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NOTES ON ICI/CHEVRON LIAISON MEETINGS

18TH AND 19TH SEPTEMBER 1978, JEALOTT'S HILL AND FERNHURST

Those attending:

Dr N Ospenson Dr H Aroyan Dr H G Franke Mr R D Cavalli Mr L Hopkins Mr A Assad*	CHEVRON
Dr L B Massie Dr R E Ridsdale	ICIA
Dr M H Litchfield Dr M S Rose+ Dr L L Smith	CTL
Dr J T Braunholtz* Dr A Calderbank Dr B G Johnen+ Mr G A Willis Dr P Slade Mr R A Morrison* Dr D Riley+	PPD

+18th September meeting only. *19th September meeting only.

The meetings were chaired by Dr Calderbank (18th September) and Dr Braunholtz (19th September).

PARAQUAT/RPAR

1. General Situation

There is growing evidence that EPA are treating RPAR more as a scientific review and are most willing to discuss the data with industry. They have no apparent desire to ban useful products and even when risk criteria have been exceeded and rebuttals failed they have turned to label changes to reduce the hazard. Nevertheless there is also evidence (e.g. 245-T developments) that apparent illogical and hasty action can follow when there is strong and vocal public reaction. Such a situation could be created with paraquat if there were to be a particularly unpleasant accidental poisoning incident in the USA. Mr Cavalli said there has been seven PQ intoxications in USA this year (all deliberate ingestions - three died). He highlighted one case in Wisconsin where the victim (who died) denied deliberatley swallowing PQ and alleged exposure to spray mist. Chevron expect this case to come to trial. (Details will be forwarded to Dr Rose)

RDC

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There is little change with regard to the proposed PQ/RPAR. (Reported in the notes of the July 1979 Meeting). The EPA Project Manager (Mr Tom Miller) is finishing off his work on Treflan (PD2/3 published in the Federal Register, 30th Aug) and is now expected to turn more of his attention to PQ. Chevron believe it will be early in 1980 before a PD-I on PQ is prepared.

2. PQ/RPAR Strategy

New information from experimental work on the previous (coniglio) RPAR triggers has been generated during the past 1-2 years. Several new reports are now available and more will be prepared before the end of the year (see Appendix 1). There was some discussion on the best method and timing of presenting this new data to EPA. It was agreed that Chevron's Don Dye should keep in close touch with Mr Miller and advise when he or his team are ready to discuss PQ. Some of the reports could be forwarded prior to the discussion, others could be brought along to the discussion. It may be necessary to treat the environmental and toxicological matters separately.

The appropriate actions will be decided after Don Dye has spoken to Miller and a date for a meeting arranged. It was agreed that both ICI and Chevron should be represented at the meeting with Miller and his team.

3. Environmental

(a) Hares: No change - all reviews and papers ready. Ammonium sulphate (at 20 kg/ha) has been used with paraquat in some trials in France as a joint CTL/SOPRA/Giban cooperation and some repellancy to hares detected. Dr Riley will arrange for the French report of the trial to be translated.

DR

(b) Birds: All work completed. The only outstanding report (on pheasant egg hatchability) is due to be issued mid October.

(c) Soil: The most important reports (relating to Frensham and other trials in sandy soil) are either complete or nearing completion (see Appendix 1), as is the review of all available soil work.

Chevron have planned their repeat Florida soil trial to start January 1980. A similar ICI trial at Goldsboro was started in July. Soil samples from the two sites would be exchanged in order to relate SAC and tight binding capacity measurements.

DR/HGF

Chevron will start an experiment in Spring 1980 at Richmond to evaluate the photodegradation of of PQ in very sandy soil (Florida soil) using the ICI protocol.

HGF

Chevron stressed that EPA are starting to pay serious attention to the effects of chemicals on non-symbiotic N-fixing soil microorganisms.

The German authorities (BAA) are expected to publish shortly data obtained from a Berlin orchard which has allegedly reached PQ saturation in its top 5 cm of soil. This is a sandy soil with high organic material content and presently contains 40 ppm PQ in the top 5 cm. ICI have now found tha phytotoxicity is due to the low pH of the soil and not PQ.

4. Toxicology

(a) Dermal: No change. This is not a trigger but recent publication of S. African incident could precipitate concern. Dr. Cavalli would review and comment to

RDC Dr. Rose on the publication (in Thorax) by mid October. He would also forward case histories of the dozen incidents of PQ exposure which occurred in the Chevron packaging plants - all satisfactorily treated and recovered.

LLS Dr. Smith would prepare a proposal for further dermal studies.

(b) Inhalation: The three inhalation studies have now been completed. The first has been reported, the second and third are scheduled to be reported October and end of December 1979 respectively. A summary report drawing

LLS/RDC together all this work will be prepared jointly by ICI and Chevron as soon as the final report is issued.

(c) Lung instillation: Work completed and reported. Zavalla has agreed to be a co-author of a paper to be published in Brit J. Ind Med. The paper has been written and the final copy will be sent to Zavalla for approval. Plan to submit for publication in October.

(d) Epidemiology: EPA have recently stressed the importance of epidemiology data in assessing actual as distinct from potential hazard. This emphasises the importance of the Malaysian study.

(i) Malaysia: The data from the Malaysian study is still being collated and statistically evaluated. Dr. Howard will be returning to Malaysia to obtain more details of the history of the various groups involved. It is expected that a draft report on the whole study will be available in December 1979.

(ii) California: CTL have been unable to find a suitable consultant epidemiologist who might be employed to evaluate the data from the Californian study (1st year). Chevron will renew their efforts to find a consultant (a man at Stamford University was mentioned).

(e) Field Exposure Studies:

(i) ICI/Chevron - California

An aerial exposure study is being jointly planned by ICI/Chevron to start in October. Difficulties are currently being experienced in obtaining a suitable cooperator to do the spraying. Assuming the trial can be organised for October then a report could be expected in January 1980.

(ii) Akesson - California

This is a trial being funded by USDA at Davis involving three groups viz. Agricultural Engineering (Akesson & Yates), Environmental Toxicology (W. Kilgore) and Medical (Dr. Barbone). Details of the proposed trial have been described by Dr. Chester who visited Davis in July accompanied by Chevron personnel. The programme is being coordinated by Dr. Wendal Kilgore and is due to start in October. Monitoring of personnel and the local area will take place before, during (two samplings middle spray schedule) and after an actual cotton desiccation spray schedule. The monitoring of the local area (Bakersfield) will be done at 10 sites which includes four town areas and six smaller communities all in about 150 mile perimeter. 25 people (pilots, loaders and flagmen) will be monitored for exposure and effects on health. Emphasis will be placed on potential for inhalation exposure. Close contact with the progress of this trial should be maintained.

Chevron (Dryden?)

It may be possible to arrange a visit to Davis at about the time (Jan/Feb) of the next ICI/Chevron liaison meeting.

(iii) Nigg - Florida

Chevron have no further knowledge as to whether this trial will be run. Nigg has still not provided a protocol. The proposal however was to use tractor mounted sprayers in orchards and possibly back-pack sprayers in golf courses.

(iv) Hertline - Hawaii

Chevron reported that some exposure studies had been carried out by a Mr. Hertline of the Poona-Papaya Co, Hawaii on operatives who have been spraying PQ and little else for 7 years with no turnover of staff. The operatives used rubber boots, overalls and respirators, and the desire was to dispense with the use of respirators.

Air had been sampled in the breathing zone and no PQ detected (limit of detection 0.07 mg/m^3). Chevron agreed to obtain more details of the spraying equipment, nozzles, pressure etc, and the equipment used to make measurements.

RDC

No decision has yet been made of what to do with the Akesson report on calculations of exposure levels, which received detailed criticism from ICI.

Dr. Massie agreed to look at the original calculations made by Dr. Barrett in this area and also to assess the relevance of calculations made of potential exposure levels of benomyl in the recently published

LBM

PD2/3 document on benomyl. A summary paper on exposure would be prepared as soon as the new results were available.

(f) Emergency Treatment

This was now believed unlikely to be a trigger. Nevertheless Dr. Cavalli has prepared a new draft of the
RDC response with more material added. This will be available for comment shortly.

(g) Reproductive effects

No further work done or needed (apart from the repeat long-term study). A response prepared by MSR is available.

(h) Teratology

Some concern was expressed by Chevron since this item originally noted as a data gap had become a possible trigger in the latest list published by EPA. Dye had questioned Miller on the significance, but Miller said there was no apparent reason and it was probably an error.

A review of PQ/teratology work is available and there is no significant area of concern.

(i) Data Gaps

(a) 2 year rat study: Study due to be terminated April 1980 and reported March 1981. At the interim kill no effects on lung noted even at top dose (150 ppm), although there was a clear effect on body weight gain at this level of feeding.

(b) Mouse study: Terminated September 1979. Due to be reported March 1981 - but could be earlier.

The "old" CTL study has now been rewritten but there are still discrepancies in the data. These are
MSR/MHL being checked and the significance of the errors will be assessed prior to a decision on whether or not to issue a revised report.

(c) Multigeneration study

A copy of the protocol of a new study with Alderley Park strain rats was given to Dr. Cavalli for comments. The study was due to start towards end September and would involve 3 generations, although a report could be prepared (specifically for EPA) at the completion of two generations. The top dose was 175 ppm PQ in the diet.

No attempt will be made to re-evaluate and rewrite the "old" CTL study.

(d) Dog study

Preliminary 6 weeks feeding (dose levels 0.3, 1.0 and 3.0 mg/kg/day) prior to a new study is due to start at Hasleton Labs, UK in October, main study to start in February 1980.

Dr. Cavalli was provided with the protocol of the preliminary feeding study. Chevron could not decide whether a new study (and of what duration) would be needed by EPA. A decision from Chevron is needed
RDC before the end of this year. In the meantime ICI will plan for a 6 month study (present EPA guideline) and provide a protocol to Chevron for comment.

(e) NCI Proposed study

ICI had received information that NCI were proposing to carry out long term rodent studies on PQ. They have been notified that new studies are in progress. ICI was informed that they would like to review the data but would not do anything in the meantime.

(f) IBT studies

Chevron have been requested by EPA to supply validation of the IBT studies done on PQ, within 2 to 5 months. Chevron are planning to respond by end of this year. From experience EPA are saying that no IBT rodent studies would be validated. Chevron have agreed with EPA that they will audit the available data from the point of view of finding any adverse effect which was not reported. The main concern with PQ is with the long term studies (rat and dog). If 80% of the raw data is available then it may well be worthwhile
RDC attempting a proper validation. Dr. Cavalli will keep ICI informed with progress reports.

ICI have had a preliminary look at the raw data available on the IBT dog study and concluded that it would be impossible to validate that study.

LABEL CHANGES

No change in policy, but it seems likely that some label changes, or changes in emphasis ultimately will be needed.

BENEFITS

The Chevron package is with ICI awaiting comments. It is a compilation of data and requires drawing together with conclusions
LH and a summary. This was promised by end February.

The ICI document on worldwide benefits was handed over at the
LH meeting as a first draft and comments from Chevron solicited.

There was some doubt as to whether USDA had been formally requested by EPA to generate benefits data. Don Dye would be asked to establish the position and Chevron would establish contact with USDA once a firm directive had been given by EPA.

PARAQUAT (Non-RPAR matters)

1. Registration Status

This is shown in Appendix 2.

Federal labels are being held up because of the impending RPAR review; nevertheless Chevron have been steadily expanding the market by obtaining State labels. There will however be no major expansion based on existing labels or arising from new use petitions presently held up by RPAR. Growth is expected in sunflower harvest aid because of the rapidly expanding acreage of this crop (sodium chlorate competition) and as a soya harvest aid.

2. Competition

Competition with glyphosate is developing in wheat, where the rate of "Round-up" is being reduced to less than 1 pint/acre (Monsanto recommendation), and in trees and vines, where there are advantages in perennial weed control. The non-restricted use classification of glyphosate is a point in its favour but more difficult to quantify. Special types of application (eg rope wick dragged along the crop) are becoming very popular.

The efforts made by Aceto to legalise "their PQ label" and sell Taiwanese PQ have been squashed by an EPA Administrative Law Judge. The statement from the hearing reads:

"A review of the case has convinced me that the registration was legally cancelled and before registration can be reinstated that data compensation provisions of the law must be met."

Chevron believe that Aceto will appeal or try a different approach.

3. Revised Specification

This was submitted to EPA on 22nd June 1979 and was acknowledged without comment.

The FAO revised specification has now been accepted for consideration by the committee meeting in Rome in October. ICI will be sending a representative.

4. Safer Formulations

(a) US Emetic petition still with FDA. No progress. Dr. Rose reported a UK suicide case in which the victim recovered after taking a lethal quantity of PQ containing emetic. The amount swallowed, the presence of emetic and other aspects of the case (eg copious vomiting and blood PQ levels) are well documented. This represents the first, fully authenticated case where the presence of emetic (plus treatment) has clearly saved a life.

(b) Stench. Chevron are not proceeding with adding valeric acid stenching agent to paraquat at present. Three of their four packaging plants are equipped and they have run one successful trial. However there is concern that the introduction of stench may cause further problems in the market place, especially in cotton desiccation where odour in other products seems to be a deterrent to sales.

5. Drift

Complaints are steadily decreasing.

Out of a total of 23 law suits, 7 are still open, 7 have been settled at a cost of $17,000 and 9 have been closed at no cost to Chevron.

Nalcatrol is on the suggested list for including with PQ applied by air in California but is not mandatory.

6. Marijuana

Califano, secretary to HEW, shortly before leaving office, made a statement alleging hazard to smokers from PQ contaminated marijuana. This statement was apparently based on views given to HEW by Dr. Renate Kimbrough, Centre for Disease Control, Atlanta. Califano's statement has recently been upheld by the new secretary to HEW, viz. Patricia Harris. Congressman Wolfe, the Chairman of the Select Sub-Committee on Narcotics Abuse, is sympathetic to the marijuana eradication program involving the spraying of paraquat and would like to extend the program from Mexico to Columbia.

It was agreed that ICI/Chevron should provide any support needed to Wolfe's Committee, or in briefing Dr. Kimbrough on the new inhalation/instillation data. The first action would
MSR/RDC probably be for Dr. Rose to help Wolfe's Committee review the data on which Califano's statement was based and also to discuss the recently generated data. It was felt important to provide this support in order to help squash the growing concern about the inhalation hazard of paraquat, which could have repercussions on the RPAR situation.

7. Publicity

It was agreed that ICI would provide Chevron with a summary
PS of its experience of Public Relations with PQ in the UK, with copies of any literature or notes used in PR exercises.

DIQUAT

1. Aquatic Tolerance Petition

Chevron recently learned that the original petition had been returned (4 months earlier) to the EPA Project Manager with a Disapproval stamp. Chemistry Section (with Dr. J. Cummings) is still the main stumbling block to progress - since the Office of General Council (OGC) had previously approved the document.

The temporary tolerance for DQ is still valid. Meanwhile the document will need to go through the whole process again with some suitable compromise or modified wording.

2. Alginates

Results in Europe have been good and generally confirm earlier findings. There will be a meeting in the UK with Barrett (WRO) about the middle of October to review progress.

Chevron have carried out limited trials in conjunction with the Aquatic Weed Control Laboratory, Denver. No US data was available at the meeting.

3. Potato Tolerance Petition

This was submitted to EPA in July 1979. A copy of the petition
AC was forwarded to ICI. This will be lodged with RATLS.

4. Long Term Toxicology/Need for Repeat Studies

(a) 2 year Rat Studies

There is an IBT 2 year rat study as well as an old CTL 2 year rat study.

Dr. Cavalli will be examining the IBT data with a view to noting any adverse findings not recorded in the original report - along the same lines as is being done with the IBT/PQ studies. This will be done before end of December 1979 and ICI will be
RDC informed of the outcome.

A Pharmaceuticals Div. 2 year rat study has confirmed the feeding level for DQ at which cataract occurs and obtained a higher no-effect level for this effect. This report has been submitted to EPA in the Potato Tolerance Petition.

CTL have carried out a full audit of their old 2 year rat study. They have found many inadequacies, including effects (eg on bile duct, liver and other organs) at the top feeding dose not completely evaluated (no histopathology) at the lower dose levels.

(b) Multigeneration Study

A CTL audit of this study has again highlighted several inadequacies. There is an indication of testicular atrophy at the top dose (500 ppm) with inadequate data available on animals fed at the lower dose (125 ppm). This report was submitted to EPA in 1967.

(c) Dog Study

This is an old CTL study and a recent audit casts some doubt on the no-effect level because of uncertainties in the weight data.

(d) Mouse Oncogenic Study

Carried out more recently at Life Sciences Laboratory. This has been submitted to EPA August 1977 in support of the Aquatic Tolerance Petition.

RDC/AC The need for repeat chronic studies with diquat will be reviewed at the next ICI/Chevron liaison meeting (Jan/Feb 1980), when the results of the audit of the IBT rat study will be known. All the chronic studies on DQ are available to EPA and adequately referenced in the Potato Tolerance Petition.

5. Ethylene Dibromide

EPA have recently pronounced that Treflan herbicide may continue to be marketed provided levels of nitrosamine are reduced to below 1 ppm in the product. Chevron had no views on what EPA's position on an acceptable level of EDB in Diquat might ultimately be - in view of recently published NCI results.

6. Formulation Problems

ICI said that the problem of hexane in drums of the product would be resolved by the first quarter of 1980 when the new process for reducing EDB levels comes into operation.

ICI have established that molybdate is unnecessary in the product which will remove the problem of precipitate formation, believed to be a combination of molybdenum and the soft iron pipes in the Chevron packaging plants.

Next Meeting

Provision fixed for January 31/February 1, 1980 at Richmond.