222 TOXICITY OF HCO-60 IN EXPERIMENTAL ANIMALS :

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HCO-60, a polyoxyethylene castor oil derivative, is used as a solubilizer of lipophilic drugs. This study was performed to examine the toxicity of HCO-60 in various experimental animals including dogs, monkeys, rabbits, guinea pigs and rats. With 1.25 or 2.5 mg/kg of HCO-60 injected i.v. to dogs, blood pressure decreased, flush, swelling and itching appeared after injection, and with 10 mg/kg of HCO-60 there was additionally a decrease of spontaneous motility. In the two higher dose groups, these symptoms paralleled an increase of histamine levels. Since degranulation was observed after injection in the mast cells of the skin, but not of the liver of dogs, the histamine in the plasma was considered to be released from the mast cells of the skin. Pretreatment with diphenhydramine, a H_1-receptor antagonist, suppressed the decrease of blood pressure induced by HCO-60. These findings show that the toxicity of HCO-60 is associated with histamine release from the mast cells. No symptoms occurred in monkeys, rabbits, guinea pigs or rats with 50 or 100 mg/kg i.v. of HCO-60, and there was no change in plasma histamine levels. This study demonstrated that the toxicity of HCO-60 is species specific to dogs among the animals tested.

223 Modifying Effects of Hepatocarcinogens or Antioxidants on Preneoplastic and Neoplastic Lesion Development in a Multi-organ Carcinogenesis Bioassay Using F344 Rats.

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Modifying potentials of various chemicals on tumor development were investigated in a multi-organ carcinogenesis bioassay using male F344/DuCrj rats. The animals were treated with N-nitrosodiethylamine (DEN, 100 mg/kg body weight, ip, single injection at the commencement of the study), N-methyl-N-nitrosourea (MNU, 20 mg/kg body weight, ip, 4 times during weeks 1 and 2), N-butyl-N-(4-hydroxybutyl)nitrosamine (BBN, 0.05 % in drinking water, during weeks 1 and 2), 1,2-dimethylhydrazine (DMH, 40 mg/kg body weight, sc, 4 times during weeks 3 and 4) and N-bis(2-hydroxypropyl)nitrosamine (DHPN, 0.1 % in drinking water, during weeks 3 and 4) for multi-organ initiation and then were given one of 4 test chemicals, including 2 hepatocarcinogens and 2 antioxidants, or basal diet for 24 weeks. All rats were killed at the end of week 28, and the major organs were carefully examined histopathologically for preneoplastic and neoplastic lesions. Modifying effects were detected in each target organ, i.e. 2-acetylaminofluorene (2-AAF) and ethionine, butylated hydroxyanisole (BHA) and catechol showed enhancing effects in the liver, in the forestomach and in the glandular stomach, respectively. The results indicated that the system could be reliably applied as a medium-term multiple organ bioassay for assessment of the modification potential of test agents in unknown target sites.