCC3* intron 5 A>G polymorphism and breast cancer risk in Finnish population

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Polymorphisms in the genes encoding for enzymes in double-strand break repair have been suggested as modifiers of individual risk for breast cancer. In agreement with this, we have previously found an association between the *XRCC3 Thr*^{241}*Met* polymorphism and breast cancer risk. Our Finnish Caucasian study population consists of 483 cancer patients and 482 healthy controls. We now explored this issue further by studying the *XRCC3* intron 5 *A>G* polymorphism, which has previously been reported to have a protective effect towards breast cancer. Odds ratios (ORs) and 95 % confidence intervals (CIs) were estimated by unconditional logistic regression after adjustment by age. Our preliminary statistical evaluations revealed no significant overall association between the *XRCC3* intron 5 polymorphism and breast cancer risk (OR 1.07, 95% CI 0.81–1.41). However, a statistically significant interaction was found with body mass index (BMI) (p for interaction = 0.046); women who had BMI less than 25.4 and carried at least one variant *G* allele were found to be at somewhat increased risk for breast cancer (OR 1.46, 95% CI 0.97–2.20). Similarly, women who had ever used HRT and carried at least one variant *G* allele had a tendency for increased risk for breast cancer (OR 1.63, 95% CI 0.93–2.84). No association was found when stratified by the use of alcohol or tobacco. The results suggest that *XRCC3* intron 5 *A>G* polymorphism may be a modest modifier of individual breast cancer risk in Finnish women. This work was supported by the Acad-

emy of Finland and EVO funds from Kuopio University Hospital.

P06

Pleural malignant mesothelioma, genetic susceptibility and asbestos exposure

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The role of *CYP1A1*, *GSTM1*, *GSTT1*, *mEH*, and *NAT2* genotypes in susceptibility to malignant mesothelioma (MM) was examined in two case-control studies, one conducted in Italy, one in Finland. Fifty-six asbestos exposed MM patients and 255 controls were recruited in Italy, 48 cases and 123 controls in Finland. NAT2 fast acetylator and low *mEH* activity genotypes were positively associated with MM in Italy, while they were negatively associated with MM in Finland. A combined effect was also observed in Italy for *NAT2* fast acetylator and *mEH* low activity genotypes (compared to *NAT2* slow acetylator and high *mEH* activity genotype combination, OR 3.5, 95% CI 0.9-14.8, *p* for trend among the six combinations = 0.007), while this combination was protective in Finland (OR 0.6, 95% CI 0.0-3.3, p for trend = 0.06). Combination of *NAT2* fast acetylator and *GSTM1* null genotype posed a significantly increased risk of MM (OR 2.4, 95% CI 1.0-5.7) compared to combination of *NAT2* slow acetylator and functional *GSTM1* genotype in the Italian, but not in the Finnish study.

P07

Glutathione S-transferase T1 null-genotype is associated with an increased risk of lung cancer

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Glutathione S-transferases (GSTs) are involved in detoxification of carcinogens, e.g. from tobacco smoke. Therefore, polymorphisms in the *GST* genes have been considered as potential modifiers of individual cancer risk. In a population-based case-cohort study where cases and the sub-cohort sample were matched on duration of smoking, we investigated the occurrence of lung cancer and histological subtypes of lung cancer in relation to deletion polymorphism in both *GSTM1* and *GSTT1*, single nucleotide polymorphisms (SNPs) in *GSTP1* (Ile105Val and Ala114Val), and a three base pair deletion polymorphism in *GSTM3*. We further investigated the effects of the *GST* polymorphisms on lung cancer risk within subgroups of subjects defined by gender and age. The results showed a 2.4-fold (CI = 1.31-4.41) increased risk of lung cancer in *GSTT1* null-genotype carriers, but no significant effects of the polymorphisms in *GSTM1*, *GSTM3*, *GSTP1-105* or *GSTP1-114*. The association was strongest in lower age groups, with a 9.6-fold increase in risk for subjects with the *GSTT1* null-genotype in the 50-55 years age interval (CI = 3.03-30.59). Positive associations were found for *GSTT1* within all major histological subtypes. Squamous cell carcinoma was the histological type most strongly associated with the *GSTT1* genotype, with a 5.0-fold (CI = 2.26-11.18) increase in risk for subjects carrying the *GSTT1* null-genotype. The effects of the *GSTT1* null-genotype seemed stronger in the presence of the *GSTM1* null-genotype or the *GSTP1-105* variant

allele. These results suggest that the *GSTT1* null-genotype is associated with an increased risk of lung cancer, especially in younger individuals.

P08

GSTM1, _GSTT1_ and _GSTP1_ genetic polymorphisms as potential genetic susceptibility factors for lung cancer in Hungary

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Lung cancer mortality rate is the highest of the world in Hungary among men. The reasons have not been understood yet. Within the framework of a multi-endpoint multicenter ongoing study, the aim of the present study was to investigate the risk of *GST* genetic polymorphisms for smoking-related lung cancer in the country. The study population comprised a total of 1100 primary lung cancer cases and 340 hospital-based non-cancer controls. The major histological types of lung cancer were squamous cell carcinoma (35.1%), adenocarcinoma (36.8%), small-cell (6.7%), and large-cell carcinoma (3.9%). Information on smoking was obtained with informed consent from the subjects in a questionnaire. *GSTM1*, *GSTT1* and *GSTP1* Ile105Val genotypes were determined from normal bronchial tissue or peripheral blood. Statistical analyses were performed by STATA 7.0. *GSTP1* Val/Val genotype was associated with increased risk for squamous cell carcinoma among ever-smoking men (OD 1.93, 95% Cl 0.96-3.88, p=0.06). *GSTM1* homozygous deletion genotype slightly increased the risk for squamous cell carcinoma among ever-smoking men (OD 1.26, CI 0.77-2.04), and remarkably for adenocarcinoma among never-smoking men (OD 3.49, CI 0.80-13.13, p=0.06) over 45 years of age. *GSTM1&GSTT1* combined homozygous deletion appeared to elevate the risk (OD 1.71, Cl 0.77-3.79) as compared to the two genotypes separately. The results suggest, that *GST* genetic polymorphisms may have special impact on the development of different histopathological types of lung cancer.
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P09

The effect of genetic polymorphisms of DNA repair and xenobiotic-metabolizing enzymes on the frequency of chromosomal aberrations and sister chromatid exchanges in human peripheral lymphocytes

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Chromosomal aberrations (CAs) and sister chromatid exchanges (SCEs) in peripheral lymphocytes are widely used as cytogenetic biomarkers of genotoxic effects. International cohort studies have linked elevated levels of CAs to cancer predisposition. The observed association between CAs and cancer might reflect individual susceptibility. We assessed the effects of genetic polymorphisms of DNA repair proteins and xenobiotic-metabolizing enzymes (XME) on the levels of CAs and SCEs in peripheral lymphocytes of 145 healthy individuals from Finland and Hungary. Genotypes of DNA repair genes *XRCC1* and *XRCC3* and XME genes glutathione *S*-transferase M1 (*GSTM1*) and T1 (*GSTT1*) and *N*-acetyltransferase 2 (*NAT2*) were determined from leukocyte DNA using polymerase chain reaction

and restriction fragment length polymorphism. In linear regression models adjusting for age, sex, smoking, and genotypes, none of the polymorphic genes significantly affected the frequency of SCEs. After Poisson regression adjustment for age, sex, smoking, and genotypes, a higher level of chromosome breaks was observed in subjects homozygous for *GSTT1* gene deletion (RR=2.45, 95% CI=1.32-4.35), slow *NAT2* acetylators (RR=1.69, 95% CI=1.02-2.90), and individuals homozygous for *XRCC1* codon 280 wild-type allele (RR=2.43, 95% CI=1.05-7.14). Our results agree with earlier findings on the influence of *GSTT1* and *NAT2* polymorphisms on lymphocyte chromosome damage and suggest that *XRCC1* codon 280 polymorphism affects DNA repair phenotype. It is presently unclear whether these or other genetic polymorphisms could explain the observed cancer risk predictivity of high CA frequency.

P10

Genetic polymorphisms in DNA repair and folate metabolism and their possible links with chromosomal aberrations

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The relevance of chromosomal aberration (CA) level as an indicator of cancer predisposition has been supported by epidemiological studies suggesting that a high frequency of CAs is predictive of an increased risk of cancer. The cancer risk predictivity of CAs was not explained by tobacco smoking or occupational carcinogen exposure and did not depend on the time between CA analysis and cancer detection, indicating that the association also concerns "unexposed" subjects but does not reflect undetected cancer. The findings suggest a role for individual susceptibility to chromosome damage. In particular, variation in DNA repair capacity, possibly related to polymorphisms of DNA repair proteins, might provide an explanation. Several of such polymorphisms have been proposed to be associated with an increased cancer risk. However, very little is known about their effects on cytogenetic biomarkers in humans. In the present study, we have examined a population of 170 occupationally unexposed Finnish subjects. We have genotyped major genetic polymorphisms in DNA repair genes *XRCC1* (codons 194, 280 and 399), *XRCC3* (codon 241), *XPD* (exon 23), and *hOGG1* (codon 326) using methods based on PCR-RFLP. Additionally, two polymorphisms in folate metabolism enzymes, *MTHFR* (C677T) and *MS* (A2756G) were examined. A preliminary analysis suggested that polymorphisms in *XRCC1* codons 194 and 280 affect the frequency of chromosome-type aberrations. Polymorphisms in *XPD* exon 23 and *MTHFR* C677T appeared to influence the level of chromatid-type aberrations.
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P11

Chromosomal aberrations and DNA repair gene variants in a radon-exposed population

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We studied the influence of various DNA repair gene variants on the frequency of chromosomal aberrations (CAs) in subjects exposed to residential radon. A group of 84 non-smoking, healthy individuals exposed to domestic radon were analysed using the fluorescence *in-situ* hybridization (FISH) technique. No association between radon concentration and CA frequencies was observed.

However, a significant increase in CAs with age and a large variability in translocation frequencies between individuals within the same age group was shown. In order to investigate the role of individual susceptibility in this variation, genotypes of DNA repair genes *XRCC1* (X-ray repair cross-complementing group 1; codons 194, 280 and 399), *XRCC3* (X-ray repair cross-complementing group 3; codon 241), and *hOGG1* (human homologue of the yeast *OGG1*gene; codon 326) were determined. Multiple regression analysis was applied to evaluate the effect of the polymorphisms and other confounding factors (age, exposure to radon etc.) on the frequency of CAs. Preliminary statistical analyses indicated no relation between the different gene variants and CA frequencies observed by FISH painting. However, the homozygous variant of *XRCC3* codon 241 appeared to be significantly associated ($P<0.05$) with two-way translocations in conjunction with age. Larger studies, both with regard to the cohort and the number of gene variants, are needed to elucidate the influence of other DNA repair polymorphisms on the yield of CAs. To conclude, the results indicate that the chromosomal translocations accumulated by age (spontaneous background) may partly be explained by defects in homologous recombination repair.

P12

Variability in the adaptive response induced in human lymphocytes by occupational exposure to low doses of ionizing radiation: influenced by polymorphisms in DNA repair genes?

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The *in vitro* adaptive response (AR) of human lymphocytes to ionizing radiation is a variable traits. Few studies have address the question weather the occupational exposure to low level of ionizing radiation might induce a similar adaptive response or not. None of them have considered the possible influence of genetic polymorphism in DNA repair enzymes on the observed variability. We have used the micronucleus assay to evaluate the adaptive ability in lymphocytes of radiological workers and the possible influence of polymorphism in the XRCC1, XRCC3 and XPD genes. The presence of AR was assessed by treating the lymphocytes with a challenge dose of 12,5 μg/ml of bleomycin (BLM), delivered at 48 h of cultivation. BLM treatment resulted in an average increase of MN frequency of 170% in controls and 108% in radiological workers [15.86 ± 5.84 and 17.95 ± 2.78 respectively]. Lymphocytes of radiological workers were less responsive to the challenge treatment with BLM as compared to controls. The hypothesized influence by genotype distribution in DNA repair genes revealed that the XRCC1-399 and XRCC3-241 variants as well the common alleles in codon 312 and 751 of the XPD gene were associated with an higher average increase of MN frequencies, although the differences were not statistically significant. Our preliminary results provide evidence supporting that the heterogeneity described in the AR may be influenced by genetic polymorphism.

P13

Characterisation of tissue distribution and genetic polymorphism of CYP2S1

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CYP2S1 is a new member of the cytochrome P450 superfamily. Interestingly, it exhibits many features typical to *CYP1* family members, e.g. dioxin-inducibility mediated by aryl hydrocarbon receptor (AHR) and aryl hydrocarbon receptor nuclear translocator (ARNT). CYP2S1 has also been shown to metabolise some aromatic hydrocarbons as well as retinoic acid, suggesting a role in metabolism of both exogenous and endogenous compounds.

CYP2S1 has low expression level in the liver, but is highly and constitutively expressed in many extrahepatic tissues. Our studies using *in situ* hybridization and immunohistochemisty show that CYP2S1 expression is strong especially in the epithelia exposed to xenobiotics, e.g. respiratory tract, gastrointestinal tract, urinary bladder and skin. High expression levels were also detected in the placenta. With respect to carcinogen metabolism, the epithelial expression is interesting, as epithelial cells also constitute common progenitor cells to tumour development. Indeed, CYP2S1 showed strong expression in many tumours of epithelial origin.

Interindividual variation in CYP2S1 expression was detected in some tissues. This may be due to differential exposure to CYP2S1 inducers or it could be caused by polymorphism(s) affecting expression of CYP2S1. In our preliminary Northern blotting experiments with placental samples, no major differences were observed in CYP2S1 expression between smokers and non-smokers.

Systematic investigation of the genetic variation of CYP2S1 in Finnish Caucasians revealed eight single nucleotide polymorphisms (SNPs) comprising nine different alleles (haplotypes). The most common variant allele was *CYP2S1*1H* harboring a substitution in the 3' untranslated region (23.8%). The two alleles, *CYP2S1*2* and *CYP2S1*3,* which carry non-conservative amino acid substitutions, *i.e.* $Arg^{380}Cys$ and $Pro^{466}Leu$, had relatively low frequencies in the Finnish study population (0.5% and 3.75%, respectively). Studies investigating the functional effect of these genetic polymorphisms are underway. PCR-RFLP based methods were developed for genotyping purposes.

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P14

CYP2S1 genetic polymorphism and smoking-related bulky carcinogen-DNA adducts in a Hungarian lung cancer population

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CYP2S1 is a newly discovered cytochrome P450 gene, which exhibits many features typical to *CYP1* family members. CYP2S1 is mainly expressed in extrahepatic tissues, including epithelial cells of bronchus, and metabolises some aromatic hydrocarbons. Genetic variants of CYP2S1 have recently been identified (Saarikoski *et al*., Mutat Res, in press). We hypothesize that genetic polymorphism of *CYP2S1* may have an impact on the activation of tobacco-smoke carcinogens, thus may influence carcinogen-DNA adduct formation in the lung. Within the framework of an ongoing study we investigated the relationships between *CYP2S1* genotypes and bulky DNA adducts from normal bronchial samples of 211 Hungarian lung cancer patients who underwent lung resection. *CYP2S1* genotypes were determined by PCR-RFLP methods. Bulky DNA adducts were determined by ^{32}P-postlabelling. Genotype distribution within the whole population was 56.4% *1A/*1A, 34.1% *1A/*1H, 6.6% *1H/*1H, 1.9% *1A/*3, 0.9% *1H/*3, and 0% *3/*3. These results are in line with the frequencies observed in Finnish Caucasians. There was no statistically significant difference in levels of bulky DNA adducts among the subgroups with

the three most frequent genotype variants either among smokers or non-smokers. There was no statistically significant difference in daily cigarette dose-dependent adduct formation within those three genotype groups. In combination with the Val allele of *CYP1B1* Leu432Val gene polymorphism, smoking subjects with *1A/*1H genotype had significantly higher level of bronchial DNA adducts than smoking *1A/*1A subjects (p=0.002). The role of *CYP2S1* as potential genetic susceptibility factor for lung cancer will be further studied in larger study population.
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MOLECULAR MECHANISMS OF DISEASES

P15

The relationship between Arg72Pro genetic polymorphism and gene mutations of TP53 and smoking-related lung DNA adducts in a Hungarian lung cancer population

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TP53 tumour suppressor gene mutations are common genetic alterations in human lung cancer. The aim of the study was to investigate the associations between Arg72Pro genetic polymorphism and mutations of TP53, and smoking-related bulky DNA adducts in Hungarian lung cancer patients who underwent lung resection. The total study population comprised 160 subjects. Arg72Pro genotype was determined by PCR-RFLP method. Bulky DNA adducts in lung tissues were determined by ^{32}P-postlabelling. Analyses of TP53 mutations have been completed in exons 5 to 9 and 11 for 50 tumours by DGGE and/or SSCP screening followed by DNA sequencing. The results indicate that 34% of the tumours carried *p53* mutation, most frequently in exon 8 (16%), and among ever-smoking men. TP53 mutation frequency was about 2.8-fold higher in squamous cell carcinoma than in adenocarcinoma. Sequence identification of the mutations is on going and will allow us to investigate whether the pattern of TP53 mutations follows that typically found in smoking-related lung cancers. The proportion of TP53 mutation carriers was clearly smaller among the Pro/Pro genotype individuals as compared to the subjects with Arg/Arg or Arg/Pro genotype. There was no statistically significant association between levels of DNA adducts and the presence of TP53 mutations or Arg72Pro polymorphism. Further analyses are in progress to confirm the observations in a larger study population.
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P16

Analysis of p53 mutations in sino-nasal cancer in a European multi-centre study

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It has long been known that risk for sino-nasal cancer (SNC) is elevated among workers in wood processing industries. The relative risks are highest, in some studies extremely high, in association to hardwood dust (oak and beech in particular) and for adenocarcinoma histology. Excess risks reported for squamous cell histology are smaller, and may also be associated with

exposure to softwood dust. However, the mechanisms by which exposure to wood dust increases the risk of cancer are not clear. Many types of environmental cancer, lung cancer in particular, show mutations characteristic to causative exposures. In an on-going project, we are currently studying *p53* mutations in SNCs from cases with and without occupational exposure to wood dust. Paraffin-embedded tissue (PET) samples of SNC were collected for DNA extraction and analysis in collaboration with national cancer registries in Denmark, Finland and France. The study population includes all incident cases of the cancer of the nose and paranasal sinuses (ICD7: 160) in Denmark for the years 1992–2002, and in Finland for 1989–2002. In France, due to a different study design and type of fixation (Bouin) often used in the pathology laboratories, the number of PET samples so far collected is smaller. The preliminary results show relatively frequent *p53* mutations in tumours from Denmark and Finland. We also examined p53 protein expression immunohistochemistry from a subset of Finnish and French tumours in a pilot study. In addition to mutation analyses, a pathology panel will carry out a review of tumour histologies for the whole tumour collection, and industrial hygienists will assess occupational exposure histories.

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P17

Expression of p53 and Bcl-2 as apoptosis-related gene products in colorectal cancer

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The p53 mutation is implicated in the pathogenesis of colorectal carcinomas. Furthermore the protooncogen Bcl-2 is known to inhibit p53-induced apoptosis and is expressed in some colorectal carcinomas. The aim of this study was to determine the expression profile of p53 and Bcl-2, and to correlate such molecular alterations with available clinicopathological variables. Expression of p53 and Bcl-2 proteins was determined in 37 colorectal tumor samples by immunohistochemistry using antibodies for p53 and Bcl-2, and LSAB2 detection kit. We found a significant correlation between p53 expression (p=0.001) and lack of Bcl-2 expression in our cases. The younger patients showed higher level of p53 expression than older ones (p = 0.004). Lack of p53 expression was higher in males than females (p=001). There was also a positive correlation between tumor cells differentiation with expression of p53 (p=0.001). We observed no significant association between Bcl-2 immunostaining and clinicopathological parameters. Due to key role of p53 and Bcl-2 expression in tumor progression and chemotherapeutic efficacy, our data indicate that group of patients with p53 and Bcl-2 coexpression (24.3%) would less likely benefit from available chemotherapeutic regimens (5FU + Cisplatin) and require especial attention in their treatment regimen. Our data also showed that 59.4% of patients with positive p53 were Bcl-2 negative indicating a double gene alteration that affects their response to available chemotherapies. Therefore, we recommend analysis of tumors before deciding on chemotherapeutic regimen.

P18

Significance of Thymidylate Synthase and Thymidine Phosphorylase protein expression in colorectal cancer

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Fluoropyrimidines such as 5-FU is given as adjuvant treatment to patients with advanced colorectal cancer. Identification of molecular determinants of 5-FU efficacy and toxicity such as Thymidylate Synthase and Thymidine Phosphorylase are critically important for more efficient and less toxic treatment. This study was undertaken to determine the significance of TS and TP protein expression in colorectal carcinomas, and their correlation with clinicopathological findings. Protein expression was determined in 37 colorectal tumors by immunohistochemistry using antibodies for TS and TP and LSAB2 detection kit. Both markers were positive in 43.2% of tumor samples. Positive TS and TP staining were significantly correlated with malignancy grade (P=0.013). There was no significant association between TS or TP immunostaining with tumor size and location or age and gender of patients. Among different G. I. malignancies studied in our lab, we observed lower frequency of coexpression of these markers in colorectal tumors. Over expression of both TS and TP may be useful indicators in predicting the antitumor activity of 5-FU in advanced colorectal carcinoma. Our data showed that 56.8% of patients were TS and TP negative indicating gene alterations affecting the tumor biology and its response to 5-FU based chemotherapy. Therefore, we recommend immunohistochemical analysis of tumor samples for TS and TP status as a valuable tool for selection of patients who will better respond to Fluoropyrimidines based chemotherapy of cancers.

P19

Evidence for the breast cancer predisposing role of the NBS1 657del5 mutation in Russia

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The NBS1 gene contributes to a variety of the processes protecting the chromosomal stability. While its homozygous truncating germ-line mutations cause a life-threatening condition called Nijmegen chromosomal breakage syndrome (NBS), the NBS1 heterozygosity does not result in obvious clinical manifestations. However, it was suggested recently in a Polish case-control study, that the founder hypomorphic mutation in the NBS1, 657del5, which occurs in approximately 0.5% of Slavic subjects, may be associated with the increased risk of breast cancer (BC). We attempted to validate these findings in another Slavic population, Russians. To overcome the difficulties related to the low prevalence of the 657del5 variant, we involved the subject groups with presumably extreme characteristics of breast cancer risk and tolerance, such as patients with bilateral breast cancer (biBC) and elderly tumor-free women. The frequency of the NBS1 heterozygosity demonstrated a trend towards gradual deviations from the most to the least susceptible groups of females: the 657del5 mutation was detected in 2 out of 173 (1.16%) biBC cases, 5 out of 700 (0.71%) unilateral BC patients, 2 out of 348 (0.57%) healthy middle-aged females and, strikingly, in none out of 344 elderly tumor-free women. The difference between the “extreme” cohorts, i.e. biBC patients versus elderly controls, approached the formal

limit of statistic significance (p = 0.046); other comparisons produced non-significant p values. In both bilateral and unilateral breast cancer cohorts, the NBS1 657del5 carriers tended to be slightly younger than non-carriers. Thus, the present report suggests that the NBS1 Slavic founder mutation may play a role in predisposition to breast cancer in Russia. Although the occurrence, and therefore the health impact of this mutation is low outside the Eastern Europe, the global-wide contribution of other NBS1 mutations in cancer incidence remains to be analyzed.

P20

***Epidermodysplasia verruciformis* human papillomavirus types and carcinoma of the conjunctiva: A pilot case-control study in Uganda**

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The association between squamous-cell carcinoma of the conjunctiva (SCC) and HIV-related immune impairment indicates a possible infectious aetiology. We studied 21 SCC cases and 22 controls with benign lesions of the conjunctiva from Uganda. A broad spectrum of human papillomavirus (HPV) types was tested for using PCR-based assays. No mucosal high-risk HPV types were detected, but Epidermodysplasia verruciformis (EV) HPV types were found in 18/21 (86%) of SCC cases and 8/22 (36%) of controls (age-adjusted odds ratio=12.0: 95% confidence interval: 1.7-312). Adjustment for level of sun exposure, but not for HIV, was possible. The strong association that we found points to a possible role of EV HPVs in the aetiology of SCC.

P21

Impaired development of mitochondria plays a role in the fetal alcohol syndrome

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A mouse model of FAS was used to investigate the effect of alcohol on fetal brain mitochondria development and the relationship to born defects of CNS. Histological examination, flow cytometry and biochemical analysis disclosed significant changes of the fetal brain mitochondria in alcohol exposure groups. The mitochondria were generally less mature and were reduced in quantity. ATP accumulation in the mitochondrial matrix was less. The activities of respiratory chain complex I, IV and ATP synthase were significantly down regulated, which resulted in low energy status of whole cells in development. At the end of the research, a new clue to the mechanism of alcohol's teratogenic action on fetal brain was drawn, of which mitochondria was the initial affected tache.

P22

Telomere length and risk for bladder cancer

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Telomeres are repetitive sequences at the ends of eukaryotic chromosomes. The telomeres protect the chromosomes from degradation and fusion, and lack of functional telomeres can cause chromosomal aberrations. This type of genetic instability can promote tumorigenesis. It is known that there is a genetic variation in telomere length in the population, independent of age and sex. We have investigated the association between telomere length and bladder cancer risk in a case-control study. The telomere length from the study participants was established from buccal cells with quantitative PCR. Patients with bladder cancer displayed shorter telomeres than the controls. It is known that oxidative stress effects shortening of telomeres. Thus, we are also analyzing whether different factors associated with oxidative stress, like smoking, occupational exposure, or polymorphisms in oxidative stress-related genes can modify the association between telomere length and cancer risk. The results from this study will elucidate the importance of telomere length as a marker for bladder cancer risk.

BIOMARKER RESEARCH

P23

Genetic variations in *GSTM1*, nucleotide excision repair and apoptotic capacity on *anti*-BPDE-DNA adduct levels in mononuclear white blood cells of highly PAH-exposed coke-oven workers

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We evaluated the polymorphisms of nucleotide excision repair (NER) genes (*XPC-PAT +/-*, *XPA* 5' non-coding region *-A23G, XPD*-exon *23 A35931C Lys751Gln*, *XPD*-exon *10 G23591A Asp312Asn*), glutathione *S*-transferase μ 1 (*GSTM1*-active or -null) and *Fas-A670G* (also know as *Apo1/CD95* one of the most important genes involved in the apoptotic pathway) on *anti*-benzo[a]pyrenediolepoxide (BPDE)-DNA adduct levels from the lympho-monocytes (LMF) of highly PAH-exposed coke oven workers. The sample cohort included 67 male Polish coke-oven workers all belonging to the high exposure group (individual urinary post-shift 1-pyrenol >2.28 μmol/mol creatinine, the proposed BEI). The bulky *anti*-BPDE-DNA adduct levels were detected by HPLC/fluorescence analysis and genotypes by PCR-RFLP.
The low DNA repair capacity of *XPC- PAT +/+* and *XPA- A23A* genotypes significantly ($p<0.05$) double up the mean *anti*-BPDE-DNA adduct levels. Moreover, as already reported in our previous studies DNA adducts are also strongly influenced by *GSTM1* genotype. The higher frequencies of workers with unfavourable *XPC- PAT +/+* and *XPA- A23A* NER genotypes, alone or combined with *GSTM1*-null belonged to the tertile with the highest adduct level (> 4.11 adducts/ 10^8 nucleotides, $p<0.01$). The few subjects with the unfavourable genotypic combination, *XPC- PAT +/+* or *XPA- A23A* NER jointly to *GSTM1*-null and *Fas A670A*, all belonged to the tertile with highest adduct level.
The modulation of *anti*-BPDE-DNA adducts in the LMF, by *GSTM1*-null, some low-capacity genotypes of NER and apoptotic pathway, may be considered as genetic susceptibility factors capable of modifying the individual response to PAH(BaP) genotoxic-carcinogenic exposure in coke-oven workers.

P24

Bulky PAH-DNA adduct level and risk of lung cancer in a Danish cohort

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Polycyclic aromatic hydrocarbons (PAHs) are widely distributed in the environment in complex mixtures such as tobacco smoke and diesel particles. After exposure via inhalation, ingestion or dermal absorption, metabolically activated PAHs can react with DNA to form covalently bound PAH-DNA adducts, that are related to their mutagenic activity. PAH adducts can be studied as biomarkers of biological effective dose in human cells. However, little is known of the predictive value of the level of adducts in terms of cancer risk. In case-control studies disease may effects the biomarker level. Until now only one prospective study (Tang *et al*., 2001, *Cancer Res.*), with 89 lung cancer cases, has investigated the relationship between aromatic adducts level and risk of lung cancer. Among current smokers a high level of adducts was associated with an increased risk of lung cancer.

In this case-cohort study, we investigate the association between bulky PAH-DNA adducts and risk of lung cancer in the large prospective population-based Danish cohort for which detailed information on smoking patterns and other lifestyle at enrolment and during the entire previous lifetime is available. This study design features pre-cancer blood samples and information on smoking patterns. Among 54,220 cohort members, 265 lung cancer cases were identified during 6 years follow up and a sub-cohort of 272 individuals was used as comparison group. Bulky adducts in buffy coat cells collected at enrolment and stored at –180° C were analysed by ^{32}P-postlabelling method using the butanol enrichment procedure.

P25

New knowledge about the impact of environmental exposure to PAHs

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The molecular epidemiology methods were used to analyze the impact of air pollution in pregnancy outcome studies in the Czech Republic. Organic compounds adsorbed to air particles (PM10) induced DNA adducts and embryotoxicity in vitro and in vivo studies. The carcinogenic polycyclic aromatic hydrocarbons (carc-PAHs) were mostly responsible for the genotoxic activity, contributing to 45-50% of all DNA adducts induced by these complex mixtures. The placental bulky DNA adducts have been studied in relation to metabolic genotypes CYP1A1, EPHX, GSTM1 and NAT2, and plasma levels of cotinine and vitamins A, C, E. DNA adducts were determined by ^{32}P-postlabeling assay. DNA adducts in placentas were affected by air pollution, smoking, genotypes, vitamin C levels. Higher DNA adducts were observed in nonsmoking mothers delivering children with IUGR (intrauterine growth retardation). In the Pregnancy Outcome Project, an increased risk of IUGR was established for mothers who were exposed to carc-PAHs > 15 ng/m^3 during the first month of gestation. Using multiple regression analysis, GSTP1, EPHX and CYP1A1 MspI genotypes decreased newborn birth weight in polluted district. Carc-PAHs seem to be an important source of genotoxic and embryotoxic activities of organic mixtures associated with urban air particles.

Recent studies on groups environmentally exposed to carc-PAHs implied the relationship between air pollution and DNA-PAH adducts as well as chromosomal aberrations by fluorescence in situ hybridization (FISH) in exposed subjects, which may be further modified by metabolic and DNA repair genes polymorphisms.

All these results indicate that carcinogenic PAHs represent a very significant group of air pollutants.

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P26

Oxidative DNA damage in workers exposed to styrene and styrene oxide

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Styrene (S) is used in the production of resins, plastics, and rubber. It is metabolized mainly in the liver to styrene-7,8-oxide (SO), its principal in vivo mutagenic metabolite. In this study we evaluated 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels in peripheral blood leukocytes of 31 workers (aged 31.6 ± 10.4, range 18-54 years) exposed to S and SO in an industry manufacturing resin products and 35 control subjects (aged 33.1 ± 11.3, range 19-57 years). External occupational exposure to S and SO was assessed by personal air sampling. At the same time 8-OHdG was determined in human peripheral blood leukocytes of workers by immunohistochemical method. Environmental monitoring enabled us to divide workers into three groups exposed to different levels of S and SO. The first group, workers equipped with personal protection devices, was exposed to levels of S 52.38 ± 18.94 mg/m^3 and of SO 117 ± 33 μg/m^3. 8-OHdG levels were 0.64. The second group, 7 workers without individual protection devices, had exposure levels of S 4.08 ± 2.25 mg/m^3 and of SO 31±19 μg/m^3. 8-OHdG concentrations were 0.88. The third group, 15 workers without individual protection devices, but who were not in direct contact with S and SO, was exposed to levels of S 0.23 ± 0.15 mg/m^3 and of SO 5.5 ± 3.9 μg/m^3. 8-OHdG levels were 0.47. In the control group, 8-OHdG levels were 0.42. The highest 8-OHdG levels of the workers of the second group clearly indicates that the lack of a personal protection device causes an alteration in exposed workers. Findings showed that S and SO exposure can result in oxidative DNA damage.

P27

Acetylcholinesterase autoimmune antibody is another marker for myasthenia gravis

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In order to know whether acetylcholinesterase (AChE) autoimmune plays a role in both myasthenia gravis (MG), which is associated with antibodies directed against the nicotinic acetylcholine receptor (AChR) in 85% of patients, and Graves' disease (GD) we analysed by ELISA the ability of sera from 22 patients with MG without antibodies against AChR, 116 with GD having the antibodies against thyroglobulin (Tg), and 50 healthy controls (CR) to react with AChE from human brain and human Tg. Results showed that significantly increased anti-AChE activity was exhibited by a high proportion of MG (50%) and nearly unchanged anti-AchE activity was observed in GD (1%) sera, being similar with CR, which no anti-AChE activity was detected. Anti-Tg activity was detected in both MG patient (22% positive) and CR (19% positive). It suggested that AChE antibody should be another marker in MG but play no role in GD.

P28

Environmental and biological monitoring of workers exposed to formaldehyde

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Personal exposures to formaldehyde (F) of Research Institute workers were performed. At the same time, biomarkers of exposure and effect, such as formaldehyde human serum albumin conjugate (F-HSA), chromosome aberration (CA) an sister chromatid exchange (SCE) were studied. The aim of this work was to verify the relationship between formaldehyde exposure and biological markers.
Individual FA levels of exposure ranged from 4.9 μg/m^3 to 269 μg/m^3. The workers at a higher level of FA, i.e. lying beyond the 75th percentile of the FA distribution, showed a significant increase of the FA-HSA with respect to other workers. No significant relationship was observed between FA and the other biomarkers. In conclusion a significant relationship was observed between environmental exposure to FA and a biological marker exposure (FA-HSA).
The markers of effect used (CA, MN and SCE) failed to indicate the presence of genetic damage or of a cancer risk at the observed levels of exposure to FA.

P29

Biological markers of exposure to environmental pollution: The EXPAH study

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Environmental pollution contains several chemical carcinogens, amongst which are polycyclic aromatic hydrocarbons (PAHs). DNA damage derived from exogenous exposure, and changes associated with individual genetic susceptibility were evaluated in a population exposed to PAHs.
Male subjects from three countries were studied: Czech Republic, Slovak Republic, and Bulgaria. Two groups were selected from each country: exposed subjects (policemen or bus drivers), and control subjects matched by age and length of employment.
Environmental exposure has been assessed over 12 months by stationary monitoring, personal exposure has been measured after a job shift. A sample of blood and urine was collected, and a questionnaire was filled out after written informed consent. Three hundred and sixty four subjects were included in the present study (mean age 34 ±9.31 years) among which 204 (56 %) were exposed to PAHs. The mean value of personal exposure was 22.05 ±26.25 ng/m^3 carcinogenic PAHs (9.07 ± 8.67 ng/m^3 for Prague, 16.99 ±29.15 ng/m^3 in Kosice and 34.88 ±26.65 ng/m^3 in Sofia, p=.0001), with higher levels among the exposed than the control subjects (29.56 ±31.38 ng/m^3 versus 12.68 ±12.88 ng/m^3, p=.0001). The percentage of aberrant cells carrying chromosomal aberrations measured with the FISH technique was significantly higher in exposed subjects than in controls, as well as genomic frequencies of stable chromosomal exchanges. Mean values of bulky DNA adducts, as well as of markers of DNA oxidative damage were also significantly different between exposed and unexposed subjects. This is the first study that includes several biomarkers of exposure, effect and susceptibility in order to study the biological effects of PAHs exposure on human health.

ENVIRONMENTAL AND OCCUPATIONAL TOXICOLOGY

P30

Biomarker study to assess health risk in human occupationally exposed to environmental benzene

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Alongside the health risk to the general public, atmospheric pollution could be considered an occupational health hazard to professional groups such as traffic police, and professional drivers working in urban areas. Among the wide variety of potentially toxic chemicals present in the ambient air of urban centers, benzene raises particular concern, due to its haematoxicity and cancer risk

In order to clarify the health risk in human exposed to environmental benzene we have organized a study to investigate biomarkers of exposure (personal passive samplers) early biological effect (micronuclei (MN) on peripheral lymphocytes) and susceptibility (MPO, GSTP1 and GSTT1 genotypes) both in 49 traffic police carrying on outdoor activities in high traffic area of Bologna city (32 no –smokers and 17 smokers, mean age 39.53±7.14), and 36 indoor workers enrolled as controls (23 no smokers and 13 smokers, mean age: 40.13±7.22).

Mean levels of individual, air borne benzene exposure – as measured during the work-shift of 4 h (from 8 a.m. –12 a.m.) – was 6 fold higher in the traffic police than in controls (24.32±14.28 μg/m^3 vs 4.39±0.99 μg/m^3, P= 0.001). MN frequency was significantly higher among the traffic police than in indoor workers (MN/1000 binucleated (BN) cells: 7.06 ±2.87 vs 4.61± 2.04; P= 0.001). All the 49 policemen were genotyped. Preliminary results indicated higher frequency of MN in subjects with GSTT1 null genotype compared with those with positive genotype (MN/1000BN: 8.30±4.64 vs 6.79±2.15), whereas no association was observed with the other studied genes.

P31

Survey of lead, chromium, nickel, cobalt levels in human milk and correlations with environmental and occupational factors

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Breast milk is not only an important source of various nutrients, but also a source of environmental pollutants, like heavy metals. With increasing environmental pollution a heavy metal exposure assessment study is necessary. The concentrations of lead, chromium, nickel, and cobalt in human breast milk were examined in Turkish mothers to clarify the effects of these important elements for infant growth. Breast milk samples were collected from 215 mothers who resided in Istanbul, aged 17–45 years during the first 2 d of their lactation periods at the Obstetrics and Gynecology Department of the Istanbul Medical faculty of Istanbul University, between November 2000 and November 2001. The concentrations were determined by inductively -coupled plasma mass spectrometry. Data, which obtained from this cross-sectional study, were analyzed using appropriate statistical methods. The average age of the mothers was 28,84±5,88. The levels of

elements that analyzed in breast milk were similar to those reported in previous reports. Women exposed environmentally or occupationally can have higher levels in their breast milk. Many factors affect the distribution of lead, chromium, nickel, and cobalt in breast milk and the health consequences to an infant. It is not clear what additional impact low-level exposure via breast milk may have on an infant born with a body burden to one of these metals. More studies on the effects of heavy metals in breast milk are necessary to clarify the effect of environmental and occupational factors. A program of breast milk monitoring would serve to provide the information needed to assess infant environmental and occupational exposures during breast-feeding and develop scientifically sound information on benefits and risks of breast-feeding.

P32

Low dose radiation induced non-targeted effects and the combined environmental exposures

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Our purpose was to study the cytotoxic and genotoxic effect of low dose alpha particle and environmental carcinogens such as toxic metals; PAHs and asbestos or its potential substitutes, alone and in different combination, to assess the contribution of non-targeted effects in environmental carcinogenesis.
Human lung fibroblasts (HFL1) and epithelial cells (BEAS-2B; A549) were treated in different combination of alpha particle radiation and hazardous physical and chemical agents and assayed for cytotoxicity (MTT-assay) and for genotoxicity (mutation) and DNA damage repair (COMET-assay). To show the genomic instability induced by radiation, the plating efficiency, micronucleus frequency and apoptosis induction (TUNEL-assay) was followed through 40 generation of cell proliferation.
Metal compounds ($CdCl_2$; $NiCl_2$; As_2O_3) in low concentration (0,5-1μM) reduced the cytotoxicity of alpha particles, depending on the compound, incubation time, cell line treated and also low doses of radiation (mGy-s) reduced the cytotoxic effect of metals.(*cross-adaptive response*). Further increase in concentrations and/or doses resulted in *additive* cytotoxic responses. The DNA damage repair study showed that the rejoining of breaks was more efficient when the cells were treated in combination with glass fibres and low dose radiation then after each single exposure. The combined treatment of BEAS-2B cells by benzo[a]pyrene+benzo[a]
antracene+chrysene enhanced the DNA adduct level, significantly (*synergistic effect*). The pretreatment of 10 mGy dose alpha radiation resulted in the reduction of the adduct level (*adaptation).*
Our results suggest that the non-targeted effects i.e.: bystander effect, adaptive response, genomic instability should take into consideration in estimating the risk from complex environmental exposures.
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P33

In-vitro model for the investigation of combined genotoxic effect of polycyclic aromatic hydrocarbons and alpha particles in cell culture

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Polycyclic aromatic hydrocarbons (PAHs) and radon are known to increase risk for lung cancer in human. The aim of the study was to elaborate an in-vitro model to explore interaction of environmental PAH and radon exposure. Three PAH model compounds benzo[a]pyrene, benzo[a]antracene and chrysene were selected for the study.. Genotoxicity of PAHs was assessed by measurement of their bulky DNA adducts using ^{32}P-postlabelling. Three human pulmonary cell lines were tested for their PAH activating capacity, A549 lung epithelial, HFL1 fetal lung fibroblast and BEAS-2B lung epithelial cell lines. The PAH activating capacity of the cell types were detected by treating the cells in culture with 4 μM benzo[a]pyrene for 24 hours at 37 °C and the following increasing order was observed among the three cell lines: A549<HFL1<BEAS-2B with BP-DNA adduct levels of 2.5, 4.4 and 215 adducts/10^8 nucleotides, respectively. At equivalent molar doses the adduct forming potential of the three PAH compounds in BEAS-2B was benzo[a]pyrene >> benzo[a]antracene ≈ chrysene. Dose-dependent DNA adduct formation was measured between 0.1 μM and 4 μM PAH concentration, and 0.2 μM concentration was selected for the combined treatment with the three compounds. Preliminary results indicated that the DNA adduct formation by the three compounds in combination was additive to synergistic as compared to the action of the single compounds. Alpha irradiation at 10 mGy dose prior to PAH treatment decreased PAH-DNA adduct forming capacity of the BEAS-2B cells. However, DNA adduct formation by the three PAH compounds remained synergistic as compared to those by the single compounds.

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European digital content sharing services for health protection of workers and workplace safety

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The WORKSAFE project aims at improving access to and use of the large amount of data related to health protection of workers and workplace safety. The wide diffusion of the information collected throughout Europe by EU and National public institutions would be of crucial interest for many organisations, professionals, and workers in order to reduce health hazards and to improve prevention and safety measures at work. Workplace safety is a major concern for millions of workers who deal with potentially dangerous substances. The large and effective diffusion of information regarding work are practices and noxious substances is a crucial need. The need for updated, reliable and "easy access" information services is also crucial and becoming urgent for both public and private organisations, also in view of the EC Directives on health protection of workers. The WORKSAFE project is delivering a new web portal collecting a large number of multidisciplinary contents in the addressed domain catalogued by using innovative semantic web approach. This will improved accessibility and usability of such information and will contribute greatly to the sensibilisation in this sector.