

Exhibit 26

CENTRAL TOXICOLOGY LABORATORY

Minutes of the ICI/Chevron Liaison Meeting held 30/31 August 1977

Present:

Dr A Calderbank)	
Dr R Hemingway)	Plant Protection Division
Dr B Johnen)	
Dr R D Cavalli)	
Dr H Franke)	Chevron
Dr J N Ospenson)	
✓ Dr M S Rose)	CTL
Dr L L Smith)	
Dr D Barrett	ICI (U.S.)

1. Progress in the treatment of poisoning:

(a) Monitoring cases

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Dr Cavalli informed the meeting that he was satisfied with the monitoring of cases in the U.S. His information indicated that there had only been one fatal case of accidental poisoning due to paraquat since 1974. He was currently involved with 2 cases of fatal poisoning which were suspected paraquat deaths resulting from deliberate ingestion. In both cases deaths were within a few days and the autopsy reports were not yet available. CTL will be kept informed by the previously agreed process. Dr Cavalli

RDC

indicated that it would be helpful if CTL informed him of poisonings when the outcome of the case was complete and the clinical details along with autopsy and tissue residues were available. This would reduce the number of communications required for a given poisoning and prevent the 'trickle' of information which he receives. He would, therefore, rather not receive the bulletins issued by the Secretary's Dept., Fernhurst.

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Dr Rose informed the meeting that CTL were continuing to assist clinicians treating paraquat poisoning with both analysis of plasma and the treatment

protocol. Regular meetings were held within CTL to collate the information on cases of poisoning. This information was made available to both PPD and Chevron. There are some problems with the current treatment and it seems that at least in 2 cases death resulted from the inhalation of vomit following copious administration of Fullers Earth. Dr Cavalli suggested that Dowex 50WX-8 resin 200-400 mesh cation exchange resin may be more palatable. It was also noted that with the introduction of an emetic formulation vomiting may have to be inhibited in order that treatment might commence. To this end preliminary results of studies carried out at the Huntingdon Research Centre indicated that Perphenazine may be an effective anti-emetic to the paraquat/emetic formulation. This work is still in progress.

(b) Research

Dr Smith outlined the CTL approach to research into paraquat toxicity. Basically the aim of this project was still to understand the mechanism of lung damage and to evaluate palliative treatments for paraquat poisoning. Although the mechanism of toxicity was not precisely understood, our understanding of the mode of action of paraquat had increased considerably over the years. Unfortunately this knowledge has not resulted in any major improvement in the treatment since circa 1975, but has been important in the critique of suggested treatments and indeed in rebuffing exaggerated claims concerning the toxicity of paraquat. Details of the research programme had previously been discussed with Dr Cavalli outside the meeting. Research into the toxic action of paraquat is continuing. Dr Smith indicated that a large number of laboratories were now using paraquat as a tool to investigate lung damage. It is important that CTL is able to communicate with those

groups and to do this CTL must be prominent in the area of paraquat research.

(c) Dermal studies at CTL

Experiments carried out by Dr Pratt on the morphological changes produced by paraquat in the skin of a variety of experimental animals (rat, rabbit, mouse, and guinea pig) confirmed that paraquat was an irritant in all the species studied. It is intended to carry out further work using the rat as an experimental model with the objective of investigating the precise morphological changes in the skin following exposure to paraquat.

The meeting was in agreement with pursuing aspects of dermal toxicity and CTL were asked by Chevron to consider investigating the chronic effects of paraquat on the skin.

(d) Epidemiological surveys

ICI: A report has been prepared by Dr K Howard of PPD on workers involved in the packaging of paraquat. Skin, eye and nose problems were found but there was no evidence of prolonged adverse effects associated with paraquat. A copy was given to RDC for comment.

Epidemiological studies were initiated by the EPA in California on 50 workers who sprayed paraquat compared with 50 who did not. The results are at present only in draft form and therefore cannot be properly interpreted. However Dr Cavalli did indicate his concern that adverse effects in lung and renal function may have been observed in those sprayers using paraquat, although those changes are not significant clinically. Dr Cavalli will advise CTL when he has further information.

RDC.

2. Improvements in paraquat analysis:

It is intended that within the next few months CTL will be able to carry out a radio-immunoassay for paraquat which has been developed by Dr Goulding's group at the Poisons Centre, London. This should permit the rapid assessment of the concentration of paraquat in the plasma and possibly other rat tissues. Dr Cavalli and ICI U.S. will be sent the methodology when the technique has been established. MSR

3. Work supported in other laboratories:(a) Fibrosis

Work is continuing at Trent Polytechnic, looking at fibrosis of the lungs, with a view to controlling the process.

(b) Antibody production to PQ

The MRC Radioimmunoassay team, Royal Infirmary, Edinburgh, have now produced a good antigen containing approximately 15 molecules of PQ attached per mole of BSA. This is some three times better than the antigen produced by the Guys group. This work will be supported for at least a further year.

(c) Microorganisms and PQ degradation

Limited support is being given to the Microbiological Research Establishment Porton, to develop microorganisms capable of degrading PQ and then to isolate the enzymes responsible.

(d) The dog work being carried out in California has now stopped. No apparent differences were seen in the lungs of those dogs which were inflated with N₂ when compared to those exposed to air.

Minutes of the Chevron/ICI Liaison Meeting held on 31st August 1977

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Present:

Dr A Calderbank)	
Dr P Slade)	
Dr D Foulkes)	Plant Protection Division
Dr R Hemingway)	
Dr B Johnen)	
Dr D Cavalli)	
Dr H Franke)	Chevron
Dr J N Ospenson)	
Dr M S Rose)	
Dr I F H Purchase)	CTL
Dr L L Smith)	
Mr M J L Clapp)	
Dr D Barrett	ICI U.S.

ActionPARAQUAT1. Industrial Biotest Laboratory - 2-year rat and dog studies

Dr Cavalli told the meeting that IBT had had severe problems at all levels within the organisation apart from right at the top, during the 60's until mid 70's. This had led to a loss in faith in IBT by the FDA/EPA, who are now asking for a complete review of all IBT studies which supported petitions. A team from Chevron recently reviewed a completed IBT study and the comments included the following:-

No concept of recording of data,

no dates recorded, only month numbers,

poor identification of animals,

one animal died 4 times,

two-thirds of the experiment were individually housed and one-third

5 per cage - no explanation and all data handled in the same manner etc.

IBT introduced a data destruction programme, having previously microfilmed the data; however the film was not available. The timing of this programme was unclear and only implemented 1 year ago (when they were already under pressure).

IBT made great use of common controls which were killed at different times from some studies.

As far as Chevron could ascertain, the raw data for both the rat and dog paraquat studies had been destroyed.

EPA have requested that Paraquat studies be reviewed. Since Chevron submitted the data to the EPA, it was agreed that they would review these studies, although PPD were the customer. Dr Franke will let Dr Calderbank have HF copies of all relevant data.

Legally, people are waiting to see what happens but as far as Chevron knew "nobody" had suffered from loss of sales.

In conclusion, there would be no new registrations until the studies have been repeated and evaluated.

2. Status of long term studies:

(a) 2-year rat study

The draft protocol for the 2-year study needs to be checked to ensure that it is in line with the latest EPA guidelines (June 1977). In particular Chevron felt that the animals should be individually housed. However, this could set a precedent for CTL with the EPA and CTL felt it did not necessarily improve the power of the test.

MHL will discuss this issue with Chevron and ICI U.S. in early October. A joint approach will be made to the EPA if necessary. In the meantime CTL will check out Life Science Research and other contract laboratories' capacity MHL for individual housing and the costs involved. The contract laboratory must also

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check this with the Home Office. Dr Cavalli will also arrange for Judy McGregor (Chevron) to comment on the protocol before MHL visit. In particular the age of the animals at the start of the experiment needs clarifying - the latest EPA guidelines suggest weanling animals. At present the preliminary study was to be carried out on the precipitated liquor (96.3% purity) and this was thought not to be acceptable. All future work should use the material straight from the plant which includes water and volatiles. The test material will be supplied from Widnes. Although the production plants at Widnes and Bayport operate the same process, it must be checked that the materials are the same. The material will need to be characterised in detail by Mond Division.

(b) Mouse carcinogenicity study

IFHP made the following comments on the previous study:

The tumour data had been handled in an unsophisticated fashion, the staff who carried out the study were no longer employed at CTL, the pathologist at that time did not believe autolysed animals should be examined and consequently there were a large number of animals in the study that were not examined, there were some inconsistencies between the protocol and the study; e.g. 11 animals in some cages; only one group finished with the correct number of animals; other groups fell in the range ± 2 .

In conclusion, considering the number of animals with no histology, the study should not be resurrected. It was accepted that the study should be repeated and the cost was discussed. After further discussion, it was agreed that as much information as possible should be salvaged from the study (i.e. the tissues should be re-read to ensure that tissues not mentioned

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in the original report were indeed normal). Chevron agreed to inform the EPA that we were reviewing the study. Having accepted that the study has to be repeated, the course of action was discussed. Three responses to EPA were seen to be possible:

IFHP

Chevron

1. Reply to EPA letter, agreeing that study not acceptable.
2. Prepare a critique of the original study.
3. Re-read the pathology (6-9 months' work, not possible within CTL) and use data as a "holding" position until repeat study carried out.

Chevron were already taking option 3 on some of their chemicals. Therefore, it was agreed to adopt option 3.

Since there was no petition rejection, Dr Ospenson will write to EPA informing them that we will be implementing an in depth review and critique of the study. Dr Cavalli will ask Judy McGregor to comment on the detailed protocol, in particular on the issue of launching the study using one batch of animals versus using replicates and the necessity of the very full pathology. Dr Litchfield will organise discussions in CTL on those issues and then discuss them further with ICI U.S. and Chevron before visiting the EPA in Oct/Nov.

NO

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MHL

(c) Reproduction study

MJLC commented on the previous study and highlighted some of the inadequacies: dates of birth missing for some of the early litters, no abnormalities changed protocol half way through study and improved recording system, but no revised protocol, stopped measuring food at one stage because 'food unsuitable', gross necropsies scheduled to be carried out but no reports available, the body weight effect reported was an artefact.

It was accepted that the study should be repeated but delayed until next March.

The proposed protocol had not been sent to the EPA for comment. Dr
Branke to check the delay.

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Dr Cavalli will arrange for Judy McGregor to comment on the protocol. In
particular, classification of EPA thinking on including teratology in the
study and the amount of pathology required is needed. MHL will discuss
this during his visit in October.

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3. Status RPAR/restricted use:

The EPA now have a new project manager reviewing Paraquat, Bill Caniglio.
He has raised questions about the following:

- a) Toxicity of paraquat to hares reported in France - ? relevance
to USA rabbit/hare etc.
- b) Toxicity to bees - he is concerned about ground dwelling bees.
- c) Effect of paraquat on bacteria - soil nitrification. (BJ stated
that there are 3 publications and 4 internal reports available
all demonstrating no effect).
- d) Could it influence the capability of ruminant animals to utilise
food? (Some work has been done in heifers and cattle).
- e) Use of paraquat in no till farming - did it alter habitat in top
6" of soil.

Other concerns relating to the RPAR were:

- (i) That the EPA were in receipt of a draft report of an epidemiology
study carried out by the State of California. Although there were no
clinically significant symptoms seen in the paraquat exposed group, the
authors claimed to have seen alterations indicative of effects on the
kidney and lungs.
- (ii) The EPA have received a draft report of an inhalation study in
rabbits carried out at the University of Iowa. This study claims that

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rabbits exposed to a paraquat aerosol developed lung changes and that the urine paraquat levels in these animals was similar to those in spray workers (Swan 1969). The authors therefore concluded that spray workers might be at risk.

PPD agreed to put together information on the environmental effects of Paraquat for Chevron. CTL will decide what other information can be used (epidemiology) to support the safe use of paraquat and critically review the rabbit study.

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MSRRestricted use category

It is likely that paraquat will be placed in the restricted use category. This should not affect sales since air application is already restricted, and it will be relatively easy for most farmers to become certified users. However the arguments for putting Paraquat in this category are based on dermal and ocular hazards which are not realistic.

4. Safer formulation:a) Stench

? Chevron are awaiting plant to come on stream. They have applied for registered label, but this should not be needed. Concentrated formulated pack should be available, 18th October?? Blue stench formulation is being marketed by ICI in Belgium and will possibly be marketed in Ireland as well.

b) Emetic

The FDA have not yet reviewed the data (August 26th). It would be useful to demonstrate benefit in a suicide case. Dr Ospenson could then go higher up the EPA tree. The emetic formulation has been on sale in Western Samoa since June. Information on the emetic is likely to become public at the

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end of this year. CTL reported that it is possible to analyse for the chemical in both blood and urine, and details will be passed to Chevron and ICI U.S. shortly.

MSR

5. Status of Paraquat Registration:

At best, tolerances and labels will remain and no new registrations will be given. Some minor changes and restrictions are expected.

6. Publications:

a) Peoples & Maddy Paper

RDC pointed out that the EPA were not too worried by this report. At least one of the authors had disassociated himself from the report.

b) RDC had already dealt with Medical World News.

c) There was considerable discussion of the proposed paraquat book. All the chapters were not complete, and the decision was deferred until all the drafts had been received.

d) The publication by Carere of his Ames' test results on a number of pesticides, including paraquat and Captan was pointed out. CTL were of the view that little more could be done at this stage.

e) This paper (Leahey) is with Chevron for comment.

RDC

f) The meeting agreed that there were no reasons why these papers should not be given at SOT in 1978, especially since there will inevitably be a number of others on Paraquat at this meeting.

7. Any other business:

Diquat Dichloride

Dr Slade stated that work was continuing and that Organics would know if they had a process by the end of the year.

Will the long term toxicology be adequate? MHL to arrange for relevant studies to be critiqued.

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MHL

8. Next meeting:

There was discussion of the proposed date for the next meeting and CTL requested that it should be immediately prior to the SOT meeting - 8-10th March 1978.

MSR/MJP 28 Sept 77.