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H-*ras* PROTO-ONCOGENE MUTATIONS OCCUR IN DIFFERENT TYPES OF ALTERED HEPATOCELLUAR FOCI (AHF) IN MALE B6C3F1 MICE TREATED WITH TCDD. D. Malarkey, T. Devereux, and R. Maronpot. National Institute of Environmental Health Sciences, RTP, NC, 27709.

Recent studies have shown that H-*ras* mutations in codon 61 occur in 51% of liver tumors from B6C3F1 mice treated with dioxin (TCDD); the most common mutation being a C -> A transversion at the first base. To gain insight into the progression of TCDD-associated hepatocarcinogenesis, the H-*ras* codon 61 mutation profile was determined in basophilic, acidophilic, and clear cell types of AHF in TCDD-exposed male mice. Thirty eight percent of TCDD-treated mice had AHF including clear cell (50%), basophilic (23%), mixed (15%), acidophilic (6%), and vacuolated(3%) cell types. DNA was isolated from formalin-fixed, paraffin-embedded AHF by the selective UV radiation fractionation method. Sections of liver were mounted on thin plastic slides and small ink dots over AHF protected the DNA from up to 4 hours of UV exposures. Each dot was used for DNA isolation and PCR amplification of H*ras* exon 2. Mutations at codon 61 were determined using a restriction fragment length polymorphism method. Twenty percent of the AHF from TCDD-treated mice had an H-*ras* mutation at codon 61. 20% of basophilic foci, 25% of acidophilic foci, and 12% of clear cell foci had a mutation, the majority of which were either an A->T transversion or an A->G transition at the second base. These findings suggest that each type of AHF can progress to either hepatocellular adenoma or carcinoma; *ras* mutation is an early event in some tumors; and that mutations at the second base occur more often at earlier stages of tumor development.

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FOREIGN-BODY TUMORIGENESIS: SARCOMAS INDUCED IN MICE BY SUBCUTANEOUSLY IMPLANTED TRANSPONDERS. Keith A. Johnson, The Toxicology Research Laboratory, The Dow Chemical Company, Midland MI. 48674

Mice used for oncogenicity studies developed subcutaneous sarcomas that incorporated an implanted glass encapsulated microchip used for individual animal identification. The sarcomas, generally fibrosarcomas, were found in a low number of mice (overall incidence <1%) and generally were noted after greater than one year post-implantation. These tumors appeared typical of foreign-body induced sarcomas (reviewed by Brand et al., CRC Crit. Rev. Toxicol.,4:353-394; 1976). These investigators found that both the surface area of the foreign body and a quiescent reaction to be essential to the development of foreign-body sarcomas. The low incidence we observed is consistent with the small size of the transponders. Previous ultrastructural investigations established the likely progenitor cell as arising from the microvasculature. Investigators using similar types of implanted devices need be aware of foreign-body tumorigenesis when evaluating the results of longterm studies using mice.

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INDUCTION OF MAMMARY ADENOCARCINOMAS IN RATS FOLLOWING INTRAVENOUS NITRO-IMIDAZOLE TREATMENT. M. Breider, M. Graziano, M. Kropko, and A. Gough. Parke-Davis Pharmaceutical Research, Div. of Warner-Lambert Co., Ann Arbor, MI 48105.

To determine toxicity of repeated intravenous doses of CI-1010, a 2-nitro-imidazole radiosensitizer and alkylating anti-cancer agent, adult Wistar male and female rats were treated intravenously (0, 5, 20, or 40 mg/kg) 5 days per week for 7 weeks. Ten rats/group were necropsied after 7 weeks and 5 rats/group were necropsied following drug withdrawal for 12 weeks (Week 19). One 40 mg/kg female, moribund sacrificed during Week 17, and the 4 remaining 40 mg/kg Week 19 females had single or multiple subcutaneous masses randomly distributed within the mammary chain. The multinodular masses were consistent with locally invasive mammary adenocarcinomas. Neoplastic cells were arranged in either solid nests, irregular ductular structures, or cribriform arrangements. No neoplasms were evident in any other male or female groups. The mechanism of this relatively acute dose-dependent carcinogenic effect of CI-1010 in female rats is not completely defined, however, CI-1010 is a potent direct-acting bacterial mutagen similar to other 2-nitro-imidazole compounds.

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CARCINOGENICITY OF PEROXISOME PROLIFERATORS. R. Cattley, Chemical Industry Institute of Toxicology, Research Triangle Park, NC 27709.

Peroxisome proliferators are a group of chemicals, including certain plasticizers, herbicides, and drugs, that produce typical hepatic effects. In rodents, peroxisome proliferators cause hepatocellular hyperplasia, increased peroxisomal volume fraction, and increased activity of some peroxisomal and extraperoxisomal enzymes in the liver. Following long-term exposure in rodents, peroxisome proliferators frequently cause increased incidence of hepatocellular neoplasia. Increased incidence of neoplasia at other sites (including testis, pancreas, and stomach) has been infrequently observed in long-term studies of certain peroxisome proliferators; however, the relationship of extrahepatic neoplasia to peroxisome proliferation has not been elucidated. Since most (perhaps all) peroxisome proliferators (and their metabolites) do not damage DNA, the mechanism of their hepatocarcinogenicity and its relevance for humans continue to be evaluated. There is evidence for elevated peroxisomal H_2O_2 and hepatocellular proliferation in the mechanism of hepatocarcinogenesis. These effects appear to be mediated by PPAR-(peroxisome proliferator-activated receptor-)a, a member of the steroid hormone receptor superfamily. Key remaining issues include (1) the requirement for PPAR-a activation in rodent hepatocarcinogenesis, and (2) differences between PPAR-a activity in human as compared with rodent tissue.