545 GENE EXPRESSION AND DNA ADDUCT FORMATION IS MODULATED BY CHLOROPHYLLIN IN NORMAL HUMAN MAMMARY EPITHELIAL CELLS EXPOSED TO BENZO(a)PYRENE (BP). *John K[1,2], Divi R[3], Keshava C[2], Orozco CC[3], Whipkey DL[1], Poirier MC[3], Nath J[2], Weston A[1,2].* [1]Genetics and Developmental Biology Program, West Virginia University, Morgantown, WV, United States, [2]Toxicology and Molecular Biology Laboratory, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, WV, United States, [3]Carcinogen-DNA Interactions Section, National Cancer Institute, National Institutes of Health, Bethesda, MD, United States.

Introduction: normal human mammary epithelial cell (NHMEC) strains were developed from breast tissue discarded at reduction mammoplasty and obtained through the Cooperative Human Tissue Network (CHTN is sponsored by the National Cancer Institute and the National Disease Research Interchange). These cell strains were used to monitor changes in gene expression and DNA adduct formation upon exposure to the pro-carcinogen BP in the presence or absence of chlorophyllin, a water soluble metalloporphyrin. Methods: following treatment of NHMEC strains (n=7) with BP (4μM) in the presence or absence of chlorophyllin (5μM), genome-wide ~3-fold changes in gene expression were monitored over 24h by DNA-microarrays. The expression of CYP1A1 and CYP1B1 was monitored using real-time polymerase chain reaction (RT-PCR) in 15 NHMEC strains. Anti-benzo(a)pyrene-diol epoxide (BPDE)-DNA antiserum was used by immunoassay to measure BP-DNA adducts in 10 strains. Results: among 7 NHMEC strains monitored using DNA-microarrays, up to 54 genes were induced upon treatment with BP alone, while 11 genes were down-regulated. Chlorophyllin pre-treatment followed by co-treatment with BP and chlorophyllin of the above 7 NHMEC strains caused up-regulation of the expression of 129 genes and down-regulation of 35 genes. Subsequently, wide inter-individual variation was observed in 15 strains for the induction of both CYP1A1 (3 to 96-fold) and CYP1B1 (2 to 43-fold) upon exposure to BP alone, and for their modulation by chlorophyllin (2 to 54-fold and 1 to 39-fold, respectively) when measured by RT-PCR. A reduction in BPDE-DNA adduct levels (48% to 86%) was observed in cells exposed to chlorophyllin following treatment with BP plus chlorophyllin. Conclusions: these results demonstrate inter-individual variation in the bioactivation of BP and the potential of chlorophyllin for reducing the formation of BP-DNA lesions. The data suggest that chlorophyllin may act as a chemopreventive agent for PAH-induced cancers in human populations. Disclaimer: the findings and conclusions in this abstract have not been formally disseminated by the National Institute for Occupational Safety and Health and should not be construed to represent any agency determination or policy.

546 RISK FACTORS FOR ORAL AND ESOPHAGEAL CANCER IN A DEVELOPING COUNTRY: A HOSPITAL-BASED CASE-CONTROL STUDY, NEPAL. *Joshi SD, Pandit N, Bk SK.* Nepal Medical College and Teaching Hospital, Kathmandu, Nepal.

BACKGROUND: Cancer of the oral and oesophagus are common in Nepal. The risk factors predisposing to cancer in Nepalese patients are not known. OBJECTIVES: To determine the role of smoking, alcohol and their combination, and diet factors in the etiology of cancer of the oral and esophagus. METHODS: Risk factors like alcohol consumption, smoking, tobacco chewing, and pre-illness diet details in 90 patients with cancer of the oral and esophagus were compared with those in age- and sex-matched control subjects. RESULTS: The risk for oral and esophageal cancer was 3.5 times higher with alcohol consumption with smoked food, 2.5 times higher for tobacco users, and 2.8 times higher each for betel nut chewers and smokers. The calculated odds ratio for the social habits and diet factors(smoked foods) was significant amongst cases of oral & esophagus cancer. CONCLUSION: Alcoholism,smoked food, smoking, and chewing of tobacco are factors predisposing to oral and esophageal cancer in Nepal. Inspite of poverty, illiteracy and work load most of the people takes local made alcohol, unfiltered cigarette smoking and chewing of tobacco with slaked lime.

547 PHOTOCHEMICAL GENOTOXICITY TESTING *IN VITRO*: A EUROPEAN COLLABORATIVE STUDY ON THE COMET ASSAY AND THE MICRONUCLEUS TEST. *Kasper P[1], Aeby P[2], Brendler-Schwaab S[3], Epe B[4], Froetschl R[1], Hertel C[4], Kirchner S[5], Meurer K[6], Plappert-Helbig U[7], Schmidt E[8].* [1]Federal Institute for Drugs and Medical Devices (BfArM), Bonn, Germany, [2]Cosmital SA (Wella AG), Marly, Switzerland, [3]Bayer HealthCare (current address 1), Wuppertal, Germany, [4]University of Mainz, Mainz, Germany, [5]F. Hoffmann-La Roche, Basel, Switzerland, [6]RCC Cytotest Cell Research GmbH, Rossdorf, Germany, [7]Novartis Pharma AG, Basel, Switzerland, [8]ZEBET, Federal Institute for Risk Assessment (BfR), Berlin, Germany.

Assays for the detection of photogenotoxicity of chemicals during exposure to UV light are required for regulatory submissions under certain circumstances e.g. for compounds developed as sunscreens or for pharmaceuticals with UV/light absorption properties and known to be present in the skin. There is still a need for well-developed protocols for such assays, in particular if mammalian cell tests are to be used. A collaborative study with seven participating laboratories was conducted to evaluate the performance of previously developed test protocols for the photo micronucleus test and the photo Comet assay with Chinese hamster V79 cells. Thirteen coded test chemicals were selected based on their ability to absorbe UV light. Eight compounds were classified as photo-genotoxic (8-methoxypsoralen, chlorpromazine, lomefloxacin, ciprofloxacin, methylene blue, proflavine, dacarbazine, doxycycline) and five as non-photogenotoxic (three phototoxic: promazine, ketoprofen, acridine; two non-phototoxic: octylmethoxycinnamat, titanium dioxide) according to published data. Each compound was tested in two independent runs in both assays by 3 – 5 different investigators. The results obtained showed a good reproducibility, both within and between laboratories. Sensitivity in detecting the photo-genotoxic compounds was high with both models while specificity appeared to be low as the three phototoxic compounds assumed to be non-photogenotoxic (based on literature data) showed predominantely positive findings. However, these results more likely reflect uncertainties in the pre-study classification due to inadequate available data. In summary, the data provide a further step in the development of reliable and robust *in vitro* mammalian cell photogenotoxicity tests suitable for regulatory submissions. An agreed standard list of calibration chemicals is considered key for any further evaluation/validation studies. (This work was supported by the German Federal Ministry of Education and Research, BMBF-project No. 0312916A/B/C/D.)

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Abstracts

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