727 INFLUENCE OF POLYMORPHISMS OF GLUTATHIONE TRANSFERASES ON RENAL CARCINOGENICITY OF HIGH DOSE TRICHLORETHYLENE (TRI) EXPOSURE.

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Recent epidemiological studies shows that high dose occupational exposure to trichloroethylene (TRI) is associate with an increased risk for renal cell carcinoma (RCC). Beside a major cytochrome P450 dependend pathway, TRI is metabolised by glutathione transferases (GSTs). It is proposed that this pathway forms DNA-reactive chlorothioketenes. In humans GSTT1 and GSTM1 represent two unrelated gene deletion polymorphisms. Fifty-seven RCC-cases with occupational TRI exposure were studied. Controls consisted from 139 patients from the same geographical region without TRI or cancer. GST-genotypes were determinated by a newly developed real-time PCR (Pharmacogenetics 10,271-247,2000).In conclusion GSTT1 polymorphism is significantly associated with RCC. Among 57 Patients previouly exposed to TRI only 3 (5%) were homozygous null for GSTT1 compared to 32 (23%) of the controls. The calculated Odds ratio is 5,4 (95%CI 1,6-18,4). Regarding the GSTM1 28 (49%) RCC patients compared to 63 (45%) controls were homocygous null (OR:0,9 ; 95%CI O,5-1,6). In the general population of Western Europe, a frequency of 25% GSTT1- and 50% GSTM1-null genotypes has been reported. Hence, in our 57 cases of TRI-exposed RCC, 7 patients (12,5%) could be expected whilst only one patient has been actually observed. In the controls the expected number of 17 (13%) was found with two null alleles for both polymorphic GST isoenzymes. These results indicate that distinct metabolic capacities can result in interindividual sensivities regarding cancer after particular occupational exposure and they imply an influence of genetic polymorphisms of enzymes of xenobiotic metabolism in this matter.

728 POTENTIAL OF TETRACHLOROETHYLENE TO INDUCE GENETIC ALTERATIONS AND CARCINOGENESIS.

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Occupational exposure to tetrachloroethylene (TCE) occurs in a number of settings in which organic solvents are used, particularly the dry-cleaning industry. Phenotypic and genotypic changes during carcinogenesis may be demonstrated by the cell transformation and tumorigenesis assays and by molecular analyses. To study the carcinogenic potential of TCE, BALB/c-3T3 cells were exposed to TCE at varying concentrations for 24 hours. Further, nude mice were injected with TCE-transformed cells. TCE caused a significant increase in transformation frequency in a dose dependent manner. Also, the cytotoxicity data indicated a dose-dependent decrease in the cell number after TCE treatment. All the mice injected with transformed cells developed tumors indicating the tumorigenic potential of TCE. DNA from both transformed and tumor cells derived from transformed cells were subjected to differential PCR to detect changes in gene copy number and gene expression of five proto-oncogenes (K-ras, c-fos, c-jun, sis, erb-B2) and two tumor suppressor genes (p53, p16). While none of the transformed cells showed changes in gene amplification, increases in the expression of c-jun and p16 were observed and sis was under expressed. Tumor cells showed increased copy number of the K-ras gene and increased expression of c-fos, erbB2 and K-ras, while c-myc and sis were under expressed. These results indicate that TCE is capable of inducing cellular and molecular changes in BALB/c-3T3 cells and that these cells then possess neoplastic potential. Further studies are in progress to investigate the molecular mechanism of TCE-induced cell transformation and tumorigenesis.

729 CIS/TRANS 1,3-DICHLOROPROPENE (DCP) IS NOT GENOTOXIC IN VIVO IN TUMOR TARGET AND NON-TARGET TISSUES.

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1,3-Dichloropropene is a soil fumigant widely used for the control of parasitic plant nematodes of various food and non-food crops. Chronic bioassays identified rat liver and mouse lung as two of the target sites for DCP-induced tumors. There is limited evidence suggesting that DCP is mutagenic (*i.e., in vitro*) primarily in test systems having limited GSH and/or GST responsible for the detoxification of DCP. In order to elucidate the role, if any, of genotoxicity in the etiology of tumors in DCP-exposed rodents, we have evaluated the following parameters in DCP-treated animals: (1) cytogenetic damage in the mouse bone marrow using the micronucleus test, (2) point mutations (lacI) in the liver and lungs of Big Blue mice, (3) DNA adducts in the livers of rats and lungs of mice using the 32P post-labeling method. In the micronucleus test, no increase in micronucleated polychromatic erythrocytes were observed in male and female CD-1 mice sacrificed at 24 and 48 h after a single oral gave dose of 38, 115, or 380 mg/kg. There was also no evidence of increased mutant frequency (10-e5) in either the liver (Control *Vs.* Treated - 10.3 *vs.* 9.9) or lungs (13.3 *vs.* 11.2) of male Big Blue B6C3F1 mice following exposure to DCP (150 ppm for 2 weeks, 5 days/week, 6 hours/day; sacrificed 17 days later). Neither the livers of male F344/N rats nor the lung tissues from male B6C3F1 mice exhibited any unique DNA adducts nor any statistical elevation in the levels of normally occurring adducts following 12 days of exposure by oral gavage doses of 12.5 or 25 mg/kg/day (rats) or inhalation to 30 or 60 ppm (mice). The failure of DCP to induce DNA adducts in vivo is consistent with the absence of DNA-binding activity for this chemical *in vitro* in the presence or absence of potentially activating enzymes and physiological levels of GSH. Based upon these studies, it was concluded that the tumors induced by DCP in rodent bioassays were likely related to a non-genotoxic mode of action.

730 TUMORIGENICITY OF AIRBORNE COMPLEX MIXTURES.

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Exposure to airborne toxic mixtures is the important contributing risk factor for high incidence of respiratory diseases including lung cancer in populations of urban areas. Various polycyclic aromatic hydrocarbons (PAHs) emitted from combustion effluents are the most important constituents of airborne complex mixtures. Their potential risk to human health is under active assessment. In this study, lung and liver tumorigenicity of six complex mixtures extracted from combustion effluents or tar were evaluated in a preweanling CD-1 mouse bioassay. Four mixture samples extracted from a natural gas flame doped with high or low amounts of toluene in the presence or absence of methylene chloride were found to be tumorigenic as compared to the vehicle-controls. The two high-toluene mixtures showed more potent in inducing lung tumors (64-76%) than tumors (43-45%) induced by two low-toluene mixtures on a weight basis (700 ug/animal). The presence or absence of methylene chloride did not significantly alter lung tumor incidence. Liver tumors were found in 10-45% of the male mice with no obvious relationship to toluene or methylene chloride doping. A mixture sample extracted from an ethylene-fueled jet-stirred reactor induced a dose-dependent increase in lung tumor incidence over a total dose range of 140-700 ug/animal. Incidence (4-23%) of liver tumors was observed in male mice treated with the low and middle dose of this mixture. An extract mixture of tar from pyrolyzed wood was also found to be tumorigenic in the bioassay. A total dose of 230 ug/animal induced lung tumors in 60% of male and female mice, and liver tumors in 35% of male mice. Different PAH compositions and combinative effects of PAHs were found to be responsible for the tumorigenic potencies of these complex mixtures.

731 ORGAN SPECIFICITY OF DNA ADDUCT FORMATION WITH AROMATIC AMINES CARCINOGENIC FOR THE RAT NASAL MUCOSA OR LIVER.

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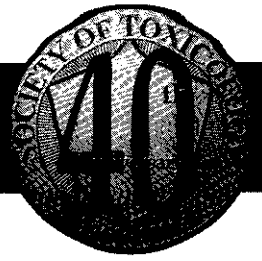
Several monocyclic aromatic amines (AA), including 2,6-xylidine (2,6-X) and phosphodiestrase inhibitors that liberate 4-amino-3,5-dichloropyridine (ADCP) have induced nasal tumors in rats, whereas polycyclic AA target the liver and other organs. To examine the molecular basis for these organotrophisms, the organ specificity of 2,6-X and ADCP was compared to that of the polycyclic AA 4,4'-methylenebis-(2-chloroaniline) (MOCA), and 2-acetylaminofluorene (AAF) for formation of DNA adducts in the nasal mucosa (NM) and liver (L) of rats. The *N*-hydroxy or *N*-acetoxy derivatives of 2,6-X and ADCP were prepared and reacted with DNA to provide reference standards for ^{32}P-postlabeling detection of DNA adducts. The AA were administered to male Wistar rats by gavage, daily for 7 days and the levels of DNA adducts measured. MOCA gave the highest levels of adducts: L >> NM . AAF gave detectable binding only in the liver which was about 25 fold less than MOCA. 2,6-X showed the highest binding in the NM > L. Despite the synthetic derivative, *N*-acetoxy-ADCP yielding an adduct from DNA reacted in solution, ADCP failed to provide any evidence of adduct formation *in*



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An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 451.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 479.

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