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INTERNAL
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CHEMICALS AND PLASTICS

SOUTH CHARLESTON PLANT P. O. BOX 8004, SOUTH CHARLESTON, W. VA- 25303

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Division
Location

Date April 29, 1976

Originating Dept.

Receiving Dept.

Copies to Dr. T. T. Szabo
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Mr. H. R. Guest

Subject Vinyl Chloride Research Project

The Manufacturing Chemists Association Vinyl Chloride Technical Panel is recommending to the industry two research programs for funding this year. These are:

1. Continued Studies on the Metabolism of Vinyl Chloride by Dow Chemical Toxicology Research Laboratory.

Cost for one year - \$133,000

2. Research Techniques and Methods for Detection and Prevention of Carcinogenesis in Industrial Workers by University of Louisville School of Medicine.

Cost for one year - \$230,000

The total cost for the program would be \$363,000. Union Carbide's allocated share of this program would be approximately \$22,000. Of approximately thirty companies involved in support, two have expressed objection to continuation of the Dow work and one has objected to the University of Louisville proposal.

The Dow proposal for continued studies on the metabolism of vinyl chloride is the third and final extension of this work. The objectives are to determine the potential of reactive vinyl chloride metabolites to bind with hepatic macromolecules in vivo and to define the various metabolic pathways responsible for the biotransformation of vinyl chloride. Successful completion of the work could lead to establishing a relationship between dose-dependent metabolism and carcinogenesis.

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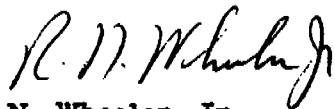
This project will have little immediate value to the PVC industry. On a long-term basis it will help the chemical industry combat the no threshold exposure for a carcinogen and may lead to less stringent future regulations. The work to date shows support for a fifty ppm VC threshold in rats and identifies chloroacetaldehyde as the carcinogen.

The University of Louisville proposal is a continuation of work now sponsored solely by B. F. Goodrich. The university has a grant from the National Cancer Institute to study carcinogenesis by existing procedures (\$2,700,000) only. This grant was complemented by funds from B. F. Goodrich for investigation of new techniques and procedures for early detection and prevention of carcinogenesis. The B. F. Goodrich grant has been exhausted and the work is currently supported by B. F. Goodrich on a month-to-month basis until new sponsorship can be obtained. The MCA Technical Panel has reviewed the total program, which would cost in excess of \$500,000 per year, and recommends support of \$230,000 for one year in selected areas such as immunological, tissue antigenic and enzymatic systems for detection of vinyl chloride and other chemical injury. There would also be some study of liver tissue and metabolites. Depending on progress and the availability of funds, the work would be continued an additional two to three years. There is no commitment currently to continue beyond one year. If new techniques and procedures are identified, then N. C. I. might provide money for further study. In any event the development of new procedures leading to early detection of vinyl chloride and other chemical injury would directly benefit workers in the chemical industry. Based on the access to B. F. Goodrich medical and health records as well as the past performance of the University of Louisville, continuation of the work should be fruitful.

Summaries of three papers from University of Louisville people in this area are attached. Details of the proposed program are available if needed.

Sponsorship of the MCA program by Union Carbide Corporation is recommended particularly since it has potential value in areas other than vinyl chloride resin.

Very truly yours,



R. N. Wheeler, Jr.

RNWJr. /pm
Attachments

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STUDIES ON THE MUTAGENICITY OF VINYL CHLORIDE METABOLITES
AND RELATED CHEMICALS

A. D. Laumbach, S. Lee, J. Wong, and U. N. Streips

V. SUMMARY

Our laboratories have utilized strains of B. subtilis and Salmonella typhimurium to investigate the mutagenicity of vinyl chloride metabolites and related compounds. The major findings reported in this manuscript are: 1) Confirmation of mutagenicity of chloroacetaldehyde and chlorooxirane. 2) Description of mutagenicity of additional potential metabolites of vinyl chloride, chloroacetaldehyde monomer hydrate, dimer hydrate, and trimer, as well as the mutagenic carcinogenic chlorooxirane homolog, epichlorohydrin. 3) Recombination repair is postulated to be the mechanism for correcting vinyl chloride metabolite elicited damage. 4) Chloroacetaldehyde affects the transformation activity of DNA only if cells are treated with the mutagen prior to the extraction of the DNA. In vitro the chemical had no effect. 5) Epichlorohydrin differs from vinyl chloride metabolites in mode of action.

URINARY AND TISSUE GLYCOSAMINOGLYCAN
PATTERNS IN HEPATIC ANGIOSARCOMA

Charles E. Kupchella and Carlo H. Tamburro

V. SUMMARY

Glycosaminoglycans were measured in urine and tissue of patients with hepatic fibrosis and hepatic cancer including vinyl-chloride-exposure-associated liver injury and angiosarcoma. Angiosarcoma, hepatitis, cirrhosis, and liver metastatic patients exhibited significantly elevated glycosaminoglycan excretion. Angiosarcoma tissue exhibited elevated glycosaminoglycan levels with the greatest increases in the heparin fraction. Histochemically, angiosarcomatous tissue gave a strong alcian-blue staining reaction which could be prevented by pretreatment with hyaluronidase. Although vinyl-chloride-exposure-associated liver injury other than angiosarcoma was not accompanied by a significantly elevated glycosaminoglycan excretion, this condition tended to be associated with a urinary glycosaminoglycan excretion pattern in which the chondroitin sulfate fraction was the only uronic-acid-positive fraction.

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IMMUNOPATHOLOGIC OBSERVATIONS IN LIVER ANGIOSARCOMA

Enrique Espinosa, M.D.

V. SUMMARY

Immunodiffusion analyses of human liver angiosarcoma associated with vinyl chloride exposure indicated presence in the tumor of an antigen not detected in normal liver and kidney but found to be present in lung and spleen. This antigen was shown to be a protein, inactivated by Pronase and trypsin, relatively susceptible to heating and to acid pH and precipitated mainly at 20-30% saturated ammonium sulfate and at 30-70% ethanol concentrations. The tumor was shown to contain several antigenic constituents of normal tissue but one normal tissue antigen was not detected. This antigen was characterized as a substance unaffected by Pronase and trypsin and inactivated by periodate. It was relatively thermostable, affected by acid pH and precipitated over a wide range of ammonium sulfate and ethanol concentrations. Tumor specimens obtained at autopsy contained bound IgG as shown by immunofluorescence and elution experiments suggesting possible in vivo binding of IgG to the tumor.