185 **DNA REPAIR IN CHROMATIN: AN OVERVIEW.** Smerdon MJ[1]. [1]Washington State University, Pullman, WA 99164-4660.

Eukaryotic DNA repair enzymes must interact with the architectural hierarchy of chromatin. For over two decades, my laboratory and others have focused on the complexities of excision repair in chromatin. A major finding was that during nucleotide excision repair (NER) in mammalian cells significant structural rearrangements occur at both the nucleosome level and higher-order levels of packaging, indicating that chromatin must be 'disassembled' during NER. In addition, the major UV photoproduct [cis-syn cyclobutane pyrimidine dimer (or CPD)] is removed in human cells at similar rates from all surfaces of the DNA helix within nucleosomes during early repair times. Furthermore, repair of DNA by nuclear extracts from Xenopus oocytes was examined in well-defined nucleosome substrates containing a cis-syn cyclobutane thymine dimmer (CTD) at a single site in a short DNA fragment, bracketed by nucleosome positioning elements (TG-motifs). NER in these extracts effectively removes the CTD, although nucleosome assembly decreases the repair rate by ~2-fold relative to naked DNA. However, extract repair within the nucleosome is >50-fold more rapid than either enzymatic photo-reversal or endonuclease cleavage of the lesion *in vitro*. Finally, several recent *in vitro* studies have examined the effects of chromatin remodeling complexes on NER of nucleosome-loaded DNA. In each case, specific DNA lesions in (or near) a nucleosome core were found to be more accessible to repair enzymes following treatment with the chromatin remodeling complexes. Taken together, these results indicate that an active process of nucleosome rearrangement may occur during excision repair in chromatin.

186 **IS CANCER RISK ONLY RELEVANT ENDPOINT FOR QUANTITATIVE ASSESSMENT OF RISKS?.** Smerhovsky Z[1], Dejmek J[1], Solansky I[1], Sram RJ[1]. [1]Laboratory of genetic ecotoxicology, Institute of Experimental Medicine AS CR, Videnska 1083, 142 20 Prague 4, Czech Republic.

The risk assessment procedures consider as critical solely carcinogenic effect of polycyclic aromatic hydrocarbons (PAHs). However, the exposure to PAHs at level common in urban environment can affect also the development of fetuses. The relation of PAH exposure and intrauterine growth retardation (IUGR) was observed in the framework of Teplice Program carried out in 90s, in the period of high environmental pollution. Now we report an analysis of additional 1440 pregnancies, conceived between October 2000 and July 2002, when the atmospheric pollution did not exceeded levels found in other Czech cities (mean conc. of PAHs=39.15 ng/m^3, carcinogenic PAHs=5.31 ng/m^3). The study included all single live births occurring in Teplice Hospital. Information on reproductive history, health and life style was obtained from questionnaires. The mean levels of PAHs were calculated using monitoring data and exposures during 9 gestational months (GM) were estimated for each mother. The pregnancies were assigned into low, medium, and high (terciles) exposure groups according to the level in each particular GM. The risk of IUGR was estimated by logistic regression. The effect of PAH exposure was adjusted to a most of potential confounders. Results showed that the IUGR occurrence is associated particularly with carcinogenic PAH-exposure, which occurred in 3rd and 4th GM. In the 4th GM, when the strength of association reached maximum, we found the odds ratio (OR) for medium exposure OR=2.13 (95% CI 1.01-4.51) and for high exposure OR=2.72 (95% CI 1.34-5.55). The recently emerging data indicates that concentrations of PAHs in urban environment are high enough to affect fetus development and these effects should be also considered as critical. *Supported by the Czech Ministry of Environment (VaV/340/2/00).*

187 **MOLECULAR EPIDEMIOLOGY OF CHILDHOOD LEUKEMIA.** Smith MT[1], Wiencke JK[2], Wiemels JL[2], Zhang L[1], Ma X[1], McHale C[1], Buffler PA[1]. [1]School of Public Health, University of California, Berkeley, CA 94720. [2]Molecular Epidemiology Laboratory, University of California, San Francisco, CA 94143.

In order to shed light on the causes of childhood leukemia, we and others have undertaken population-based case-control studies of this disease incorporating biological sampling and molecular biological tools. Our study, based in Northern California, aims to enroll up to 1,000 cases and incorporates molecular cytogenetic characterization of the cases. Various specific chromosome translocations and inversions, including t(8;21), t(15;17), inv(16), are found in acute myeloid leukemia (AML), and in childhood acute lymphocytic leukemia (ALL) t(12;21) and t(1;19) are common. We sequenced the genomic translocation breakpoints of 56 patients with childhood ALL or AML harboring t(12;21), t(8;21), t(15;17), inv(16), and t(1;19) and demonstrated, with the notable exception of t(1;19), that these rearrangements are commonly detected in the neonatal blood spots (Guthrie cards) of the cases. These findings show that most childhood leukemias begin *in utero* and that maternal and peri-natal exposures are likely to be critical. Indeed, we have reported that exposure to indoor pesticides during pregnancy and the first year of life raises leukemia risk, but that later exposures do not. We have also examined aberrant gene methylation in the different cytogenetic sub-groups and have found striking differences between them, suggesting that epigenetic events are also important in the development of some forms of childhood leukemia. Further, at least two studies now show that the inactivating *NQO1 C609T* polymorphism is associated with leukemias arising in the first 1-2 years of life and polymorphisms in the *MTHFR* gene have been associated with adult and childhood ALL. Thus, we are investigating if low folate intake and compounds that are detoxified by NQO1 are important in elevating leukemia risk in children.

188 **COORDINATED REGULATION OF GENE EXPRESSION BY LOW DOSE ARSENIC.** Snow ET[1,2], Sykora P[1], Schuliga M[1], Hu Y[1,2]. [1]Deakin University, Sch. Biol. & Chem. Science, Melbourne, Australia 3125. [2]NYU Sch. Medicine, Inst. Environmental Med., Tuxedo, NY 10987.

Environmental exposure to arsenic is a serious world wide health problem. Chronic exposure to arsenic is known to cause skin, lung, and bladder cancer, vascular disease, peripheral neuropathies, and increased risk of diabetes. The risk of increased cancer due to arsenic appears quite high, although questions regarding the shape of the dose response curve remain. Doses of As(III) that produce molecular responses relevant to carcinogenesis seem to be in the range of 0.01 to 10 μM. These concentrations are within the range of total arsenic species found in the blood of people chronically exposed to high levels of As. We have found that exposure of human keratinocytes and fibroblasts to low, micromolar concentrations of As(III) for 3 to 72 hours alters cellular response to active oxygen by modulating the expression of multiple genes involved in cellular redox control and base excision repair (BER). Multiple redox genes such as thioredoxin, thioredoxin reductase, glutathione reductase, and others are up-regulated in parallel by 5 to 20 μM As(III). Somewhat surprisingly, BER activity (especially DNA ligase activity) shows a small, but significant, increase at submicromolar As(III). However, greater than 1 μM As(III) causes a significant dose-dependant decrease in steady state mRNA levels for DNA ligase I, DNA polymerase β, XRCC1 and DNA ligase III, among others. Clearly inhibition of DNA repair by As(III) is primarily due to decreased expression of multiple DNA repair genes. However, sub-acute exposure to low doses of As(III) appears to cause more of a protective than a toxic response. Our work and that of others gives strong molecular evidence for a non-linear cellular response to As that would predict a threshold in the dose response for arsenic-induced carcinogenesis.