162.1

Monitoring Acrylamide Biomarker and Reproductive Toxicity

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Acrylamide is a classical neurotoxin and reproductive toxin that humans are exposed to in the workplace and by ingesting contaminated water. Since acrylamide toxicity is related to cumulative dose, the pharmacokinetic profile and distribution is an important consideration. The highest concentration of acrylamide following single or multiple exposure is in erythrocytes, but significant accumulation also occurs in the testes. The current study was undertaken to evaluate a biomarker for acrylamide-adducted hemoglobin in exposed rabbits and to correlate levels with changes in sperm parameters. Rabbits were treated with repeated doses of acrylamide by the i.p. route (6.25mg/kg qod for 30 days). Serial blood and semen samples were obtained before, during and following exposure. The acrylamide adduct was detected as early as day four, while sperm abnormalities were not noted until two weeks after treatment began. In most animals, adduct was still detectable 30 days after terminating treatment. Sperm counts returned to normal two weeks after terminating exposure while live:dead sperm ratios returned to baseline about five days after the last treatment.

162.2

FACTORS INVOLVED IN SAFETY EVALUATION OF TRANS-ANETHOLE (TA). P. Newberne, T. Adams and J. Hallagan. Boston Univ. Sch. Of Med., Boston, MA 02118 and Flavor Extract Manufacturing Association, Washington, D.C. 2006.

Trans-anethole imparts an anise-like flavor to a number of foods and beverages; it occurs naturally in essential oils and in leaves and roots of many plants. Animal studies in rats and mice revealed a tumorigenic effect at high dose levels in female rats only, associated with metabolism of more TA to trans-anethole the epoxide (AE), a hepatotoxin related to liver damage and tumor induction. At low levels TA is detoxified in rodents and humans mainly by O-demethylation with AE a minor pathway; at high levels in female rats a metabolic shift results in increased epoxidation and formation of AE as a major pathway. Chronic intake of high levels of TA results in a continuum of hepatocellular injury, necrosis and proliferation, and ultimately liver neoplasms, not observed at low exposure. Neither TA nor AE have been shown to be genotoxic and the weight of evidence suggests a non-genotoxic mechanism for liver tumors as noted above. Low levels of exposure to TA should effectively eliminate or sharply reduce human population risk. (This research supported by the Flavor Extract Manufactures of America).

162.3

EFFECT OF THE PCBs 2,2',4,4',5,5'-HEXACHLOROBIPHENYL (PCB-153) AND 3,3',4,4'-TETRACHLOROBIPHENYL (PCB-77) ON CELL PROLIFERATION AND THE ACTIVATION OF THE TRANSCRIPTION FACTORS NF-κB AND AP-1 IN RATS TREATED WITH DIETHYL-NITROSAMINE (DEN). J. C. Tharappel, L. W. Robertson, E. Y. Lee, B. T. Spear and H. P. Glauert. University of Kentucky, Lexington, KY 40506

Polychlorinatedbiphenyls (PCBs) are environmental pollutants that are complete carcinogens and have promoting activity in two stage hepatocarcinogenesis. In the present study we evaluated their effects on the activation of hepatic NF-κB and AP-1 and on cell proliferation in rats. All the animals in this study received a single dose of DEN (150 mg/kg) followed by four biweekly injections of PCB-77 or PCB-153 (100 or 300 μmol/kg), or both PCBs (each 100 μmol/kg). Ten days after the last PCB injection, all animals were sacrificed; 3 days before sacrifice all animals were implanted with Alzet osmotic pumps containing 5-bromo-2'-deoxyuridine (BrdU). There was a significant increase in the DNA binding activities of NF-κB and AP-1 in hepatic nuclear extracts from rats in the high dose groups and in rats receiving both PCBs. The number and volume of altered hepatic foci were increased in rats administered PCBs, with the highest increase seen in rats administered PCB-77. The BrdU labeling index was increased in all treatment groups and was higher in focal cells. This study shows that both PCBs alone or in combination increase the DNA binding activities of NF-κB and AP-1, the number and volume of altered hepatic foci, and hepatic cell proliferation. (Supported by ES-07380 and CA-01688).

162.4

ACUTE EXPOSURE TO RESIDUAL OIL FLY ASH DOES NOT ENHANCE PULMONARY INFLAMMATION IN MICE RECOVERING FROM *PNEUMOCYSTIS CARINII* INFECTION. NC Long, RM Molina, AG Harmsen*, & JD Brain Physiology Prog. Harvard Sch. of Public Health, Boston, MA 02115 and *Trudeau Institute, Inc, Saranac Lake, NY 12983

Humans who breathe high levels of urban particles are at increased risk for cardiopulmonary morbidity and mortality. The acute increase in symptoms, hospital admissions, and deaths is seen primarily in individuals with pre-existing cardiopulmonary disease. However, previous results from our lab showed that exposure to residual oil fly ash (ROFA) did not augment the inflammatory response of SCID mice to *Pneumocystis carinii* (*Pc*) (*FASEB J* 12(3) A791, 1998). In the present study, we investigated the effect of ROFA exposure in Pc-infected SCID mice reconstituted with immune competent spleen cells, and hence were in the process of clearing their infection. While reconstitution provides these mice with T and B cells necessary to clear *Pc*, it also sets into motion an inflammatory cascade that can damage the host (*J. Immunol.* 155:3525-29, 1995). We compared uninfected SCID mice to reconstituted *Pc*-infected SCID mice (10^5-10^6 *Pc* nuclei/lung) on days 13 and 14 post-reconstitution, when the inflammatory response is at its peak. We instilled mice from both groups with 0.625, 6.25 or 25 mg/kg ROFA or saline (both in volume of 2.5 ml/kg). One day later, bronchoalveolar lavage (BAL) was analyzed for parameters of injury and inflammation, including differential and total cell counts, albumin levels, and lactate dehydrogenase and myeloperoxidase activities. Both spleen cell reconstitution of *Pc*-infected mice, and ROFA instillation increased BAL parameters ($p<0.05$). More importantly, we saw a significant interaction between *Pc* and ROFA ($p<0.05$). ROFA instillation decreased the neutrophil counts, and albumin levels in BAL from reconstituted mice. Our data did not support the hypothesis that a single exposure to ROFA enhances the lung inflammatory responses in mice recovering from *Pc* infection. Supported by NIH HL-43510 and ES-00002.

162.5

PENTOSIDINE LEVELS IN RAT LUNGS AFTER SILICA INHALATION. DW Porter[1], M Iqbal[2], H Klandorf[2], VA Robinson[1], M Barger[1], JYC Ma[1], D Ramsey[2], A Khan[2], JL McLaurin[3], V Castranova[1] and A Teass[1]; [1]HELD, NIOSH, Morgantown, WV; [2]West Virginia University, Morgantown, WV; [3]DBBS, NIOSH, Cincinnati, OH.

Occupational exposure to crystalline silica (quartz) has been associated with oxidative lung damage and fibrosis. These oxidants can be generated directly from silica particles as well as from silica-activated phagocytes. Pentosidine is a non-enzymatic glyco-oxidation protein adduct that has been suggested as a biomarker for oxidative stress. The potential of pentosidine as a biomarker for silica-induced oxidant injury and fibrosis has not been investigated. As a first step in assessing this possibility, the concentration of pentosidine was determined in the lungs of silica exposed rats. Rats were exposed to filtered air (control) or silica aerosol of 15 mg/m^3 (6 hr/day, 5 days/week) and bronchoalveolar lavage samples and lung tissue were evaluated at various times throughout the 116 day exposure. Alveolar macrophage (AM) chemiluminesence, a measure of AM activation and reactive oxygen species production, was higher in silica-exposed rats than controls. Lung lipid peroxidation, an indicator of oxidative damage, steadily increased during exposure and was significantly elevated above control after 41 days exposure. Lung hydroxyproline, a marker of lung fibrosis, was significantly elevated above controls after 116 days exposure. In silica exposed rats, lung pentosidine levels were increased to 148% of control after 10 days exposure, and further increased to 239% by 116 days exposure. These data provide the first indication that lung pentosidine levels correlate with lung oxidative injury and fibrosis in silica-exposed rats. Further evaluation of pentosidine as a biomarker for silica-induced oxidative damage and fibrosis is warranted.

162.6

MALIGNANT NEOPLASMS OF THE NASAL/PARANASAL SINUSES. A SERIES OF 259 PATIENTS IN MEXICO CITY AND MONTERREY. IS AIR POLLUTION THE MISSING LINK? L.Calderon-Garciduenas,R.Delgado,A.Meneses, A.Calderon-Garciduenas,L.Ruiz,J de la Garza,H.Acuna,A.Villarreal-Calderon.Toxicology Curriculum,UNC at Chapel Hill,NC,USA, Institutos Nacionales de Pediatria y Cancerologia,Mexico DF,and Hospital de Especialidades #25,IMSS,Monterrey,NL,Mexico.

Air pollution is a serious health problem in major cities in Mexico.Residents in Metropolitan Mexico City(MMC),and Monterrey are chronically and sequentially exposed to potential atmospheric carcinogens.We surveyed all new cases of nasal/paranasal malignant neoplasms admitted to an adult oncology hospital in MMC (1976-1997)and to a terciary hospital in Monterrey(1993-1998). The MMC hospital had a 4fold increase in nasal/paranasal neoplasms for the period 1995-1997.Nasopharyngeal carcinoma(npc),non-Hogdkin's lymphoma(NHL)(T/NK nasal),adenocarcinoma &melanoma were predominant.69% of males reported occupations with outdoor exposures>10h/day.The 2 major neoplasms were EBV-related.For Monterrey,npc,melanoma and NHL predominated,with a 2fold increase in the 1996-1998 period.This is an awareness report; its main objective is to bring attention to the potential risk for nasal and paranasal malignant neoplasms in adults with prolonged outdoor exposures to highly polluted urban atmospheres,in a scenario where EBV seems to be playing a major role.Supported in part by NIEHS training grant #T32 ES07126.

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