

THE TOXICOLOGIST

An Official Publication of the
Society of Toxicology

Abstracts of the
28th Annual Meeting

Vol. 9, No. 1, February/March 1989

493 INVESTIGATION OF STRUCTURE-ACTIVITY RELATIONSHIPS BETWEEN NTP TEST CHEMICALS AND MONONUCLEAR CELL LEUKEMIA USING A CELLULAR TRANSPLANT MODEL. M P Dieter, C W Jameson, J E French, R R Maronpot, R S Chhabra, and P C Chan. NIEHS, National Toxicology Program, Res. Tri. Park, NC.

The efficacy of the short-term assay for predicting the outcome of 2-year studies for positive or negative trends for leukemia was evaluated with 13 chemicals. Male Fischer rats were injected with leukemic mononuclear cells from spleens of syngeneic donors. The effects of chemical dosage on tumor progression were evaluated 60 days later. In all cases the short-term assay accurately predicted the results for leukemia in 2-year tests. In transplant recipients dosed with chemicals positive for leukemia there were dose-related increases in spleen weights and WBC counts, and decreases in RBC indices and platelet counts by comparison with responses in rats with transplants but no chemical treatment. The reverse was true for chemicals that caused negative trends for leukemia in 2-year tests. These data were confirmed by histopathological examination of spleen and liver. There were examples of structure-activity relationships for chemicals that were both positive and negative for leukemia. Dichlorvos and other chemicals containing the dimethyl ester of phosphoric acid enhanced tumor progression, while short-chain glycol ethers inhibited and/or arrested tumor progression.

494 *IN VIVO* INTERMEDIATE TERM SCREENING TESTS FOR GASTRIC CARCINOGENS AND PROMOTERS BASED ON QUANTITATIVE ANALYSIS OF PEPSINOGEN 1 (Pg 1) ALTERED PYLORIC GLANDS. K Ozaki, M Tatematsu, H Tsuda, and N ITO. 1st Dept. Pathol., Nagoya City Univ. Med. Sch., Nagoya, Japan.

Pg 1 altered pyloric glands (PAPG) in glandular stomach have been considered to be preneoplastic changes. In order to establish an *in vivo* intermediate-term assay for gastric carcinogens and promoters, we used PAPG as a marker. Male WKY rats were treated first with a single dose of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG, 160 mg/kg body weight) and two weeks later were administered MNNG, N-ethyl-N'-nitro-N-nitrosoguanidine, N-nitroso-N-methylurea, 4-nitroquinoline 1-oxide, or catechol as gastric carcinogens or sodium taurocholate as a gastric promoter, or 3'-methyl-4-dimethylaminoazobenzene, N-butyl-N-(4-hydroxybutyl)nitrosamine, dihydroxy-di-n-propylnitrosamine, 9,10-dimethyl-1,2-benzanthracene, sodium ascorbate, or phenobarbital as non-gastric carcinogens and promoters. Animals were sacrificed at 16 weeks and sections of pyloric mucosa were investigated for Pg 1 immunostaining. The numbers of PAPG were significantly greater ($p < 0.001 \sim 0.05$) in all the gastric carcinogen and promoter groups than in the controls. However, in the other treatment groups, the induction of PAPG was not significantly modified. Thus, gastric carcinogens and promoters could be positively detected within 16 weeks using this experimental approach.

495 HUMAN BREAST CANCER CELLS AS MODELS FOR INVESTIGATING Ah RECEPTOR-MEDIATED PROCESSES. M Harris, M Romkes and S Safe. Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, TX.

The dose-response effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), 2,3,7,8-tetrachlorodibenzofuran (TCDF) and 1,2,4,7,8-pentachlorodibenzo-p-dioxin (PeCDD) as inducers of aryl hydrocarbon hydroxylase (AHH) and ethoxyresorufin O-deethylase (EROD) were determined in several human breast cancer cell lines (eg. T47/D and MCF-7 cells). The cell lines were highly responsive to the induction of effects by TCDD and TCDF (EC_{50} values were approximately 10^{-9} M); these results, coupled with the low activity of the PeCDD congener were consistent with an Ah receptor-mediated induction process. This mechanism of induction was supported by studies using [3 H]-2,3,7,8-TCDD in which specifically bound cytosolic and nuclear receptor complexes were identified. The identification of the cytosolic and nuclear receptor complexes which sedimented at approximately 9 and 6.5 S respectively, further confirms the utility of the human cells as models for investigating Ah receptor-mediated processes.

496 EVALUATION OF PHYSICO-CHEMICAL FACTORS AFFECTING SKIN PENETRATION AND CARCINOGENIC POTENCY OF MINERAL OILS CONTAINING POLYCYCLIC AROMATIC COMPOUNDS. T A Roy, J J Yang, S W Johnson, and C R Mackerer. Mobil Environmental and Health Science Laboratory, Princeton, N.J. Sponsor: C V. Kommineni

A comparison of the polynuclear aromatic compound (PAC) content and skin carcinogenicity was made for a series of complex oil mixtures. Results showed a significant correlation ($r=0.84$) between the 3-7 ring PAC content and the carcinogenic potency, as determined in a mouse skin-painting bioassay, for oil samples ranging from those with median (50% recovered) boiling points above $\sim 500^\circ\text{F}$ to those with initial boiling points of $\sim 1070^\circ\text{F}$. Two variables not considered in the original correlation study, oil viscosity and oil dermal penetration rate, were subsequently measured and their correlation with the carcinogenic potency of the oils determined using simple and multiple regression techniques. Although a weak correlation was observed between oil viscosity and the dermal penetration rate of 14C-benzo[a]pyrene from the oils (co-linear variables), no statistically significant correlation was observed between viscosity or penetration rate and carcinogenic potency or between transformations or combinations of viscosity and penetration rate data and carcinogenic potency. It is suggested that the repeated dosing of mice in a two-year skin-painting bioassay results in the attainment of a steady-state concentration of the oils in the skin compartments such that the concentration of 3-7 ring PAC at the sites of cutaneous metabolism, and the concentration of carcinogenic metabolites is proportional to the 3-7 ring PAC content of the applied oil.