Reprinted from the *International Journal of Cancer*
© International Union Against Cancer
Printed in Switzerland

Int. J. Cancer: 15, 429-437 (1975)

RECEIVED
RESEARCH & DEVELOPM.
JUN 17 1975
W. M. SMITH

RECEIVED
JUN 5 - 1975
IAI.

HUMAN, RAT AND MOUSE LIVER-MEDIATED MUTAGENICITY OF VINYL CHLORIDE IN *S. TYPHIMURIUM* STRAINS

by

H. Bartsch, C. Malaveille and R. Montesano
International Agency for Research on Cancer, Unit of Chemical Carcinogenesis, 150 Cours Albert Thomas, 69008 Lyons, France

Exposure of S. typhimurium *strains TA 1530, TA 1535 and G-46 to vinyl chloride increased the number of His⁺ revertants/plate 16, 12 or 5 times over the spontaneous mutation rate. After 6 h of exposure to vinyl chloride, the mutagenic response for TA 1530 strain was enhanced 7-, 4- or 5-fold when fortified postmitochondrial liver fractions from humans, rats or mice were added. The enzyme-mediated vinyl chloride mutagenicity was dependent on an NADPH generating system and the enzyme activity was localized in a liver microsomal fraction; 9,000 × g liver supernatant was three times more active than microsomes, while liver cytosol or alcohol dehydrogenase did not affect the mutagenicity. Phenobarbitone pretreatment of rats and mice increased the mutagenic response by up to 15-40% as compared to untreated controls. The relative mutagenic activities of VCM, taking the value from mouse liver as 100, for TA 1530 strain mediated by 9,000 × g tissue fractions were: rat liver, 80; mouse and rat kidney, 20 [illegible] human liver (from four biopsy specimens), 170, 64, 70 and 46. Chloroacetaldehyde and chloroacetic acid, a urinary metabolite of VCM, showed toxic effects, while chloroethanol was weakly mutagenic for TA 1530 strain.*

Vinyl chloride monomer (VCM) is extensively used for the production of polyvinyl chloride and other plastic material, and also as a propellant for aerosols. Carcinogenicity in rats, when exposed to 30,000 ppm VCM in air, was first reported by Viola *et al.* (1971). Subsequently, Maltoni and Lefemine (1974) showed that angiosarcomas of the liver, as well as other tumours, were induced in rats and mice exposed to various doses of VCM by inhalation. Recently, cases of angiosarcoma of the liver have been found in workers exposed to VCM during the polymerization process and a causal relationship between VCM exposure and this type of tumour in man has been established (Creech and Johnson, 1974; Heath *et al.*, 1974; Lee and Harry, 1974; IARC, 1974). The systemic action of this carcinogen and its low chemical reactivity suggest that the biological effects of VCM are dependent upon its metabolic activation. In these studies, we report the mutagenicity of VCM and its presumed metabolites in *S. typhimurium* strains, mediated by liver and other tissue fractions of rat, mouse and human origin.

MATERIAL AND METHODS

Chemicals

VCM (purity 99.9%) was generously provided by Rhône-Progil, Lyons, France, contaminated with ethanol (30 ppm), water (20 ppm), methylchloride (<20 ppm) and non-volatile substances

Received: October 16, 1974.

RSV 0012326

RECEIVED
RESEARCH & DEVELOPMENT
JUL 23 1975
W. M. SMITH

TYPE ABSTRACT HERE

H.MARCQ, M.JOHNSON, C.WHETSTONE, C.LEROY, Med. Univ.S.C., Charleston, B.F.Goodrich, Akron, and Conoco, Inc., Ponca City. *In vivo* skin capillary abnormalities in vinyl chloride workers.

Workers (Ws) exposed to vinyl chloride (VC) have proliferative small blood vessel and interstitial fibrotic lesions of peripheral (acro-osteolysis [AOL], Raynaud's phenomenon [RP] and scleroderma [SD]-like skin changes) and visceral (angiosarcoma [AS] and hepatic fibrosis [HF] of Banti type) areas. In the present study *in vivo* widefield capillary microscopy (which has demonstrated a distinctive pathologic pattern whose severity correlates with visceral involvement in idiopathic SD) has been used to examine 152 VC Ws and 50 control non-VC manual Ws. 44 VC Ws selected on the basis of known pathology (RP,AOL,HF,AS and skin lesions) revealed a high proportion with SD-like capillary abnormalities (CA). Since many VC Ws had been reactor cleaners (RC), the trauma and cold exposure of RC could explain the CA seen. Comparison between 108 VC Ws (including those who had never been RC) and 50 non-VC Ws showed that CA were significantly more common in the VC Ws (p <CA part) [illegible] with AS, HF, active AOL and SD-like changes had more CA than those with healed AOL, varicus skin rashes and RP alone (p <0.001). Among 108 VC Ws no correlation was found between CA and history of RC. Further studies early in VC exposure are needed to determine whether a subpopulation "susceptible" to the microvascular effects of VC can be detected. Capillary observations are proposed as a non-invasive technique to monitor VC and possibly identify more serious VC related vascular and visceral disease at a preventable stage.

Author: Name and full address _____

_____

_____

_____ Telephone _____

Copied by MCA 7/30/75 for VC Technical Panel distribution