0, 1-25, 25-50, 50-75, 75-100% on each focus. The tumor grade, pathological stage and pretreatment serum PSA levels were correlated with PSP94 expression in both groups. In Group 1, PSP94 positive staining was seen in 100% of low grade tumors and 12.5% in high grade tumors. In Group 2, a decreased PSP94 expression was observed in low grade tumors while a significant higher PSP94 expression was noted in high grade tumors (36%). No significant correlation between PSP94 expression levels and the other variables was noted in both groups.PSP94 expression in untreated prostate cancer has an inverse correlation with the tumor grade ($p<0.001$),while in neoadjuvant hormonal therapy group, an increased PSP94 expression was observed in high grade tumors . This discrepant expression pattern suggests that the regulation of PSP94 may be altered under androgen deprivation conditions.

1122 PROSTATE CANCER RISK FACTORS IN AN AREA OF COAL, IRON, AND STEEL INDUSTRIES.

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Epidemiological and toxicological data point to an impact of cadmium and polycyclic aromatic hydrocarbons on prostate cancer. Aim of the study was to identify possible risk occupations in an industrial center of the German coal, iron and steel industries. Occupations performed for more than 6 months and life time smoking habits of 238 cases with histologically proven prostate cancer and of 414 controls with benign prostatic hyperplasia were examined with a questionnaire. Confounder-adjusted odds ratios were estimated by Fisher's exact test and logistic regression analysis. No differences in the smoking habits described by pack years could be found between cases and controls. Confounder-adjusted odds ratios for both age (OR 2.56) and duration of employment (OR 2.22) were elevated in a subgroup of underground hard coal miners. An elevated prostate cancer risk was also observed for painters/varnishers (OR 2.84 adjusted for age, OR 2.91 adjusted for duration of employment). Steelworkers showed no increased risk (OR 0.93 adjusted for age, OR 0.94 adjusted for duration of employment). Businessmen showed a remarkably low prostate cancer risk (OR 0.38 adjusted for age, OR 0.37 adjusted for duration of employment). Coal dust components and dietary factors due to high energy expenditure must be discussed as possible risk factors for prostate cancer in hard coal miners.

1123 OCCUPATIONAL AND NON-OCCUPATIONAL RISK FACTORS IN BLADDER CANCER PATIENTS IN AN INDUSTRIALIZED AREA IN EASTERN GERMANY.

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Several occupational bladder carcinogens are metabolized by polymorphic enzymes. Therefore, the distribution of the polymorphic enzymes N-acetyltransferase 2 (NAT2; substrates: e.g., aromatic amines), glutathione transferase M1 (GSTM1; substrates: e.g., reactive metabolites of polycyclic aromatic hydrocarbons), and glutathione transferase T1 (GSTT1; substrates: small molecules with 1-2 carbon atoms) were investigated in bladder cancer patients in the former center of the chemical industry in Halle-Wittenberg in the former German Democratic Republic. Occupations performed for more than 6 months by 136 patients of the urological clinic in Wittenberg were examined with a questionnaire. All patients had a histologically approved transitional cell cancer of the urinary bladder. In addition, several occupational and non-occupational risk factors were considered. The genotypes of NAT2, GSTM1, and GSTT1 were determined from leucocyte DNA by PCR. Compared to the normal population in Central Europe, in the entire group the percentage of GSTT1 negative persons (22.1 %) was ordinary, the percentages of slow acetylators (59.8 %) and of GSTM1 negative persons (58.8 %) were slightly elevated. Shifts in the distribution of the genotypes were observed in subgroups who had been exposed to asbestos (6/6 GSTM1 negative, 5/6 slow acetylators), chlorinated solvents (9/15 GSTM1 negative) or who did work in rubber manufacturing (8/10 GSTM1 negative). The overrepresentation of GSTM1 negative bladder cancer patients in the industrialized area, which was more pronounced in several occupationally exposed subgroups, points to chemoprotection by the enzyme GSTM1 in bladder carcinogenesis.

1124 DECREASE OF GLIAL FIBRILLARY ACIDIC PROTEIN IN RAT FRONTAL CORTEX FOLLOWING ALUMINUM TREATMENT.

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Aluminum lactate was either intraperitoneally administered or stereotactically injected bilaterally into rat cerebral ventricles. Rats were sacrificed at various times after aluminum treatment and frontal cortex, hippocampus and striatum were dissected out. A microtiter plate based sandwich ELISA was used to measure glial fibrillary acidic protein (GFAP) concentration. GFAP levels were significantly decreased in frontal cortex seven days after lateral ventricular injection or fourteen days post systemic treatment. In contrast, neither hippocampus nor striatum had any significant changes in astrocytic intermediate filament protein. These results suggest a selective and progressive diminution of astrocytic responsivity in frontal cortex following either systemic or intraventricular aluminum dosing. An increased level of GFAP is considered a marker of reactive astrogliosis and has been reported in aluminum exposed rabbits. The depression of GFAP levels reported here in a species not forming neurofibrillary tangles (NFT) may reflect extended impairment of astrocytic function and suggests that these cells may be the primary targets of aluminum neurotoxicity.

1125 TRIMETHYLTIN ACTIVATES GLIA TO RELEASE TNF-α THROUGH REACTIVE OXYGEN SPECIES PRODUCTION.

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The trisubstituted organotin compound trimethyltin (TMT) is highly neurotoxic after *in vivo* exposure eliciting both neuronal and glial responses in the central nervous system. Recently we demonstrated that *in vitro* TMT-induced neural cell death in the presence of glial cells is reduced by a TNF-α antibody, suggesting that glial cells support neural cell death through TNF-α release. Thus, in this study we evaluated the ability of TMT to activate glia to release TNF-α and other cytokines, and the molecular mechanisms involved. Exposure of a mixed population of glial cells (astrocytes + microglia) to TMT is followed by a dramatic change in morphology and a dose dependent TNF-α release, significative from 1 μM TMT. Differently, no release of IL-6 is detectable. TMT induces TNF-α release from both highly enriched culture of astrocytes and highly enriched culture of microglia, suggesting that both cell populations are sensitive to the compound and collaborate to TNF-α production. It has been demonstrated that TNF-α release often occurs after reactive oxygen species (ROS) production in dependence of NF-κB activation. TMT 0.5 - 2.5 μM induces a dose dependent ROS production in glial cells that precedes TNF-α release. Both ROS production and the release of this cytokine are completely prevented by the use of ETYA 50 μM (a non-metabolizing analogue of arachidonic acid) and indometacine 10 μM. These results suggest that TMT-induced release of TNF-α from glial cells is dependent by the production of ROS as a consequence of the metabolism of arachidonic acid through the activation of cicloxygenase. (Acknowledgments: this work was supported by CNR grant n° 97.04658.CT13.)

1126 CYTOKINE AND GROWTH FACTOR GENE EXPRESSION IN RESPONSE TO TRIMETHYL TIN (TMT)-INDUCED NEUROTOXICITY IN THE ADULT RAT HIPPOCAMPUS.

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Cytokines and growth factors are proposed to play a role in the homeostasis of the central nervous system (CNS) and its response to injury and disease. A role for these pleiotropic mediators in the early activation of microglial and astrocytic reactions to neural injury constitutes a dominant theme in contemporary neuroscience literature, despite the fact that most data are derived from *in vitro* preparations. Understanding the earliest events associated with toxicant-induced brain injury is necessary to detect and modify CNS damage following injury or disease. Here we examined the *in vivo* expression of interleukin-1alpha (IL-1alpha), interleukin-6 (IL-6), transforming growth factor-beta (TGF-beta), brain-derived neurotrophic factor (BDNF), and nerve growth factor (NGF) using the TMT model of neuronal injury (8mg/kg i.p.) using semi-quantitative Reverse Transcription-Polymerase Chain Reaction (RT-PCR) at 24 hours post TMT. This timepoint was chosen based on reports in the literature that mRNA for TGF-beta and IL-6 are up-regulated at this time with other types of nerve injury. No significant changes for

BDNF, NGF, or IL-1alpha were seen. mRNA for TGF-beta and IL-6 were increased slightly less than 2 fold, which is a very small increase, but is consistent with published reports. These results suggest that these neuroimmune/neurotrophic mediators do not play a crucial role in the activation of microglia and astrocytes following toxicant-induced injury to the CNS. Additional toxicants need to be examined in order to determine the generality of these observations to the neurotoxic condition.

1127 ORGAN DISTRIBUTION OF TIN AND TRACE ELEMENTS IN MICE GIVEN TRIMETHYLTIN (TMT) – RELATION TO THE TMT TOXICITY.

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Trimethyltin has been recognized as a potent neurotoxic substance. There is no information available concerning its possible interaction with trace elements in the body. In the experiments performed in male mice (CD-1, Charles River) TMT was injected ip in the form of chloride at the dose of 2.5 $mg.kg^{-1}$. The concentration of Sn and various trace elements was determined in the liver, kidneys and in the brain of intoxicated mice divided into 4 subgroups sacrificed at various time intervals (24^{th} –168^{th} h) of the experiment using AAS. The results were compared with the values received in corresponding control group. The concentration of Sn in the liver decreased during the experiment to 10.8%, in the kidneys to 10.6% and in the brain to 12.5% of the value at 24^{th} h. The significant increase of the level of zinc, copper and manganese in the liver at 24^{th} h and 48^{th} h was noticed. Only negligible changes of the trace element levels in the brain – the main target organ of TMT toxicity - were demonstrated. A potent metal binding chelator sodium *N*-benzyl-4-*O*-(β -D-galactopyranosyl)-D-glucamine-*N*-carbodithioate (BLDTC) injected simultaneously sc with TMT decreased the concentration of tin in brain (by 5.1%). The changes of trace element levels in the liver were also corrected. The results suggest the liver might play a role in the acute toxicity of TMT. This hypothesis is supported by the fact that TMT increases the level of lipid peroxidation (measured as malondialdehyde production) not only in the brain but also in the liver as has been demonstrated in the parallel experiment in mice done in our laboratories.

1128 MANGANESE (Mn) EXPOSURE PROMOTES CELLULAR OVERLOAD OF IRON (Fe) IN CULTURED NEURONAL AND NEUROGLIAL CELLS IN VITRO.

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Our recent studies indicate that Mn exposure potently inhibits aconitase, an enzyme possessing a [4Fe-4S] cubane cluster and regulating the expression of some critical proteins involved in cellular Fe regulation (Zheng, et al., Brain Res. 799:334, 1998). This study was performed to test the hypothesis that disruption in Fe regulatory processes by Mn may lead to an altered cellular Fe status in 3 major types of brain cells. The cultured astrocytes, oligodendrocytes or PC12 cells were exposed to Mn as $MnCl_2$ in culture medium. Cellular Fe uptake was determined by quantitation of residual ^{59}Fe radioactivity in cells following addition of 1.5-2.0 μM ^{59}Fe as $FeCl_3$ in culture medium. In astrocytes, Mn exposure greatly increased cellular ^{59}Fe uptake (5.3 fold at 100 μM, $p<0.0001$) as compared to the controls. The effect was dependent upon Mn concentrations within the range of 10-100 μM. While incubation of astrocytes with 50-250 μM MPP^+ or 10-100 μM Hg did not affect cellular Fe uptake, the treatment with 100-250 μM MPTP showed a significant decrease (-26-69%, $p<0.05$) in Fe uptake compared to controls. When the oligodendrocytes and PC12 cells were incubated with 100 μM Mn, the treatment raised cellular Fe by 3.2 fold ($p<0.0001$) and 2.7 fold ($p<0.026$) in oligodendrocytes and PC12 cells, respectively. Our results demonstrate that Mn, but not MPTP or MPP^+, promotes the cellular overload of Fe. The deleterious effect of Mn on cellular Fe status appears to occur in major cell types of the CNS, but the astrocytes seem to be more sensitive to Mn than other cell types tested. (Supported by Calderone Foundation and other private funds.)

1129 MANGANESE (Mn)-INDUCED NEUROTOXICITY: IN VIVO INTERACTION WITH IRON (Fe).

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Our in vitro studies have shown that Mn exposure promotes cellular Fe overload in cultured neuronal and neuroglial cells (Zhao and Zheng). The current study was designed to investigate whether Mn alters Fe homeostasis in blood, CSF and brain. Groups of 8-10 rats received saline, Mn (36 mg/kg/wk, ip), Fe (250 mg/kg/wk, sc), or Mn (ip) plus Fe (sc) for 4 wks. Mn and Fe concentrations in tissues and body fluids were determined by AAS. While Mn injection alone caused a 32% decrease in plasma Fe ($p<0.01$) and no changes in plasma total iron binding capacity (TIBC), it increased CSF Fe by 3 fold ($p<0.01$) as compared to the controls. In rats treated with either Fe alone or Fe combined with Mn, both Fe and Mn levels in plasma and CSF were significantly increased. Combined exposure of Mn with Fe in rats greatly increased Mn concentration in striatum (4.5 fold), substantia nigra (6.2 fold), hippocampus (2.7 fold), frontal cortex (3.3 fold), and choroid plexus (8.3 fold); however, the same treatment raised Fe content selectively only in striatum (1.5 fold, $p<0.05$) and choroid plexus (2 fold, $p<0.05$). Northern blot analyses showed that none of the above dose regimens altered the expression of brain MT-I. In addition, we found that chronic Mn exposure appeared to increase the expression of glutamine synthetase by 34% ($p<0.05$) compared to controls. Our results indicate that Mn exposure seems likely to facilitate Fe transport from blood to CSF and increase Fe levels in selected brain regions. (Supported in part by NIEHS RO1 ES08146 and P20 ES06831.)

1130 MANGANESE TOXICITY IN CATECHOLAMINERGIC CELLS.

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Manganese (Mn) is an essential nutrient that, at excessive levels, produces extrapyramidal symptoms resembling those observed in patients with Parkinson's disease. Mn toxicity was tested in human neuroblastoma cells (SK-N-SH) and in a mouse catecholaminergic cell line (CATH.a). Mn was demonstrated to be more toxic (EC_{50} = 33 μM) towards the catecholamine producing CATH.a cells when compared to the non-catecholaminergic SK-N-SH cells (EC_{50} = 300 μM). This observation implicates catecholamines in the toxicant response. The Mn toxicity in the CATH.a cell line was augmented (EC_{50} = 1 μM) by pretreatment of the cells (36 hours) with an inhibitor of glutathione synthesis (1 mM L-BSO). Protection from Mn toxicity was observed with vitamin C (250 μM). The studies also evaluated the effect of Mn on tyrosine hydroxylase (TH), the rate limiting enzyme in catecholamine production. Exposure of cells to Mn produced an increase in the activity of TH (as normalized per cell). This effect was not mediated by the ability of Mn^{+2} to substitute for Fe^{+2} in the active site of TH due to the fact that addition of Mn^{+2} directly to the metal deficient enzyme did not restore activity. These results suggest that while toxic to catecholamine cells, Mn^{+2} has the potential to simultaneously upregulate biogenic amine biosynthesis.

1131 METHYLMERCURY ALTERS GLUTAMINE SYNTHETASE PROTEIN LEVELS IN NEONATAL RAT CORTICAL ASTROCYTE CULTURES.

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Glutamine synthetase (GS, EC 6.3.1.2) is a glial specific enzyme localized largely in astrocytes. GS is responsible for detoxification of NH_4^+ in the brain via its ligation to glutamate, forming the non-excitotoxic amino acid glutamine. Inhibition of GS activity produces neurodegeneration likely due to increased levels of NH_4^+ and glutamate, decreased glutamine levels, or both. Previous in vitro studies suggest mercurials inhibit GS activity. Since methylmercury (MeHg) preferentially accumulates in astrocytes, we examined its effect on GS, as a potential mechanism for MeHg-induced neurotoxicity. Primary neonatal rat cortical astrocyte cultures (20-24 days in vitro) were treated with 0.5, 1, or 2 μM MeHg for 0 to 48 hours. Total cellular proteins were collected and immunoreactive GS protein levels were determined by Western analysis. MeHg initially decreased GS protein levels with the largest decrease (~ 50%) occurring at 12 hrs. By 24 hrs, protein levels had

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