cates a correlation between benzene exposure only and leukemia induction. Consequently benzene has been classified as a human carcinogen both by international (WHO, IARC) and national agencies; uncommon for a carcinogenic compound for human exposure a limit of 50 ppm has been set. On the other hand, benzene exposure in industrialized societies is nearly ubiquitous with gasoline as the leading exposure source. Clinically benzene exposure also has been linked to myelodysplastic syndrome and osteosclerosis indicating a toxic mechanism rather than carcinogenic; therefore it remains unclear whether leukemia is a primary response to benzene or secondary e.g. as the result of bone marrow proliferation. Sensitivity towards benzene toxicity has been linked to high activities of the isoenzyme CYP2E1 and bone marrow myeloperoxidase, and low activities of quinone oxidoreductase NQ01 and GSH-*S*-transferase. Benzene is metabolically activated to benzene epoxide mainly in the liver with very low concentrations of P450 2E1 in the bone marrow, therefore the reactive intermediate(s) likely have to be transported to the bone marrow for leukemia induction. This mode of action may justify a threshold; an uncommon mode of DNA damage besides direct structural changes may also be responsible, since the redox active intermediates hydrochinone and benzochinone are particularly toxic to the DNA introducing nonspecific oxidative damage. Based on likely mechanisms of leukemia induction and mechanism of benzene toxicity we will reevaluate whether a threshold for this carcinogen is appropriate.

P3-06

SENSITIVITY OF HUMAN PROGENITORS CORD BLOOD CELLS TO TETRACHLOROETHYLENE: CELLULAR AND MOLECULAR END-POINTS

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The International Agency for Research on Cancer (IARC) currently designates tetrachloroethylene (perchloroethylene, PCE) as carcinogenic in animals. PCE is considered to be possibly carcinogenic to humans with regard to occupational exposure. Human exposure to PCE can produce oesophageal cancer, cervical cancer, non-Hodgkin's lymphoma, urinary bladder cancer and leukaemia.

The data presented showed that PCE modulates the expression of some genes implicated in cancer induction, cell differentiation, cell-cycle progression, survival and clonogenic potential of human cord blood cells.

The genes modulated, after exposure to the compound, were involved in inflammatory responses like the mitogen-activated protein kinase14 (MPK 14), or in tumor and metastasis progression like the matrix metalloproteinase 17 (MMP 17), in cell proliferation like c-jun and c-fos and moreover in the apoptotic process like interferon alpha-inducible protein (IFI), BAX and BCL-2.

Flow cytometry analysis of cord blood cells showed that PCE treatment induced a statistically significant increase of necrosis after 24 h, while the clonogenicity of Human Colony Forming Unit-Granulocyte/Macrophage (CFU-GM) and of Burst Forming Unit-Erythrocyte (BFU-E) progenitors did not change.

In conclusion, these results showed that PCE affected different pathways involved in cancer induction, but its action on cell proliferation and differentiation is not clearly understood.

P3-07

THE INFLUENCE OF PLATINUM-BASED DRUGS ON THE AMOUNT OF METALLOTHIONEIN

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Neoplastic diseases represent one of the most prevalent human disorders. Many of those are generally treated by platinum-complexes. Effectiveness of such treatment depends on the therapeutic concentration of the drug, commonly influenced by binding to proteins

(e.g. metallothionein). Metallothionein (MT) is a well-known molecular protein maintaining metal ion homeostasis. The aim of this work was to study the interaction of MT with Pt compounds. The proper interaction was observed in our experiments in vitro by means of electrochemical techniques using the oxidation-reduction and/or catalytic signals (metallothionein-SH groups reduction, Brdicka reaction, and H-peak). Our suggested technique was used for blood serum analysis from the patients treated with standard platinum compounds. The MT amount was increased more than 10 times in these patients' serum in comparison with non-treated patients. The results thus show that the MT amount has a significant negative influence on the therapy of neoplastic diseases.

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P3-08

INFLUENCE OF TCDD-INDUCED CYP1A1 ON THE FORMATION OF REACTIVE OXYGEN SPECIES IN LIVER CELLS

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2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD), was classified as a group I carcinogen by the International Agency for Research on Cancer (IARC). It acts through an aryl hydrocarbon receptor (AhR) mediated mechanism, active in humans and experimental animals. The activated AhR, a nuclear transcription factor, forms in the presence of TCDD an active heterodimer with the aromatic hydrocarbon nuclear translocator (ARNT) protein and induces (or suppresses) the transcription of numerous genes, including cytochrome P450 1A1 (CYP1A1). It has been hypothesised that TCDD may be indirectly genotoxic via generation of reactive oxygen species (ROS) by inducing CYP1A enzymes. This may lead to DNA damage via direct interaction or via generation of reactive metabolites from endogenous compounds.

We determined the formation of ROS with the 2′,7′-dihydrodichlorfluorescein diacetate (H_2DCFDA) fluorescence assay after incubation of the human hepatoma cell line HepG2 and primary rat hepatocytes with TCDD. Additionally, the amount of the oxidative damage marker 8-oxo-2′-deoxyguanosine (8-oxo-dG) was measured after incubation of cells with TCDD using HPLC-MS/MS.

Incubation of cells with TCDD for 48 h caused increased levels of ROS in primary rat hepatocytes as well as increased levels of 8-oxo dG in DNA compared to untreated cells. In the HepG2 cell line no or much lower effects were observed for both the H_2DCFDA assay and 8-oxo-dG levels.

P3-09

EFFECT OF TUMOR PROMOTERS ON DNA DEMETHYLASE ACTIVITY AND DNA HYPOMETHYLATION

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DNA hypomethylation is found in most tumors including colon and liver cancer and has been proposed as a mechanism for tumor promoters. Colon (deoxycholic acid and quercetin) and liver (dichloroacetic acid and Wy-14,643) tumor promoters have demonstrated the ability to induce DNA hypomethylation. To determine whether the DNA hypomethylation resulted from increased DNA demethylase activity, male F344 rats were administered 300 mg/kg deoxycholic acid or 50 mg/kg quercetin by oral gavage for four days. Some rats also received 8.0 gm/kg methionine in their diet concurrently with the tumor promoters to determine whether it would prevent any increase in demethylase activity similar to its ability to prevent DNA hypomethylation. After two but not four days of treatment, deoxycholic acid significantly increased DNA demethylase activity in nuclear protein extracts from colonic mucosa. Methionine decreased the enhancement by deoxycholic acid of demethylase activity. In B6C3F1 mouse liver, both 500 mg/kg dichloroacetic acid and 50 mg/kg Wy-14,643 increased DNA demethylase activity concurrently with their ability to induce DNA hypomethylation. Administering methionine (450 mg/kg) 30 min after each dose of the promoters, prevented their induction of DNA