

Exhibit 29

ICI PLANT PROTECTION DIVISION

p/2/2.5.

MEETINGS WITH CHEVRON, 30TH JUNE AND 2ND JULY 1980

file

15 JUL 1980

SUMMARY

Chevron now confidently expect that an RPAR will not issue on paraquat before early 1981 (latest date published by EPA is October 1980), and the chances of an RPAR being issued at all seems to be declining. As we already knew Clement Associates have been assigned the job of reviewing the data base on PQ for EPA.

A Senate House Committee has decided there is no increased health hazard from smoking paraquat treated marijuana and accused the HEW of interpreting data to support its own pre-determined conclusions of harmfulness.

There have been no accidents with PQ in the USA in over 12 months and the number of attempted suicides is still low. Chevron are having relative success in treating PQ poisoning cases, which may be due, in part, to the smaller quantities generally ingested.

Chevron have re-activated the emetic petition with EPA by submitting an alternative product formulation.

A useful visit was made to the University of California (Davis) where an EPA funded paraquat aerial spray exposure trial was conducted last Autumn. This was jointly organised by the Depts of Agricultural Engineering, Environmental Community Health and Medicines. The data has not yet been fully analysed and assessed, but there appear to be no problems regarding exposure levels of PQ. This supports the conclusions from the joint ICI/Chevron study conducted in California about the same time.

Chevron has lost its law suit against EPA which claimed that EPA's use of Chevron's pre-1970 data to support "Me-too" registrations was unconstitutional. Chevron have appealed against the decision. The Registration Division of EPA has been instructed that it must not act until after the appeal, the date of which has not yet been fixed. It could take 6 months or longer.

Aceto has still not filed a PQ registration application.

Chevron sent a delegation to EPA to demonstrate how their efforts in "Product Stewardship" - advice on medical treatment, drift control etc - with paraquat has helped to reduce risk. This was apparently very well received and not previously appreciated in EPA, and Chevron believe there is now a good chance that any prospective registrant will have to demonstrate similar capabilities before being granted a "Me-too" registration.

YAS16

We updated Chevron on all the repeat PQ chronic studies.

Dr D Clegg (Canada Food & Drug Directorate and past chairman of WHO expert Committee) has been given the job of evaluating all the audits of IBT studies on behalf of EPA. We had a useful discussion with him at the Downingtown Conference concerning our current cataract problem in the repeat PQ rat study. He told us that a major US company had a similar (but more severe) cataract problem in a repeat IBT study on one of its products. There may be some merit in establishing contact with the Company to share our respective data base on incidence of cataract in controls.

We were also able to confirm that Chevron has a problem in its repeat IBT rat study on Orthene, since there is a brain cholinesterase effect at the lowest feeding level.

Pressure is developing in the USA against 2,4-D - suspect oncogenic and alleged delayed neurotoxic effects. More products showing oncogenic potential at high doses are coming through the RPAR process after risk/benefit analysis.

ENVIRONMENTAL HEALTH CENTRE, RICHMOND

Present:	Dr J N Ospenson	}	Chevron
	Mr R D Cavalli		
	Dr J Ford (for PQ Poisoning incidents)		
	Dr T B Hart	}	PPD
	Dr A Calderbank		

1. Paraquat Chronic Rat Study

The subject of the incidence of cataract in this study was discussed in detail and Chevron updated with the latest information (at week 115/116). viz Males sacrificed at week 112/113.

- (i) Ophthalmoscopy just prior to termination revealed a further progression in the degree of severity since the last assessment (3 weeks previously). Although there was an increased incidence of early stages of cataract in the control groups, the gap between the controls and lowest dose group had widened.
- (ii) There were no treatment related effects with regard to blood chemistry, haematology or urine analysis.
- (iii) Highest mortality in the females is now in Group 3 at about 45%. The females are scheduled for eye examination at week 118. This may coincide closely with the time when the group reaches 50% mortality (termination criteria). The following was agreed, according to the options:
 - (a) If termination criteria on the females is reached before 118 weeks. Carry out ophthalmoscopy immediately before termination. Provide Chevron with the eye results before termination (if logistics allow).

- (b) If females survive to 118 weeks before reaching termination criteria. Carry out ophthalmoscopy as previously arranged. Communicate data to Chevron.

Two options then remain. If the termination criteria is reached within two weeks, i.e. between 118 and 120 weeks, the animals may be sacrificed without further ophthalmoscopy. If the termination criteria is reached after this period, i.e. longer than 2 weeks after the last eye examination then a further cataract assessment should be made and the results communicated to Chevron prior to termination.

The following points arose during further discussion of this subject:

- (i) Difficult to decide what the regulatory implications might be, but it was felt that there was no added risk from the food residue point of view. We may however need to provide what human data could be made available on exposed groups, (packers/formulators or sprayers). Personnel in Chevron formulation plants would not be suitable because they handle many different products in addition to paraquat. Plant personnel on manufacturing sites would not be suitable since they are more exposed to intermediates than paraquat itself. We would need to discuss (within ICI) the value and relevance of a study on packers at the Yalding and Mond sites. It was however felt important to carry out an ophthalmoscopic examination on the Malaysian sprayers previously involved in the recent epidemiology study, since their history of paraquat exposure is well documented. This will be further discussed within ICI.
- (ii) The importance of obtaining background information on the natural occurrence of cataract in different strains of rat was discussed. Chevron have contacted CIIT for information since it is known that they have carried out several cataract studies. One major US Company has a cataract problem with one of its compounds (repeat IBT study) - see note of AC/MHL discussions with Dr D Clegg, Canada HPB. Chevron were in favour of asking Dr Clegg to put ICI in touch with this Company. This possibility would be further discussed in ICI.
- (iii) Detailed comparison of DQ and PQ with regard to the incidence and development of the eye lesion should be made (this is already in hand).
- (iv) We would need to try to establish if it is a chronic effect caused by continual exposure in the diet over a long period or an acute or sub-acute effect caused by relatively short exposure to senile rats.
- (v) A literature search should be carried out to assemble any information on chemically induced cataract in humans. (Some drugs were thought to produce this effect).
- (vi) The paraquat dog study should be extended to at least 2 year duration.

- (vii) ICI and Chevron would separately consider other possibilities for experiments or information gathering and firm proposals for action agreed at our September meeting in England.
- (viii) Huntingdon Research Labs were said to have a chronic study on a bipyridylium compound (unspecified) which is currently showing cataract. CTL is already trying to elicit further information.
- (ix) Dr D Clegg (Canada) has undertaken to review IBT data validations on several products, including PQ, for EPA. (see notes of discussions with Dr Clegg - Appendix 1).

2. Epidemiology and Exposure Studies

- (i) Paper for publication of the clinical aspects of the Malaysian study has now been agreed and submitted for publication (Brit. J. Ind. Med). This paper will be published concurrently with the exposure study carried out on the same group of workers.

Chevron made several detailed comments on the draft paper and report of the latter study. Some more general comments were:

- (a) The paper for publication should relate more directly to the epidemiology study. The full report is very difficult to follow.
- (b) The relationship to the rat dermal LD50 should be more explicitly stated and the variation in the published figures for the LD50 values explained. The significance of the "worst" exposure data should be more thoroughly explained. Consider expanding this section and possibly including information on excretion and non-accumulation of paraquat.
- (c) Keep to a single set of units in the text to express exposure, e.g. mg/kg/day.
- (d) There should be a reference to the more recent (CTL/Huntingdon generated) data on inhalation.
- (e) The interpretive aspects of the work needs to be more thoroughly brought out in order to derive maximum benefit from the publication and to try to avoid any misinterpretations.

At a later meeting (at Central Research) Dr Stelzer stressed the importance of providing EPA with the full reports of both the epidemiology and the exposure study before the papers appear in print.

- (ii) Chevron are still having difficulty locating a suitable consultant epidemiologist to review the data from the Californian epidemiology study commissioned by EPA. Cavalli is still hopeful that he will have the data reviewed by the time of our next meeting in England (Sept/oct).

- (iii) Chevron were provided with a summary of the results of the Californian aerial exposure study. They are currently reviewing this, together with the Rose/Smith "Assessment of the Potential Inhalation Hazard Associated with the Use of Paraquat".
- (iv) No further information was available from the proposed exposure studies of Nigg (Florida), Lavy (Texas) and Hertline (Hawaii).
- (v) Discussions with Professor Akesson (Davis, California) concerning his EPA-funded aerial exposure study with PQ are recorded in a separate note.

Poisoning Treatment/Incidents

There have been six suicides and no accidents with PQ this year in the USA. Five out of eight attempted suicides using PQ in 1979 survived after treatment.

Patients need to be admitted within 24 hours of PQ ingestion (they are rarely admitted in under 12 hours) and Chevron are still advising haemoperfusion or dialysis, following treatment with clay adsorbent.

A recent attempted suicide patient (12 hours after ingestion showing 3.2 ppm PQ in plasma and 700 ppm in urine) was alive 14 days after ingestion. The patient (female) was still on dialysis after this time and blood levels were 0.1 ppm. The kidney was still functioning.

Cavalli promised to write-up and forward to ICI the records of incidents and successful treatment which have occurred at the Chevron PQ packing sites.

We should forward a copy of Dr Hart's letter to the BMJ rebutting an earlier paper alleging lung damage from inhalation of nebulised PQ.

Central Research, Richmond

Present:	Dr H G Franke	}	Chevron
	Dr L Stelzer		
	Mr C Freeman		
	Dr T B Hart	}	PPD
	Dr A Calderbank		

Paraquat/RPAR Status

A recent (April 1980) EPA publication provides information on all products under RPAR and pre-RPAR review. Paraquat is still in the latter category. Three triggers are now listed as:

1. Medical treatment (lack of antidote).
2. Chronic toxicology
- and 3. Data gaps (oncogenicity and mutagenicity).

However because of the continual change in stated triggers and because experience with other products has shown that new triggers can appear, even after PDI (First Position Document) has been issued, we believe we should continue to be prepared to answer all of the most likely triggers highlighted earlier. In fact "chronic toxicology" could relate to almost anything, including effects on wildlife.

Messages received from Don Dye (Chevron's representative in Washington) are that pressures on paraquat seem to have relaxed somewhat. EPA have contracted out the review of PQ data to Clement Associates (ICI learned of this independently through contact with Dr M B Green, former Mond Div employee, now with Clement Associates). Chevron now believe that it will be at least early 1981 before an RPAR is issued, and they also believe there is a 50:50 chance that an RPAR may not be issued at all. Some of the reasons for this more relaxed view are:

- (i) the effect of Dr Rose's input into the marijuana saga (see below) which has received more favourable publicity.
- (ii) negligible accidents and few suicides in the USA and relative success in treatment of poisoning incidents (see above).
- (iii) no significant oncogenic concern regarding paraquat (contrast most compounds in RPAR).
- (iv) the apparent receding in significance of the EPA sponsored Californian epidemiology study.

Reports received from Chevron, and independently through contacts at the Downingtown Conference, are that Clement Associates are making a poor job of the reviews undertaken under contract from EPA.

It was agreed that neither ICI nor Chevron would supply Clement Associates with data which had not first been sent to EPA. There seemed little value to be gained from discussions with the EPA paraquat RPAR manager until after Clement Associates had completed its reviews.

Paraquat "Me-too" Registrations

A delegation from Chevron (Tanner, Enin, Ford and Stelzer) had a meeting earlier this year with Ed Johnson and Doug Kemp of EPA. This took the form of a 1 hour presentation from Chevron in which they described how their "product stewardship" is instrumental in minimising serious problems from drift in aerial application, accidents and poisonings. This was illustrated by slides presented at technical fly-in meetings, meetings with growers, meetings on drift control, Chevron aerial application handbook, nationwide network for treatment of poisoning, work with hospitals, analytical service etc.

Chevron said that the presentation was extremely well received and that Ed Johnson admitted he had no previous idea of all these measures taken to avoid mis-use, prevent accidents and treat poisoning cases. He asked if Chevron would repeat the exercise to a bigger EPA audience, including Taylor (product manager) and some from the Toxicology Branch. This is currently being arranged.

EPA will not grant a "Me-too" registration if the "incremental risk" is increased. Chevron argue that there will be an incremental risk if other Companies market paraquat without all the above back-up advice and service. It is possible that EPA may grant a conditional "Me-too" registration on the condition that the competitive company demonstrates its ability to offer similar services.

Aceto at present has no registration application pending.

Law Suit

Chevron has lost its law suit against EPA in opposing the right of EPA to allow data submitted by Chevron pre-1970 to support registration applications by other companies, with regard to naled (insecticide) and paraquat (see Appendix 2). Seven similar suits brought by 19 companies are still pending and they are slowing down the "Me-too" registration process considerably. EPA hopes that the decision on the Chevron case will influence other courts in EPA's favour.

Chevron have now filed an appeal - the date of the hearing could be the end of this year, or even later. The Registration Division of EPA have been notified that they must not grant any naled or paraquat registrations until after the appeal is heard.

Marijuana

A US Senate House Committee has recently (June 1980) concluded that marijuana smokers are unlikely to inhale enough paraquat in a year of smoking to permanently damage their lungs. (see press report, Appendix 3). This is in conflict with the position taken by HEW, who have now lost credibility on this issue. It is suggested in the press release that HEW interpreted the data base so as to justify its predetermined conclusion of harmfulness.

Emetic

Chevron have re-activated the emetic petition. This has been done by submitting an alternate formulation for registration (which usually gets more rapid response from EPA), referring to the original emetic petition.

Inhalation Studies

The CTL response to the EPA questions on the first two Huntingdon reports has not been forwarded to EPA. Chevron would prefer to await the third analytical report with the summary which will draw together the conclusions from the three reports.

Soil Studies

Chevron have finally (in May this year) laid down a new high rate/long term PQ residue trial in very sandy soil (Florida). They have completed the soil analyses of the samples from the ICI PQ & DQ high rate trials in Goldsboro. The results will be forwarded to Goldsboro.

Photodegradation

Chevron have agreed to set up a degradation study of PQ in very sandy soil using samples in quartz flasks exposed to sunlight, following essentially the same protocol as that used at JH. They plan to start the study in July (1980).

Diquat

- (i) Specification: There will be a need to submit a revised specification for DQ to EPA only if the higher levels of 2,2'-bipyridyl found using the new analytical method are above the level quoted in the specification.

ICI will provide Chevron with details of the current analytical data. The specification to Chevron will need to be renegotiated.

The earlier notification to EPA of change in formulation (omitting molybdate) has been accepted by EPA.

There has been no response to date on Chevron's letter concerning ethylene dibromide content in DQ.

- (ii) Potato and Water Petitions: Still no response from EPA.

Trials with DQ/alginate are planned for later this Summer.

Morfamquat

Pressures on 2,4-D in USA are mounting (suspect oncogenic and delayed neurotoxic effects) and Chevron are still keen to evaluate morfamquat more fully. A summary of the available toxicological data has been prepared by CTL and forwarded to ICIA who are currently preparing a legal agreement.

A CALDERBANK

AC/DC
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