changes in DNA methylation patterns and histone H2B variant regulation as key players in iAs-mediated carcinogenesis and EMT. Using Methyl-seq, we show genome-wide and gene-specific changes in DNA methylation patterns that correlated to changes in gene expression in response to iAs exposure. After removal of iAs exposure, we observe moderate reversal of DNA methylation changes, gene expression patterns, and EMT. We also identified ten histone H2B variants that are dysregulated during iAs-mediated carcinogenesis using top-down mass spectrometry. These variants are possibly modulating DNA compaction around the nucleosome, thereby altering gene expression patterns in chronically iAs-treated cells. Our studies indicate that inorganic arsenic-mediated carcinogenesis is instigated, in part, by changes to the epigenome including DNA methylation and histone H2B variants.

1890 Regulation of Chromatin Assembly and Cell Transformation by Exposure to a Physiologically-Relevant Concentration of Formaldehyde

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Formaldehyde (FA) is an environmental and occupational chemical carcinogen. Most studies of FA-induced carcinogenicity have focused on DNA damage and mutagenesis induced by DNA adducts and DNA-protein crosslinks, however, little is known about the molecular mechanisms responsible for FA-induced epigenetic dysregulation. Previously we demonstrated that exposure to 0.5mM of FA dramatically decreases lysine acetylation of the N-terminal tails of cytosolic histones H3 and H4, thereby inhibiting chromatin assembly. Endogenous FA concentration in human blood ranges between 20 μM and 100 μM. Thus, to test whether similar outcomes can be seen at a more relevant FA dose, we treated human BEAS-2B cells with 100 μM FA and studied its effect on histone modification, chromatin assembly, transcription, and cell transformation. Continuous exposure of cells to the physiologically relevant concentration of FA significantly reduced the levels of cytosolic H3K9&K14Ac and H4K12Ac. The reduction was likely due to the formation of FA-histone lysine adducts given that lysine formylation and Schiff base were detected by mass spectrometry in cells. Cellular fractionation and Western blot analysis show the amount of histone H3 in chromatin fraction decreases by about 20%; chromatin immunoprecipitation assays show the level of histone H3.3, an H3 variant, is significantly reduced at the majority of loci tested, suggesting that FA compromises chromatin assembly at a physiologically relevant concentration. Moreover, knockdown of the H3.3 gene, which mimics inhibition of chromatin assembly, altered expression of a number of cancer-related genes deregulated by FA and facilitated FA-mediated anchorage-independent cell growth. These results suggest that defective chromatin assembly may play important roles in FA-induced transcriptional deregulation and cell transformation. *This work was supported by NIH grants 1R01ES026138-01, 5P30ES000260, 5R03ES024147, and 1R01GM099409 as well as National Natural Science Foundation of China Grant 31329003.*

1891 Characterization of Functional and Molecular Endpoints of Potential Adverse Health Effects Associated with Age, Diet, and Occupational Exposure in an Animal Model

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The exposome is the measure of all exposures of an individual in a lifetime from conception to death and how those exposures affect health. An individual's exposome is highly variable and dynamic throughout their lifetime. The goal was to design an exposure paradigm that would address multiple exposome components, including lifestyle (e.g., diet), age, and occupational exposure (welding fume; WF) in a controlled animal model. Functional and molecular endpoints predictive of adverse health effects in recovered biological fluids of exposed animals that are translatable to human populations were examined. Male Fischer 344 rats were maintained on a high fat western (HF) or regular (REG) diet for 24 wk. At wk 7 during diet maintenance, groups of rats were exposed by inhalation of stainless steel WF (20 mg/m^3 x 3 hr/d x 4 d/wk x 5 wk) or filtered air (control) until wk 12 at which time some animals were euthanized. A separate set of rats were allowed to recover from WF exposure until the end of the 24 wk period. Whole blood and bronchoalveolar lavage fluid were collected at 7 wk (baseline before WF exposure), 12, and 24 wk to assess blood cell differential and to recover serum, peripheral blood mononuclear cells (PBMCs), and lung phagocytes for epigenetic analysis and immune response. Significantly elevated % change in body weight and serum triglycerides were observed in groups maintained on the HF diet. At nearly all time points, phagocytosis of bacteria by recovered phagocytes and PBMC telomere length were significantly decreased in the REG+WF, HF+air, and HF+WF groups compared to the REG+air group. A significant decrease also was observed in telomere length over the 24 wk regimen in all groups. In summary, age, diet, and occupational exposure (WF inhalation), important exposome components, altered immune response and epigenetic endpoints in rats. An animal model may be advantageous for studying the exposome because of the ability to control all external exposures and to measure potential adverse health outcomes of each animal over its entire lifespan and to link a specific internal biological response/endpoint with a specific exposure.

1892 Combinatorial Effect of Butyl Benzyl Phthalate and a High-Fat Diet on Epigenetic Regulation of Adipogenesis and Obesity

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Obesity has reached epidemic proportions worldwide. Exposure to endocrine disrupting chemicals (EDCs) such as those found in plastics may influence the development of obesity. Our studies investigate the effect of the EDC butyl benzyl phthalate (BBP) in combination with a high-fat environment on epigenetic regulation of obesity. We hypothesize that BBP and a high-fat diet (HFD) act synergistically to enhance obesity via epigenetic regulation of microRNA (miR) promoter methylation. C57Bl/6 male (8 weeks old) mice were fed chow diet (CD) (4% kcal from fat) or HFD (60% kcal from fat) with or without BBP (3 mg/kg/day) for 16 weeks when body and white adipose tissue (WAT) weights were measured. 3T3-L1 preadipocytes were treated with BBP, palmitic acid (PA), or a combination of both to induce adipogenesis. Adipogenic characteristics and epigenetic regulatory mechanisms were analyzed in mature adipocytes. Mice fed HFD+BBP had significantly increased body weights compared to HFD alone, CD, and CD+BBP fed mice ($P<0.01$ for HFD and $P<0.001$ for CD groups). Mice fed HFD+BBP also had significantly larger WAT weights compared to HFD ($P<0.01$) or CD groups ($P<0.001$). BBP (1 μM, 10 μM, 50 μM) exposure in 3T3-L1 cells induced adipogenesis in a dose-dependent manner, and BBP+PA increased adipogenesis over individual treatments with a significant upregulation of adipogenic gene expressions compared to PA alone ($P<0.001$). BBP significantly upregulated miRs-34a, 103, 107, and 125a expression in mature adipocytes ($P<0.01$). BBP+PA further significantly upregulated miR-34a, 103, 107, and 125a expressions compared to control or PA alone ($P<0.01$). DNA methyltransferase (DNMT) 1, 3a, and 3b gene expressions were significantly decreased with BBP treatment ($P<0.01$) and further decreased in combination with PA ($P<0.001$). Concurrently, global DNA methylation was significantly reduced with BBP treatment ($P<0.05$) and further decreased with BBP+PA treatment ($P<0.001$ compared to control; $P<0.05$ compared to PA alone). In summary, BBP and a high-fat environment increased obesity in mice and increased adipogenesis *in vitro*. BBP and PA increased adipogenic miR expression while decreasing DNA methylation and DNMT expression. We are currently investigating miR promoter methylation in adipogenesis. This suggests that an HFD and EDC exposure can worsen an individual's metabolic health by altering the epigenome program.

1893 *N*-Ethyl-2-Pyrrolidone and DNA Methylation: Identification and Verification of Target Genes by Next-Generation Sequencing and Mass Spectrometry

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N-ethyl-2-pyrrolidone (NEP) is frequently used as an industrial solvent and classified as a reproductive toxicant. However, no studies are available on the mode-of-action of NEP. Therefore, we orally exposed rats (n=5 per dose group) to 0, 5, 50, and 250 mg NEP/kg/d up to 28 days and studied the influence of NEP on DNA methylation, an early epigenetic event, in tissue samples of the liver, kidney, adrenal gland,

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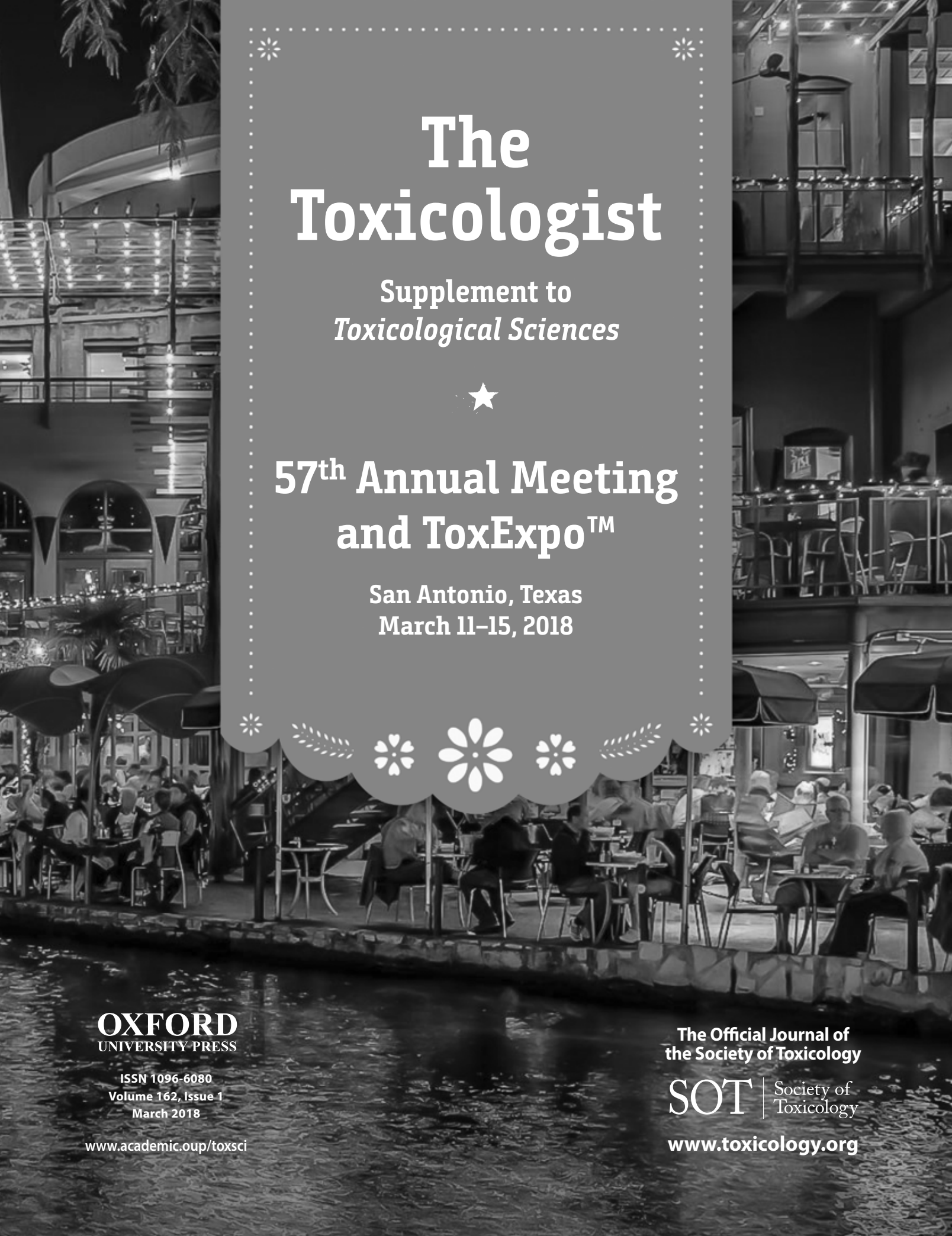

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