Metabolism and excretion patterns of intravenously administered disodium [^3H]cromoglycate (100mg/kg body wt.) were examined in a further four groups of rats: (1) controls; (2) phenobarbitone-pretreated; (3) disodium cromoglycate + phenobarbitone-pretreated; (4) disodium cromoglycate-pretreated. As before, no metabolites could be detected in bile or urine. Biliary excretion of radioactivity in rats in groups 2 and 3 was significantly lower than in the controls; this was accompanied by an increase in the urinary excretion of radioactivity. Disodium cromoglycate pretreatment alone caused no significant differences from controls. The overall elimination rate (i.e. urinary plus biliary) was similar in all groups.

It has been shown (Hargreaves & Lathe, 1963) that many compounds that are actively secreted into the bile can inhibit each other's excretion. It is suggested that phenobarbitone decreases the active secretion into the bile of disodium cromoglycate by competing for uptake into the hepatic cell from the plasma.

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Induction of Aryl Hydrocarbon Hydroxylase in Various Tissues of the Rat by Methylenedioxyphenyl Compounds

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Safrole (4-allyl-1,2-methylenedioxybenzene) has been shown to produce liver tumours in rats and mice (Homburger *et al.*, 1961; Long *et al.*, 1963; Epstein *et al.*, 1970). Further work has shown that methylenedioxyphenyl compounds produce both induction (Parke & Rahman, 1970; Wagstaff & Short, 1971) and inhibition (Anders, 1968; Freidman *et al.*, 1971) of hepatic drug-metabolizing enzymes. An important detoxification system of potential carcinogens present in many mammalian tissues is aryl hydrocarbon hydroxylase (Conney *et al.*, 1957; Wattenberg *et al.*, 1962). The effects of some methylenedioxyphenyl compounds, namely safrole, isosafrole and piperonyl butoxide (an insecticide synergist), on aryl hydrocarbon hydroxylase, with 3,4-benzopyrene as substrate, have been determined in various tissues.

Young male Wistar albino rats were fed on a diet containing 0.25% isosafrole (1,2-methylenedioxy-4-propenyl-benzene), and at various intervals after administration the activities of benzopyrene hydroxylase were determined in the liver, lung, kidney, gut and spleen. In all tissues except the spleen considerable induction (between 200 and 1200% of control values) of benzopyrene hydroxylase was observed. Maximum enzyme activities were reached within 14 days. In addition, there were large increases in hepatic biphenyl (a type I substrate) 2-hydroxylase and 4-hydroxylase activities, microsomal protein, liver weight, cytochrome P-450 content and apparent cytochrome b_5 content. In contrast, hepatic aniline (a type II substrate) 4-hydroxylase activity was inhibited. The redox difference-spectral absorption peak at 455nm observed by Parke & Rahman (1971) with liver microsomal preparations after pretreatment with safrole or isosafrole was also observed in microsomal preparations from kidney of the rats treated with isosafrole. This could be due to the interaction of isosafrole or a metabolite with the kidney microsomal haemoprotein (Lake & Parke, 1972). Polycyclic hydrocarbons have been shown to give extrahepatic induction of aryl hydrocarbon hydroxylase activity, whereas phenobarbitone produces no increase in the activity of this enzyme (Wiebel *et al.*, 1971) or other extrahepatic drug-metabolizing enzymes (Feuer *et al.*, 1971). The increase in extrahepatic aryl hydrocarbon hydroxylase activity after treatment with safrole or isosafrole correlates well with the reported carcinogenicity of these compounds.

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