

23 JUL 1973 NTF

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For the attention of Miss N. T. Frost

Your ref                      Our ref

Date

17th July 1973

From ICI PPD/T/3/AJD/ii

Dear Norma

Paraquat Toxicity

1. At a recent meeting arranged by ICI (J) between Nichino and Dr. Robertson and Mr. Veitch of PPL, Yoshida who is the Nichino President took the opportunity of summarising his company's work on paraquat toxicology. That such a technical subject should be discussed at such a meeting again emphasises how important our distributors consider the problems of paraquat toxicity to be, both in relation to reregistration (see my letter of 19th March) and to sales against competition from Round-up.

I have enclosed the written summary of Nichino's work. They consider it very important that they should continue to do toxicological work of their own and be seen to be doing this work by the relevant Japanese officials. Their technical resources are very small, but their interests are as much political as technical. They also want to persuade Takeda to be seen to be doing practical work in this field, and although in the past Takeda have been reluctant to involve their Pharmaceutical staff in Gramoxone toxicology, this situation may change.

Naturally, ICI (J) will try as far as possible to monitor all further work done in Japan and it will be very much easier to do this if we are able to keep the distributors informed as to what IHRL are currently doing. In this context I have already given Nichino a copy of Table 3 (Paraquat Antidotes) from Fletcher's "Paraquat Poisoning" review, which otherwise I have kept confidential according to your instructions. Nichino would now like further experimental details and results, (see page 2 of their summary) especially for prednisolone, butazolidine,  $\gamma$ -tocopherol and oxygen. The only relevant report we have is IHR/178 but this only really covers reaction to multiple doses of paraquat. They would also like, if possible a more complete list covering all chemicals tested to date as antidotes and they are particularly interested in any data on erithrobic acid (erythro-ascorbic acid ?).

Miss N. T. Frost

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Although IHRL do not appear to be very optimistic about CNS active emetics, such as apomorphine, these drugs do seem to be of at least theoretical interest as possible Gramoxone adjuvants in the sense that their action, although delayed, will still draw attention to the would-be suicide more quickly than might otherwise be the case, and also they must increase the chances of successful treatment by forced diuresis. If this is so I would like to suggest this area as a possible research project for Takeda or Nichino if and when they ask us for ideas as to what they might do. Would you please ask IHRL to supply ICI (J) with any relevant background data on this subject in the form of reviews or references to likely candidate chemicals for testing.

From ICI's point of view the probable best we can hope for on the technical side is that Nichino or Takeda will come up with some preliminary results or new ideas that could be tested more rigorously at IHRL. However, politically, I think Dr. Robertson will confirm that it is important that Nichino should be supplied with all their requested data as a matter of urgency and that they should be involved in some practical work of their own.

You will see from their summary that they also asked about possible solid formulations of paraquat. We discussed the problems of production and deliquescence, but I would appreciate more details as to why the metallic salt formulations were dropped. Also will you please supply chemical details of the stented formulations now on trial in UK.

2. In your letter to me of 16th May you ask about the distribution of the booklets "The Treatment of Paraquat Poisoning: a Guide to Doctors". These have been supplied to our distributors and a total of about 10 hospitals, which have in the past requested copies after treating Gramoxone cases. Normally, a doctor or hospital confronted with a poisoning case will contact one of the distributors who may or may not pass the enquiry over to Tanaka-san of the PP Department in ICI (J). Up till now it has not been policy to advertise Gramoxone toxicity by taking the initiative of widely distributing treatment booklets or, for example, supplies of bentonite. This policy may however change in the future.

Again in the context of advice to hospitals, would you please provide a detailed reference to the best techniques for forced diuresis and can you please confirm that we should definitely contra-indicate the use of oxygen therapy.



17th July 1973

Paraquat Reregistration

1. I should like to re-emphasise the importance of getting pre-publication information on the WHO/FAO January 1973 meeting as requested via JRD's most recent Japan report, OV/73/3. If we can only claim the present temporary ADI and tolerances, the Ministry of Health here will be fairly critical in its examination of our data. Our petition will be submitted in early August and we must have some understanding of the WHO/FAO position by then.

The phrase "restricted to trained professional personnel" on P433 of the 1970 WHO/FAO Summary caused some consternation amongst the distributors, including Takeda, when it was translated literally into Japanese. It has now been retranslated as "restricted to experienced professional growers". What does it really mean?

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2. With reference to your letter to me of 14th May, would you please provide a summary of all toxicological results on the gut metabolites as soon as possible, bearing in mind our intended submission in August. Also, I had hoped that there would be available a summary review on animal metabolism, excretion and accumulation of paraquat. Can you confirm that the only such summary available is in your "Addenda" to WHO/FAO of June 1972.

3. Finally we have been asked to produce a detailed summary of paraquat crop residues world-wide. The most suitable document we have is the report by R. H. McKenna describing paraquat residues from 1964 and 1965 field trials. Can you please supply similar reports for previous field trials from which he derived some of the data in his general Summary in Table XIII. In particular we would like the data, including rates and numbers of applications and harvest intervals, for pre-emergence weed control (other than lettuce) and for top-fruit weed control such as vines pears and peaches; also is there any more recent data, as for example on citrus, vine or tea, other than that produced in Japan.

Again please remember that we would like to submit all this data in early August if possible. Sorry.

Yours sincerely



A. J. Davidson

cc: Mr. W. G. L. Austin, Far East and Pacific Dept.  
Dr. A. Robertson, PPL, Fernhurst

\* P.S. Also in the 1970 WHO/FAO summary there is a misprint on p431/2  
The aerosol concentrations should be  $0.1 \text{ mg/m}^3$