EXHIBIT 40

FILED UNDER SEAL

21/39/2

Dr. G. Weston Hurst
to see / return please

Dr. W. G. Toland
Manager, Research & Development
California Chemical Company
Ortho Division
Lucas Street & Ortho Way
Richmond, California
U. S. A.

TWR:rmb

AABN:EE

24th March 1964

Dear Bill,

Paraquat Toxicology Studies

Thank you for your letter of the 24th February, which has resolved a number of the points at issue.

We agree that the 14-C labelled paraquat studies in the cow should be delayed. Points of detail about the tests can be settled by discussions nearer to the time that the tests are to be started. Presumably the results of Calchem's own work on residue levels in American forage crops will provide the answer to one of your questions. Recent work at I.H.R.L. indicates that there is no metabolism of paraquat in the animal and it is therefore doubtful if the use of ring labelled paraquat in the cow will add significantly to the information in this experiment.

We agree that it is our responsibility to "initiate, authorise and finance" all toxicological work necessary for U.S.D.A. registration and for the submission of a petition to the U.S. F.& D.A. We appreciate that in developing protocols with Dr. Calandra, Calchem's intention was to be helpful. We would, however, prefer to have the visit reports of discussions with the U.S. D.A. so that we are in a position to form some judgment of our own on the points giving rise to difficulty.

We note that you do not now intend to proceed with the registration of a liquid formulation of paraquat for home use and that it will not therefore be necessary now to investigate the effects of a 1 quart per U.S. gallon dilution, as suggested in your letter of the 15th January. We have ourselves decided against the marketing of a liquid formulation for home use in the United Kingdom, and have, as you may know, developed a granular formulation for this market.

In your earlier letter (15th January), the high dilution suggested for testing was 2 quarts paraquat formulation per 100 U.S. gallons, equivalent to a concentration of 0.18 per cent w/w, whereas your letter of the 24th February refers to a dilution of 1 gallon paraquat per 100 gallons U.S. We will conduct our tests with the more concentrated solution, unless we hear from you to the contrary. The earlier tests on dermal toxicity were conducted with dilutions of pure paraquat. We will endeavour to provide the additional evidence that the formulation is not more toxic than can be accounted for by its paraquat

content. We will also examine whether the addition of a surface active agent to the dilution increases the skin penetration. To this end, will you please let me have the details of the surface active agent used by you (Ortho 77), and if this is not readily available in the U.K., arrange for a supply to I.M.R.L. as a matter of urgency. You may rest assured that the necessary tests will be begun without delay.

We are glad to learn that you intend to deal with the supposed hazard to animals from bedding straw and to children and pets from sprayed herbage by studying residue levels. As we hope here to be able to show that paraquat adsorbed on base exchange materials is not absorbed through the skin, the combined information should be adequate to deal with these two questions.

We note your reference to Dr. Leary's opinion that additional toxicological information will not justify altering the proposed labelling cautions. While we agree that the chances do not appear to be high, we would hope at least to argue the case with Dr. Leary once more when submitting the further information on dermal toxicity which we are now in process of obtaining.

We have already submitted full details of our proposed reproductive study to the U.S. F.D.A. for their opinion, and have not yet had a reply. We are, of course, prepared to modify the plan of our experiments to accord with any suggestions received from them.

Determination of the subacute inhalation toxicity of dilute paraquat will best be done by Dr. Calandra since Industrial Bio-Test carried out the previous study of this kind, and I am writing to instruct him accordingly. Such experiments can be made to yield any result one chooses by manipulation of the particle size of the aerosol, and if comparison between the various dilutions is to have any value it must be done under the same experimental conditions. What is badly needed to give some practical meaning to these experiments is a study carried out in American field conditions to determine what amount of respirable mist is actually being generated when paraquat is used. As with residues, there would be no point in attempting to relate results obtained in U.K. conditions to those of the U.S.A. What are Calchem's intentions on this question ?

From : Dr. A. A. B. Swan

To : Dr. F. G. Toland

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24th March 1964

We note there is no reference in your most recent letter and attached scheme of tests to experiments on the inhalation of dusts. There is no clear indication from the previous correspondence that the request for this work had been made by the U.S. D.A. It is our view that it is not possible to design animal experiments which have any practical meaning in this context, and we would not contemplate embarking on these without direct discussion with the particular official raising the query. There is also no mention in the list of tests of the work on mallard and pheasant, mentioned among the list of tests in your letter of the 15th January. These would clearly best be done on U.S. strains, and if they are still required we will initiate them with Dr. Calandra. Will you please let us know what the latest position is ?

Yours sincerely,

(Dictated by Dr. Swan and signed in his absence)

Copies to :

Dr. G. R. Boom, Plant Protection Ltd.

Mr. T. O. Hutchison, I.C.I. (New York), Inc.

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