

August 2, 1956

Dr. George F. Kirby
Ethyl Corporation
P.O. Box 341
Baton Rouge 1, Louisiana

Dear George:

I send you herewith, at Mr. Shea's suggestion, a proposal for an investigation of the new manganese compound at the estimated cost indicated. This is my last act before leaving town for a vacation. I'll be out of my office until around September first, and I doubt that anything much can be done about this work until after that date. However, this gets it under way, so far as my present task is concerned.

After talking with the people in Detroit about this some days ago, I came to the conclusion that we should have some information as soon as may reasonably be possible, to enable us to (1) give advice concerning the potential hazards of manufacture on a scale that would involve more than mere experimental use; and (2) to learn whether or not there are appreciable hazards in the introduction of this compound in the desired concentration in gasoline, with or without tetraethyl lead.

These represent certain of the problems on which information is fairly crucial in an early stage of the exploitation of the developmental work. They are not all, but the experiments outlined in a general way are the minimum that can be considered if the product has real hope of being marketed and used. I am led to believe that the prospects are good and that we should not delay much longer. If you and your associates feel differently, it is up to you.

We are taking an independent look at the potential hazards of the manufacturing processes, in terms of other products and intermediate reactions, and we believe that the reworking of the reaction mass to separate out the desired materials is the worst problem, in terms of skin contact and perhaps other forms of exposure.

If you will consider this and let me know your opinion about it in due course, I shall be guided accordingly.

Sincerely yours,

Robert A. Kehoe, M.D.

RAK:vr

Encl. *Proposal
letter 8/9/56
R.A.K.*

Dr. George F. Kirby - (2) - August 2, 1956

P.S.

I include in the attachments, a copy of a summary of the most pertinent information gained in the preliminary observations on this compound identified by the earlier code designation at Detroit.

R.A.K.

Dictated but not read.

KE 0019278

PROJECT PROPOSAL

Sponsor: Ethyl Corporation
1600 West Eight Mile Road
Ferndale 20
Detroit, Michigan

Project: An investigation of (1) the effects of repetitive skin contact with AP-3 and (2) the toxicity of vapors of the compound.

Date
Submitted: July 27, 1956

Procedure: The investigation will be carried out in such a manner as to obtain the information required to provide suitable safeguards for the public health and to serve the best interests of the sponsor.

- I. A study of the percutaneous toxicity.
 - a. Two gasolines, with and without lead tetraethyl, will be used.

The following concentrations of AP-3 in each gasoline will be tested: 0.0, 0.1, 0.6 and 4.0 grams per liter. One group of 6 rabbits for each preparation will be needed. The periods of contact will be 2 hours on each of 5 days per week for a maximum period of 24 weeks.
 - b. The experimental design of this phase will be similar to that of (a) excepting in the concentrations. Four other concentrations will be selected after an evaluation of the previous results and they shall be of such order as to provide adequate dose response curves for the compound in each gasoline.
- II. A study of the toxicity of vapors of AP-3.

Each experimental group of animals will consist uniformly of 20 mice, 10 rats, 4 rabbits, 5 guinea pigs and 2 dogs.

 - a. Preliminary tests to establish atmospheric concentrations which will be lethal to animals exposed therein for a period of 1, 4 and 8 hours and a concentration which will be nonlethal to animals exposed therein for a single continuous period of 7 hours.
 - b. Exposure of animals to the nonlethal and 1/2 of the nonlethal concentration for 7 hours on each of 5 days per week until the mortality reaches 50 per cent, or for a maximum period of 6 months.
 - c. Exposure of animals to 0.1 of the nonlethal concentration. Animals will be exposed for 7 hours on each of 5 days per week for a maximum period of 1 year.

Procedure
continued:

- III. Analytical requirements.
 - a. The development and selection of analytical methods for the quantitative estimation of the compound (or manganese) in air and in excreta and body tissues.
 - b. Analyses of body tissues and excreta.
 - (1) 24 rabbits, 3 from each group of I. a
 - (2) Selected tissues and samples from animals in II. a, b and c.
 - (3) Establishing a time-storage curve in the animals of II. c.
- IV. (Optional)
A basic study of the excretion and deposition of AP-3 when given intravenously in sublethal amounts to rabbits.
 - a. Rate of elimination from the blood.
 - b. Rate of excretion in the urine and feces.
 - c. Deposition in the body tissues.

Estimated
Costs:

I.	a.	\$8,700	
	b.	\$8,700	\$17,400
II.	a.	\$5,600	
	b.	\$7,600	
	c.	\$13,200	\$26,400
III.	a.	\$3,600	
	b-1	\$5,000	
	2	\$9,000	
	3	\$1,000	\$18,600
IV.		\$1,000	\$1,000
Total estimated cost			\$63,400

The final costs are calculated upon the actual expenses incurred in carrying out the project. The cost of additional work beyond the scope of the proposal will be calculated upon actual expenditures and shall be by mutual agreement.

Reports: Progress reports will be submitted at intervals of 3 months and a terminal report will be submitted upon completion of each phase of the project.

From the Kettering Laboratory in the Department of Preventive Medicine and Industrial Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio.

Approved: _____

Robert A. Kehoe, M. D.
Director

KE 0019280