PHARMACODYNAMICS OF VINYL CHLORIDE IN RATS IN RELATION TO ITS ONCOGENICITY by T. Green and D. E. Hathway (ICI, Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire SK104TJ, England)

Inhalational exposure of rats to 3% (v/v) of vinyl chloride for 12 months elicited epidermoid and mucoepidermoid carcinomas in the para-auricular region of surviving animals (P. L. Viola, Abstracts of Tenth International Cancer Congress, Houston, Texas, May 22-29, 1970; P. L. Viola, A. Bigotti, S. A. Caputo, Cancer Res., 1971, 31, 516.) Those key observations plus confirmation of the Zymbal-gland carcinomas and the discovery of liver and spleen angiosarcomas in rats (C. Maltoni, Advances in tumor prevention, detection and characterization (Cancer detect and prevention, Proc. Second International Symposium on Cancer Detection and Prevention, Bologna, April 9-12, 1973), Excerpta Medica, Amsterdam, 1974, Vol. 2; C. Maltoni and G. Lefemíe Accad. Nazionale dei lincei, 1974, Ser.8,56,1), as well as a small incidence of liver angiosarcomas in human subjects, make a better understanding of vinyl chloride metabolism and disposition desirable. Furthermore, production of angiosarcomas after i.p. injection (Maltoni) implies that vinyl chloride itself and not a photolysis product is the causative agent.

After acute i.e. administration of 450 mg/kg^{-1} of (^{14}C) vinyl chloride to rats, unchanged vinyl chloride (95% of the dose) and $^{14}CO_2$ (0.5%) were exhaled by the lungs and residual ^{14}C excreted by the kidneys, but after similar dosing with 250 ug/kg^{-1}, $^{14}CO_2$ (15% of the dose) and vinyl chloride (less than 5%) were exhaled and 75-80% was excreted predominatly

via the kidneys. These results suggest nonlinear kinetics and th saturable mechanism of biotransformation is (are) implicated. Th main eliminative route for lipid-soluble, water-insoluble and highly volatile vinyl chloride is pulmonary and the highly effici arterial-alveolar transfer leaves relatively little unchanged mat available for biotransformation in successive passes through the liver. Furthermore, elimination patterns after i.p. and i.v. injections and the relationship between the size of an oral dose and the proportion metabolized confirm the suppositions. Autoradiograms of sequential longitudinal sections through whole animals that were exposed to (^{14}C) material show (i) discrete localization in sectional tubules (possibly of the Zymbals glands) in the para auricular region, and (ii) the passage of ^{14}C through the lungs, liver and kidneys. Finally, the rate of pulmonary elimination for vinyl chloride exceeds that for CO_2, and there is a more rapid elimination of pulmonary--than of urinary--excretion products.

A first metabolic pathway seemingly involves peroxide decompositi and leads to CO and to CO_2 via formaldehyde. Recognition of carboxyhaemoglobin proves CO production, and besides direct measurement of $^{14}CO_2$, the presence of ^{14}C-labeled urea, methionine and N-formylcysteine urinary metabolites provides convincing evidence for the rest of this metabolic pathway. Chloroacetic acid results either through peroxide rearrangement or via epoxidation.

These findings are relevant to the oncogenicity of vinyl chloride

Critique of "PHARMACODYNAMICS OF VINYL CHLORIDE IN RELATION TO ITS ONCOGENICITY" by T. Green and D. E. Hathway (ICI Central Toxicology Laboratory, Alderley Park, Macclesfield, Cheshire SK104TH, England)

The results of the studies by T. Green and D. E. Hathway support generally those which we have reported. "Preliminary Studies of the Fate of Inhaled Vinyl Chloride Monomer (VCM) in Rats" by Hefner, Watanabe, and Gehring. Both studies show clearly that the metabolism of vinyl chloride is saturable. The methods used by Green and Hathway would not differentiate two metabolic pathways. Therefore, the existence of a primary saturable pathway and a secondary unsaturable pathway indicated by us was not verified.

The metabolic products reported by Green and Hathway are somewhat different than those proposed by us. As yet, we have not found evidence of ^{14}C-labeled urea in the urine of rats exposed to ^{14}C vinyl chloride by inhalation. If it is present, it must be only a small fraction of the vinyl chloride converted to metabolites. With regard to the other metabolites, it is too early to use the results of our studies to either confirm or refute. It is notable that Green and Hathway have proposed a peroxidative metabolism of vinyl chloride. This is one of the three possible pathways conceived by us.

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ADDENDUM TO PREVIOUS REPORT ENTITLED "PRELIMINARY STUDIES OF THE FATE OF INHALED VINYL CHLORIDE MONOMER (VCM) IN RATS"

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