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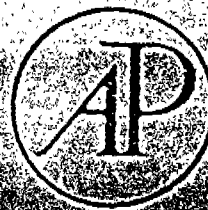
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Formation and Inactivation of a Chemically Reactive Metabolite of Vinyl Chloride¹

D. PESSAYRE,² J. C. WANDSIEBER, V. DESCATOIRE, J. Y. ARTIGOU,
AND J. P. BÉNHAMOU

Unité de Recherches de Physiopathologie Hépatique (U.S.E.R.M.),
Hôpital Beaujon, 92118 Clichy, France

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Formation and inactivation of a chemically reactive metabolite of vinyl chloride (Pessayre, D., Wandsieber, J. C., Descatoire, V., Artigou, J. Y., and Bénhamou, J. P. (1979) *Toxicol. Appl. Pharmacol.* **49**, 545-548). The mechanisms responsible for, and properties of, the metabolite activation of vinyl chloride were investigated in the rat. With [¹⁴C]-vinyl chloride, the metabolite formed in hepatoma and in a [¹⁴C]-labeled intermediate was covalently bound to microsomal proteins. Formation required NADPH, was decreased by CO, SKF-525-A, or glutathione, and was increased by 1,1,1-trichloro-2,2,2-trifluoroethane (CCl₃CF₃). Inhibition of a 5-μ vinyl chloride atmosphere decreased by the conversion of *P*-450 or by glutathione. Pretreatment of the animals with DD1 or phenobarbital increased the microsomal protein levels and the formation of the metabolite. In the presence of 10 *P*-450 and increased the *in vitro* formation of cytochrome *P*-450. The metabolite of vinyl chloride, but (2) decreased the *in vitro* reversible formation of 10 *P*-450. The results of pretreatment of the animals with glutathione during inhibition of vinyl chloride. These results are consistent with the views that (1) vinyl chloride is activated by cytochrome *P*-450 into its chemically reactive epoxide, (2) the epoxide may be inactivated by epoxide hydrolase or by conjugation to glutathione, (3) pretreatment with DD1 or phenobarbital increases both the formation rate of the epoxide and its inactivation rate by epoxide hydrolase, and (4) the rate of *P*-450 destruction is related to the formation rate of the epoxide. Strong glutathione depletion seems related to only that fraction of the formed epoxide which has escaped inactivation by microsomal epoxide hydrolase and is converted in the cytosol.

Vinyl chloride (chloroethylenes) is mainly used in the manufacture of plastics. Polymerization of this monomer leads to polyvinyl chloride, the most widely used synthetic material (Berk *et al.*, 1976). In workers exposed to vinyl chloride, angiosarcomas of the liver and/or hepatic fibrosis have been

observed (Berk *et al.*, 1976). Hepatic angiosarcomas and liver lesions have been reproduced in experimental animals chronically exposed to vinyl chloride (Gorkelson *et al.*, 1961; Lester *et al.*, 1963; Vosh *et al.*, 1971; Maltoni and Talamone, 1975; Prodan *et al.*, 1975).

Several carcinogenic and/or hepatotoxic compounds are transformed by the hepatic microsomal mixed-function oxidase system (MFO) into chemically reactive metabolites that (1) covalently bind *in vitro* to microsomal proteins, (2) covalently bind *in vivo*

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²Present address: a few days from the Fonds d'Etudes de la Médecine Interne.