lation sensitive restriction digestion, arbitrarily primed PCR, and electrophoretic separation of PCR products. Analysis focused on common and unique regions of altered methylation (RAMs) with increasing dose of CSC, and between precancerous and tumor tissue. The number of common RAMs in precancerous tissue increased from 6 to 15 to 24 when comparing 3 and 9 mg CSC, 9 and 18 mg CSC and 18 and 27 mg CSC, respectively. Tumor tissue as compared to 18 and 27 mg CSC-promoted precancerous tissue shared 21 and 20 RAM, respectively, and exhibited 8 unique RAMs. Those RAMs that are seen in the precancerous tissue and carry forward to the tumors are likely to play a key role in tumorigenesis. Twenty-two CpG sites in a 5' region of the Ha-ras promoter were unmethylated in precancerous and tumor tissue; but, a generalized decrease in methylation was observed close to the transcriptional start site. Ha-ras expression increased with 18 and 27 mg CSC promotion, and more so in tumor tissue. These data support our hypothesis that tumor promotion involves an instability of the epigenome, providing an environment where changes in the methylation status of specific regions of the genome accumulate progressively. This facilitates the aberrant gene expression involved in the clonal expansion of initiated cells that leads to tumor formation.

53 KIDNEY TOXICOGENOMICS OF CHRONIC POTASSIUM BROMATE EXPOSURE IN F344 MALE RAT

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Potassium bromate (KBrO3), used in both the food and cosmetics industry, is a drinking water disinfection by-product that is nephrotoxic and carcinogenic to rodents. To gain insight into the carcinogenic mechanism of action and provide possible biomarkers of KBrO3 exposure, the gene expression from chronically exposed male F344 rat kidney was investigated. Animals were exposed to KBrO3 in drinking water for 52 and 100 wk. Kidneys were removed, frozen, then used for Affymetrix microarray analysis. Gene expression patterns were examined in a non-cancer (20 ppm) and cancer-causing dose (400 ppm) at 52 wk, and compared to 100 wk high (400 ppm) and adenoma gene expression. Statistical analysis revealed 144, 224, 43, and 994 genes out of 15919 from the 52 wk low, 52 wk high, 100 wk high, and adenomas respectively, were significantly altered. Gene ontology classification of the 52 wk high dose showed alterations of genes involved in oxidative stress, lipid metabolism, kidney function/ion transport, and cellular function. In a comparison of kidney development gene expression, alterations were seen in the adenomas but not in the 52 wk bromate-treated kidneys. However, the high dose, but not the low, reiterated the adenoma expression pattern with early kidney development genes being up-regulated and adult phase genes being down-regulated. Moreover, eight genes which could serve as biomarkers of carcinogenic exposure were identified. The most promising of these was Pendrin, or Slc26a4, a solute carrier of chloride and iodide active in the kidney, thyroid and inner ear. All these tissues are targets of KBrO3 toxicity. Expression array results were verified with real-time PCR. Taken together, the analysis from this study identifies potential biomarkers of exposure and illuminates the carcinogenic mechanism of action for KBrO3. [Although this work was reviewed by EPA and approved for publication, it may not necessarily reflect official Agency policy]

54 GENE EXPRESSION PROFILING OF MOUSE SKIN AND PAPILLOMAS FOLLOWING CHRONIC EXPOSURE TO MONOMETHYLARSONOUS ACID IN K6/ODC TRANSGENIC MICE

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Methylarsonous acid [MMA(III)], a common metabolite of inorganic arsenic metabolism, increases tumor frequency in the skin of K6/ODC transgenic mice following a chronic exposure. To characterize gene expression profiles predictive of MMA(III) exposure and mode of action of carcinogenesis, K6/ODC mice were administered 0, 10, 50 or 100 ppm MMA(III) or 75 ppm sodium arsenite in their drinking water for 26 weeks. Skin and tumor gene expression changes were determined using Affymetrix Mouse Genome 430A 2.0 GeneChips® and MAS 5.0 normalization procedures. Differential gene expression was determined using linear regression and a regularized t-test (Bayesian procedure). Functional gene categorization was assessed using the Database for Annotation, Visualization and Integrated Discovery 2.0 (DAVID, Dennis and Hosack et al. 2003). Linear regression analysis revealed changes in multiple cytoskeleton and cell cycle-related genes including enabled homolog (Enah) and the tumor suppressor gene p27 (Cdkn1b). The dose-dependent decrease in p27 mRNA we observed in mouse skin is consistent with the previously reported reduction in p27 protein observed in arsenical-induced urinary bladder lesions. Using a regularized t-test, significant changes were also observed in multiple oncogenes including changes in c-myc (Myc), fra-1(Fosl1), and v-maf (Mafb). Significant increases we observed in c-myc mRNA in mouse skin and papillomas are consistent with increases in c-myc during arsenic-induced mouse liver carcinogenesis. Since c-myc protein can bind the promoter of p27 and regulate its transcription, the molecular changes observed in our study are likely related and also important in MMA(III)-induced mouse skin carcinogenesis. Additional gene expression changes we observed in chromosome maintenance and steroid metabolism genes may also contribute to the carcinogenesis process in mouse skin. [This abstract does not necessarily reflect EPA policy.]

55 CORRELATION BETWEEN GENE EXPRESSION IN HUMAN CELLS AND TUMOR INITIATION IN SENCAR MICE ON EXPOSURE TO A STANDARDIZED COMPLEX MIXTURE DERIVED FROM DIESEL EXHAUST

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Human exposures to polycyclic aromatic hydrocarbons (PAH) occur as complex mixtures of PAH, some of which are carcinogenic. Standardized Reference Material (SRM) 1650a (diesel particulate) and SRM 1975 (diesel exhaust extract), was obtained from the National Institute of Standards and Technology. Gene expression patterns were investigated in MCF-7 cells exposed to SRM 1650a alone or in combination with individual PAH (24h). Gene expression was monitored using high density oligonucleotide arrays (U133A, Affymetrix). Global gene expression analyses revealed alterations in at least 223 RNA transcript species by at least 2 fold. Among several other genes, increase in expression of CYP1A1 and CYP1B1 was observed in response to benzo[a]pyrene (BP) exposure. Additive induction of similar genes was noticed on co-treatment with SRM 1650a plus BP. Unlike BP and SRM 1650a, no change in expression of CYP1A1 and CYP1B1 was observed when MCF-7 cells were exposed to Dibenzo[a,l]pyrene (DBP). To study the effect of complex PAH mixtures on the metabolic activation of carcinogenic PAH to DNA-binding derivatives and to relate the results with gene expression studies in human cells, mouse skin initiation-promotion tumorigenesis model was utilized. Results indicate that although SRM 1975 had a weak tumor-initiating activity, on co-treatment with BP an increase in tumors per tumor bearing animal was observed. On the contrary, SRM 1975 did not cause any modification in the tumor-initiating activity of DBP. These results not only provide a transcriptional signature to chemical carcinogen exposure but also suggest that understanding the relationship between tumor induction and gene expression may allow the prediction of early carcinogenic effects of these environmental mixtures.

56 COMPARISON OF GENE EXPRESSION CHANGES IN PANCREAS OF RATS FED DIETS CONTAINING WYETH 14,643, DIETHYLHEXYLPHTHALATE OR AMMONIUM PERFLUOROOCTANOATE (APFO)

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The non-genotoxin APFO (300ppm in the diet) has been shown to induce pancreatic acinar cell tumours in rats. In order to identify pancreatic gene expression changes that are associated with pancreatic carcinogenesis male Sprague Dawley rats (6-7 weeks old) were fed either: (1) the potent pancreatic carcinogen Wyeth 14,643 (Wy) in the diet at 50ppm (carcinogenic dose) or 20ppm (non-carcinogenic dose), (2) the weak (or non-) pancreatic carcinogen diethylhexylphthalate (DEHP, 12000ppm) or (3) APFO at 300ppm for up to 4 weeks. Transcriptional profiling at, 1, 7 and 28 days, using a rat 60mer oligonucleotide array containing ~22,000 genes was performed on pancreas. Luminator software was used to compare lists of significantly ($P<0.01$) regulated genes. This analysis identified several pancreatic gene expression changes, unique to Wy 50ppm-exposure, that were associated with carcinogenesis including: up-regulation of early growth response 1 (EGR1), TPA-inducible sequence (TIS11), and growth arrest and DNA damage 45 alpha (GADD45α) and down-regulation of thymine-DNA glycosylase (TDG). Induction of the proliferation- and DNA-damage-associated genes TIS11 and GADD45α and repression of the DNA-repair enzyme TGD were time-dependent. Although alteration to carcinogenesis-associated genes such as GADD45α, TGD and TIS11 were not always significant in APFO-exposed animals the trends in these gene changes over time were similar to those occurring with Wy 50ppm treatment and more pronounced than those observed in the DEHP-exposed animals.

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, and poster sessions of the 45th Annual Meeting of the Society of Toxicology, held at the San Diego Convention Center, San Diego, March 5–9, 2006.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 500.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 534.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

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