TO: . Greg Hoenes, Dick Andersen

~~TGG~~: ~~JCL~~: MMG: ~~AJO~~: RF
XF: Desk

FROM: T. G. Grumbles
DATE: June 14, 1989

Interoffice Communication

SUBJ: TOXICOLOGY TESTING CONSULTANT FOR ALUMINA PROJECT

VISTA

Attached is the proposal from Dr. Jenkins for costs and time involved in preparing a protocol for our alumina toxicity testing. I am asking for your approval to use him to proceed with development of a protocol and identification of a laboratory to do the testing. At that time, we will review the protocol and have a quantitative estimate of what the actual testing will cost.

In summary the attached indicates:

1. Development of the protocol and identification of a laboratory will cost approximately $3,500.

2. Our goal, evaluating low level exposure effects, is attainable but not by using standard protocols.

Please contact me with your approval proceed.

T. G. Grumbles

dlj

Attachment

cc: J. R. Drumwright, K. L. Fogg-LCCP

TOXICOLOGY RESOURCES

20622 LAVERTON DRIVE KATY, TEXAS 77450
(713) 578-0200

5 June 1989

Thomas G. Grumbles
Environmental Quality Manager
Vista Chemical Company
900 Threadneedle
Houston, Texas 77079

Dear Tom,

Think you for the opportunity to participate in your planned inhalation toxicology studies of Vista Alumina. This promises to be a most interesting project. I have read several reviews on alumina pulmonary toxicology and understand your concerns with potential low level effects such as drying of skin and mucosal tissues, tightness in the chest, sinus effect and nose bleeds. I am confident that a set of experimental animal protocols could be devised to address most, if not all, of your concerns.

I am enclosing a proposal covering what, in my opinion, would be required to initiate these studies. After you have had a chance to read it, please contact me with any questions or if you would like to meet to discuss it.

Sincerely,

Larry Jenkins

Lawrence J. Jenkins,
President

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Proposal

The following general statements apply to any endeavor involving the use of experimental animals. Animal studies can address many of the signs associated with chemical toxicity, but few of the symptoms (which are more subjective). Similarly, experimental studies do not need to be limited or constrained by standard protocols such as those required along with registration activities (such as FIFRA, etc.), since those protocols are designed to serve a specific purpose. They should, however, be thoughtfully considered, planed with great care, executed properly (and, even though not specifically required, in accordance with Good Laboratory Practices) and intelligently and objectively interpreted. Also, experimental animal studies should use no more animals than necessary, be of humane design, and should be intended to obtain information that is necessary and which cannot be obtained from other readily available sources. In my opinion, the studies we discussed in our meeting of 15 May 1989 fulfill these requirements and are amenable to the necessary design criteria.

In my opinion, standard FIFRA (and other) protocols will not give the information that is desired. Those protocols are designed for a different purpose, which is the prediction of safe use levels of the chemical in question for the purpose of registration of that chemical. They

include a large amount of gross and microscopic pathologic evaluation and use that pathology as end point of the study. Much of this information is already available (Brooks, 1986; Dinman, 1988) and has been used in setting guidelines for industrial exposures. The question at hand is whether physiological changes occur at lower thresholds than have already been reported for pathologic changes.

I recommend the development of a series of screening protocols, utilizing physiological measurements as well as pathologic evaluation. Much of our present day practice of occupational health is based on the assumption that thresholds exist; that is to say that there are exposure levels which do not elicit a given response. At present, many occupational exposure guidelines consider that physiological thresholds (which may or may not be reversible, but usually are) exist and are usually below thresholds for pathologic changes, which are frequently less reversible.

Not all of the questioned manifestations of alumina exposure are directly amenable to animal experimentation. For example, the question of tightness in the chest cannot be measured in an animal model; however, physiological changes (as, for example) in pulmonary compliance and resistance which would lead to the symptom of tightness in the chest are measurable. Since one of the basic questions is whether other thresholds of toxicity (or physiological alterations) exist and, if so, whether they occur at lower

concentrations than would be predicted from pathologic changes, pathologic observations would be included as an integral part of any exposure protocols.

There is an ever increasing pressure to minimize the use of animal experimentation and, in its place, utilize various *in vitro* methods, some of which involve cell culture, to predict many of the things acute animal studies are currently used for. This includes things such as Draize tests for ocular and dermal irritation. This concept has achieved a great deal of support for evaluating such things as cosmetic ingredients. Recently, the Environmental Protection Agency has requested that more clinical observations be included in standard FIFRA submittals and that procedures which require fewer animals be used in acute toxicity testing which use end points such as lethality observations for LD50 determinations. For many reasons, including issues of sensitivity and specificity for other than acute irritation responses, there are no *in vitro* model to address your questions regarding some of the potential lower-level exposure sequelae to alumina, so the use of animal protocols is perfectly appropriate and necessary.

I estimate the following committment would be sufficient to initiate your project:

1. A thorough review of the literature regarding alumina toxicity, including the various on-line data bases of the National Library of Medicine and preparation of a physiologically-based protocol would take 40 to 45 hours. The hourly rate would be $75.00

2. Interaction, discussions and negotiations with laboratories, except that which incidentally occurs during protocol preparation, is not included in the above time estimate.

3. Identifiable expenses are not included in the hourly rate. These expenses include telephone, travel, computer time, mileage, parking, photocopies etc. They are billed, when accumulated, without the addition of any overhead.

4. Any travel time to monitor a laboratory study would be separately negotiated.

Bibliography

Brooks, Stuart M. (1986). Pulmonary reactions to miscellaneous mineral dusts, man-made mineral fibers, and miscellaneous pneumoconioses. In *Occupational Respiratory Disease.* (J.A. Merchant, ed.) p. 401-410. NIOSH Publication No. 86-102. U.S. Department of Health and Human Services.

Dinman, B.D. (1988). Alumina-related pulmonary disease. *J. Occup. Med.* 30, 328-335.

National Library of Medicine. (1989) Hazardous Substances Data Base, Toxicology Data Network. The National Library of Medicine, Bethesda, Maryland.

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