an toxicological effect to nude mice, include the tumors formed in with 10/10 frequency in the prostate and 7/10 of lymph node metastasis. It also be found furtherly that the lymph node metastasis in nude mice given an injection of PC-3M cells in the prostate is a selective process favoring the survival and growth of a special subpopulation derived from primary tumor with specific genetic alterations. Identification and further characterization of the toxicology of the PC-3M may allow a better understanding of the tumor cells in toxicology.

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P4-07

Expression of vascular endothelial growth factor isoforms and receptors throughout acetaminophen-induced liver toxicity and regeneration

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Acetaminophen is a widely used analgesic and a known hepatotoxic agent. Vascular endothelial growth factor is a growth factor with multiple functional roles. The aim of this study was to determine the expression of VEGF and its receptors in liver after the administration of a toxic dose of acetaminophen in rats.

Eleven groups of adult male rats received a dose of 3.5 g/kg b.w. of acetaminophen per os. The rats were killed post administration at 0–288 h. Blood and liver tissue were extracted. Determination of the serum enzyme levels of ALT, AST and ALP was performed. Liver injury and regeneration were assessed with haematoxylin–eosin specimens, thymidine kinase assay and Ki-67 expression. RT-PCR, Western blotting and immunohistochemical methods were used for assessment of VEGF isoforms and VEGFR1 and VEGFR2 expression.

Maximal expression of AST and ALT was observed at 24–48 and 24–36 h, respectively, with another peak of expression at 192 h post administration. ALP was increased post 72 h peaking at 192 h. Centrilobular necrosis was observed at 48–72 h and thorough restoration of the liver microarchitecture was observed at 288 h. Liver regeneration lasted from 36 to 144 h according to the results from thymidine kinase and Ki-67. VEGF and VEGFR2 m-RNA and protein levels presented with a three-peak pattern of expression at 12–24, 72–96 and 192–240 h post administration. Significant difference was noted between periportal and perivenular immunohistochemical expression.

VEGF proves to be a critical molecule during acetaminophen-induced liver regeneration. It presents with three peaks of expression. The first two peaks are associated with the initial inflammatory reaction to the noxious stimulus and the hepatocyte regenerative process where as the third one could be important for remodeling of the tissue architecture.

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P5 Neurotoxicity

P5-01

Evaluation of in vitro neurotoxicity of methyl mercury, PCB153 and PCB126

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Methyl mercury (MeHg) and polychlorinated biphenyls (PCBs) 126 and 153 are persistent environmental pollutants, and seafood represents the main source of human exposure. These compounds are known developmental neurotoxicants, as evidenced by animal studies and observations in humans. Aim of this study was to evaluate the effect of MeHg (0–5 μM) and PCBs (0–100 μM) in a battery of in vitro cell systems, with the goal of developing a potentially useful in vitro screening system. Cell viability was assessed by measuring MTT reduction and Trypan blue exclusion. The studies were carried out in six different rat or human cell lines: rat PC12 pheochromocytoma cells and human SH-SY5Y neuroblastoma cells were used as models of neuronal cells; rat C6 glioma cells and human 1321N1 astrocytoma cells were used as model of astrocytic cells; rat 3T3 fibroblasts and human prostate PZ-HPV-7 cells were used as non-nervous-system cell lines. Additionally, primary rat astrocytes, as well as hippocampal, cortical and cerebellar neurons were also utilized. The results obtained with MTT indicate that: (1) MeHg is more toxic than PCB126 and PCB153; (2) nervous system-derived cell lines are more sensitive than non-nervous cell lines to all contaminants; (3) neuronal cells are more sensitive than astrocytic cells in case of MeHg, but not PCBs; (4) human neuronal cells

are more susceptible to the toxicity of MeHg and PCBs than rat-derived neurons; (5) primary neurons, but not primary astrocytes, are more sensitive to MeHg and PCBs toxicity. Results obtained with the Trypan blue exclusion assay reflect similar effects, though these are seen at higher concentrations. These in vitro results are in agreement with in vivo findings for MeHg, but further studies are needed to elucidate the differences between PCB126 (dioxin-like PCB) and PCB153 (NDL-PCB).

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P5-02

Chronic noise stress-induced alterations in the expression of *Hsp70*, *c-fos*, DNA damage and Fas/FasL expressions in discrete brain regions of albino rats

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Brain is more susceptible to stressors than any other organ. Exposure to continuous loud noise is a serious environmental health problem due to excess production of oxygen free radicals. The aim of the present work was to evaluate the effects of oxidative stress in discrete (cerebral cortex, cerebellum, midbrain, pons-medulla, hippocampus and hypothalamus) brain regions and neuronal dendritic changes after the rats were exposed to chronic noise (100 dBA/4 h/day for 30 days). Expression of *Hsp70*, *c-fos* mRNA (RT-PCR), Fas/FasL protein expression (immunoblotting and immunohistochemistry) and DNA damage in discrete brain regions were studied. Results showed that neuronal dendritic count in the hippocampus and medial prefrontal cortex were reduced significantly ($P < 0.01$) in the second and third order dendrites after 30 days of noise exposure when compared to control animals. Excessive free radical generation produced by noise stress led to increases in lipid peroxidation level, superoxide dismutase activity, *Hsp70*, *c-fos* mRNA expression, DNA damage, Fas/FasL protein expression and concomitant decreases in the activity of catalase, glutathione peroxidase and depletion of reduced glutathione in all the brain regions. This study suggests that 30 days of noise exposure causes oxidative stress in all the brain regions and alteration in neuronal communication in HIP and mPFC and this finding may be applicable to human, are working/living in noisy environment.

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P5-03

Cytokine response in repeated skin irritation measured by stratum corneum tape stripping

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Cytokines play an important role in immune and inflammatory reactions. Little is known about cytokines involved in chronic irritant contact dermatitis. Our aim was to investigate the cytokine response in chronic skin irritation measured by a non-invasive stratum corneum (SC) tape stripping method. A repeated sodium lauryl sulfate (SLS) exposure test was used as a model for chronic irritation.

Methods: Eighteen healthy volunteers were exposed to SLS on the volar forearm. A patch with 0.1% SLS was applied for 6 h, 4 days a week, during 3 weeks. Four days after the last exposure the SC at the treated and an untreated control site was removed by means of 20–30 times tape stripping. Presence of interleukin-1α (IL-1α), IL-1 receptor antagonist (IL-1RA) and IL-8 was analyzed using ELISA. The cytokine concentrations for each strip were normalized for soluble protein content.

Results: IL-1α decreased by 30% after repeated exposure compared to untreated skin ($p = 0.04$), while IL-1RA increased 10-fold and IL-8 increased 4-fold (both $p < 0.001$). The IL-1RA/IL-1α ratio for the SLS-treated skin increased 15 times ($p < 0.001$).

Discussion: The balance between IL-1RA and IL-1α is important in the down-regulation of the inflammatory response. An increase in this ratio has also been described in other chronic disorders like atopic dermatitis and psoriasis. We found that the response in IL-1RA and IL-1α after a repeated irritation is opposite to that after a single irritation (Perkins et al., 2001). The increase in IL-8 was found in both single and repeated irritation.

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