P-23

THE ALTERATION OF OXIDATIVE DAMAGE AND ACTIVITIES OF METABOLIZING ENZYMES IN RATS TREATED WITH PEROXISOME PROLIFERATORS

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The phthalates have been shown to produce hepatic peroxisome proliferation and certain peroxisome proliferators (PPs) are also known to increase the incidence of liver tumors in rodents. In this study we investigated the correlation between oxidative injury, changes in peroxisomal and microsomal enzymes and tumor formation in PP-treated rats. For the investigation of oxidative damage and enzymes assays, the rats were treated with phthalates or clofibrate following dosages for 14 days; di-2-ethylhexyl phthalate (DEHP), dibutyl phthalate, butylbenzyl phthalate: 50, 200, and 1000 mg/kg, clofibrate: 100 mg/kg in corn oil. In GST-P foci bioassay, rats were pretreated with diethylnitrosoamine, and then orally administered with phthalates (1,000 mg/kg), phenobarbital (PB, 40 mg/kg) or clofibrate (100 mg/kg) for 3 months. Both phthalates and clofibrate significantly increased the relative liver weights, but markedly decreased the relative weights of adrenal gland. Whereas the protein level of P4504A1, activity of carnitine acetyl CoA transferase and palmitoyl-CoA oxidation were markedly increased, the activities of microsomal enzymes such as 1A1, 1A2, 3A4 and UDP-glucuronyltransferase were significantly decreased by PPs treatment. The malonedialdehyde contents in livers were dose-dependently enhanced in PPs-treated groups, but formation of 8-hydroxydeoxyguanosine in hepatic DNA was increased in only clofibrate and DEHP groups. In GST-P foci bioassay, DEHP, PB and clofibrate formed much more foci than control. In summary these

results indicate that PPs selectively induce the enzymes involved in lipid metabolism, and that oxidative damage may be an important factor in carcinogenicity of PPs.