R N Wheeler

DOW CHEMICAL U.S.A.

1603 Building
July 26, 1979

MIDLAND, MICHIGAN 48640

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RECEIVED
AUG 6 1979
R. N. WHEELER, JR.

Mr. Joseph T. Seawell
Vinyl Chloride Project
CMA
1825 Connecticut Ave., NW
Washington, D.C. 20009

cc: T. J. Benya, Ethyl Corp.
J. Stafford, ICI, England
CMA Vinyl Chloride Research Coordinators

INTRATRACHEAL INSTILLATION OF PVC DUST

The attached preliminary protocol from the University of Tennessee will be discussed at the September 20 Research Coordinators' Meeting.

Sincerely yours,

T. R. Torkelson, Sc.D.
Chairman, Vinyl Chloride
Research Coordinators

Encl.

DOST

ETHYL CORPORATION

TOXICOLOGY AND INDUSTRIAL HYGIENE DEPARTMENT

ETHYL TOWER. 451 FLORIDA

BATON ROUGE. LOUISIANA 70801

504/388-7858

July 16, 1979

T.R. Torkelson
1603 Building
Dow Chemical, USA
Midland, Michigan 48640

Dear Ted:

Enclosed is a copy of a research proposal from the University of Tennessee, Materials Science Toxicology Laboratories, for studying pulmonary effects by PVC dust.

This proposal is a result of our initial conversations concerning the potential hazards associated with PVC dust exposure in the workplace.

Dr. Autian has considerable expertise in the area of plastic toxicology studies and is quite interested in pursuing the PVC dust problem.

I would appreciate receiving your comments and those of the Vinyl Chloride Research Coordinators - CMA regarding this proposal.

Thank you for your assistance in forwarding copies to the coordinators as discussed during our telephone conversation.

Best regards,

Sincerely,

Theodore J. Benya, Ph.D.
Toxicologist

TJB:sbb
Attach.
cc: G.L. Ter Haar
J. Autian

UCC
024913

Materials Science Toxicology Laboratories

COLLEGE OF DENTISTRY & COLLEGE OF PHARMACY

UNIVERSITY OF TENNESSEE CENTER FOR THE HEALTH SCIENCES
MEMPHIS, TENNESSEE 38163

Dr. John Autian, *Director*
(901) 528-6020

Dr. W. Homer Lawrence
Associate Director and
Head, Animal Toxicology
(901) 528-6068

Dr. Elwood O. Dillingham
Head, Cellular Toxicology
(901) 528-6072

Dr. Loys J. Nunez
Head, Biomaterials
(901) 528-6078

Dr. James E. Turner
Head, Pathology
(901) 528-6364

June 13, 1979

Dr. Theodore J. Benya, Toxicologist
Ethyl Corporation
Toxicology and Industrial Hygiene Department
Ethyl Tower, 451 Florida
Baton Rouge, Louisiana 70801

Dear Ted:

I am a little late in sending you the informal proposal developed by Dr. W. H. Lawrence and myself, and I hope this has not inconvenienced you. Please review what we have said and then let us know if it can be developed into a full-fledged proposal. I will be out-of-town for the next two weeks, and thus you may wish to talk to Dr. Homer Lawrence (901: 528-6068) if questions arise.

Hoping to hear from you soon.

Sincerely,

John Autian, Ph. D., Director

cc Dr. W. H. Lawrence

JA/rw

UCC
024914

Materials Science Toxicology Laboratories
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TO: Dr. Theodore J. Benya, Toxicologist
Ethyl Corporation

FROM: Drs. John Autian and W.H. Lawrence
Materials Science Toxicology Laboratories

DATE: June 12, 1979

SUBJECT: Proposed Carcinogenic Study of PVC Dust

PROPOSAL FOR A FEASIBILITY STUDY TO EXAMINE THE POTENTIAL CARCINOGENICITY OF PVC DUST

Introduction

Because of the possible relationship between exposure to PVC dust and lung disorders, it became desirable to initiate a short-term feasibility study to assess the possibility that PVC dust might be implicated in pulmonary tumorgenesis. The latent period for such tumors, if induced by PVC dust, is unknown but tumor induction often is not observed until after a considerable lapse of time.

This proposal is designed as a six-months study, but sufficient animals will be treated to provide for a number of animals remaining after completion of the six-month design to permit extending the study, without the delay of starting over from the beginning, for a long r peri d of tim if results from the

six-months study would suggest it might be fruitful. These 'extra' animals will be held until the histological evaluations f the six-month tissues have been completed; at this time a decision will be made whether or not to continue the observation period, and if so, the schedule to employ.

General Procedure

The PVC dust to be evaluated will be supplied by the Ethyl C rporation (Dr. Benya). A specified quantity of the dust will b administered by intratracheal instillation in a manner similar to that described by Davis, et al. (Br. J. Cancer, 31:129, 1975). A similar procedure was used by Stenback and Rowland (Scand. J. Resp. Dis., 59:130, 1978) to study talc and benzo(a)pyrene in Syrian golden hamsters.

Male rats of the Wistar strain, weighing 100 to 150 grams at the initiation of the study, are recommended. The test sample is prepared for administration by suspending it in normal saline, by sonication immediately prior to administration, so that 0.2 ml. of the suspension will contain the desired quantity of PVC dust (about 3 to 5 mg.). Each rat is anesthetized and a cannula is passed through the larynx and the 'dose' (0.2 ml. of the suspension) is given by intratracheal instillation. In order to produc maximum exposure in a minimum period of time, it is proposed that this procedure be repeated three (3) times per week for five (5) weeks for a total of fifteen (15) 'doses'. Control rats will be administered 0.2 ml. of saline in the same manner.

It is recommended that 10 rats from the PVC dust treatment group and 10 of the controls be sacrificed, autopsied and tissues taken for histopathology at the following times (from date of initiation of treatments): (a) six weeks, (b) three months, (c) four months, (d) five months, and (e) six months. The remaining rats will be held until the tissues from the six months sacrifices are examined histologically, at which time a decision will be made as to whether to continue the study or not. At autopsy, the trachea, lungs, liver, and kidneys will be removed and preserved in 10% buffered formalin for histological processing and evaluation. In addition, if suspicious lesions of other tissues or organs are observed during the autopsy, they will be removed and preserved for histological examination.

To conduct the study as envisioned in this outline, it is desired to have about 100 rats which have been treated with the 15 intratracheal instillations of the PVC dust suspensions, plus 100 saline-treated controls. In-as-much-as Ishinishi, et al. (Environ. Health Perspect., 19:191, 1977) reported a survival of 30% to 71% of the rats in their various groups after 15 weekly instillations of this type (mean of all groups was 41% survival), it is suggested that each group be initially composed of 200 rats to provide approximately 100 at the end of the 15 'dose' treatment schedule.

Comments

There are many modifications or variations of this procedure which could be employed. This particular procedure is suggested

because this methodology of administering a powder or similar material into the lung area is reasonably well established. The rather frequent treatment of rats proposed here is an attempt to demonstrate in a rather brief period, if possible, a reaction which might occur much more slowly from a more conservative treatment schedule.

A six-months study is rather short for assessing a material for its ability or tendency to produce tumors. The experimental design, however, provides the flexibility of extending the observation period, without a loss of time, should it appear desirable.