NOTES ON ICI/CHEVRON LIAISON MEETINGS - 7-9 MARCH, 1978 (RICHMOND)

Those attending for Chevron:
Dr J N Ospenson
Dr H G Franke
Dr L Stelzer
Mr Art Assad
Dr Jared Abel
Mrs B Tucker
Dr R D Cavalli
Dr J Ford
Ms W Sim
Mr Boykin Witherspoon
Mr Carl Tanner

For ICI:
Dr A Calderbank
Dr P Slade
Dr B G Johnen
Dr M S Rose
Dr D W Barrett

(Not all were present throughout the Meetings.
RPAR and toxicology (Tucker, Sim did not attend). Witherspoon attended only for the Oleoresin discussion and Tanner attended only on the last day).

Drs Ospenson and Cavalli had just returned from Washington having visited EPA, along with Don Dye, to discuss the Industrial Bio-Test situation and also the PQ RPAR status. Senior management in Chevron are extremely concerned about the latest revelations emerging from EPA probing of the IBT records that four Companies were alleged to have submitted IBT data to EPA knowing it had been falsified. Lab records from one of the Companies, viz Chevron, have apparently been turned over to the Department of Justice for investigation, referring specifically to the two year animal study on Orthene. (See Appendix 1 - Washington Post, 9 March 1978, page 1). Most of the toxicological work on Chevron's products has been done by Industrial Bio-Test.

PARAQUAT

1 RPAR Status

Dr Ospenson reported that he and Cavalli and Dye had met the previous day with the EPA PQ Project Manager, Bill Caniglio. Caniglio is still working on his position paper - a document of about 40 pages, which was freely discussed with the Chevron personnel. He now expects that a decision on PQ by the EPA Working Party, to whom Caniglio will present his paper, will be made in 3 to 5 weeks time.

Caniglio has apparently shown considerable energy and enthusiasm in pursuing references and contacting and discussing issues with many people.

About a dozen or so triggers are discussed in the document and although Caniglio was helpful in suggesting how some of these might be overcome by label changes or other means, Chevron are now much more concerned that an RPAR on PQ is a very real possibility.

Of the possible triggers four areas (Inhalation, dermal, reproduction and soil) were highlighted as more serious than the others with inhalation toxicity well in front as of major concern. The possible triggers are:-

Inhalation Toxicity

There were two revelations in this area -

(i) Caniglio had received results of some work done in 1973 (unpublished) from Dr Zavalla (Iowa State University) in which minute quantities of PQ (1.2 pecogram) deposited, using special equipment, into rabbit lung had caused fibrotic change.

This result had caused Caniglio to question the PQ aerosol "no effect" level.

(ii) EPA had done some field work, spraying PQ by air and measuring the percentage range of particle size. The Chevron people were given a 20 sec view of a page full of data, with no details of equipment, sampling techniques etc. The significant claim from this work was that the proportion of particles in the 1-5 micron range (respirable) could be as high as 40%!

This data had been taken further by an EPA man (Mr Carrol Collier) who had done theoretical calculations of potential exposure levels to applicators, flagmen, cotton workers in gin factory, general populace etc. Many of these theoretical exposure levels were apparently higher than the concentration in air which could be regarded as safe. The "trigger concentration" was given as an LC50 for product as formulated of 0.04 mg/litre. (No time of exposure or method of dispensing the product was provided). Using Gage's figure for LC50 of respirable PQ would give a result several fold higher than the above "trigger".

Dermal hazard

Concern was expressed of data in an early CTL report (IHR 172, Jan 1965, by Mc Elligot) in which effects on rabbits was recorded at dermal doses as low as 2 mg/Kg. Mr Collier had also done some interesting theoretical calculations of exposure to knapsack sprayers based on this figure. However we believe this trigger can be easily rebutted since later work showed that the earlier results were obtained due to oral intake. When care was taken to avoid oral contamination a figure of 24 mg/Kg was obtained as a no-effect level for acute dermal exposure. Chevron are taking steps to contact McElligot and will then report back to Caniglio.

Reproduction

There is a suggestion from three sources that PQ has an effect on reproduction and the main concern relates to loss of fecundity (male potency) in mice Pasi et al Mutation Res 26 (1974), 171-175.

McElligot showed testicular changes due to PQ (species and dose?) and Lutz ? showed PQ caused changes in sex organs of chickens.

PQ accumulation in Soil

Concern was expressed about the apparent finite capacity of very sandy soils to deactivate PQ.

Caniglio suggested this problem could be alleviated by labelling to avoid such soils (as is done with muck soils in the USA). JNO offered to take Caniglio to see the high rate PQ trials on 98% sand soil in Florida (since learned that these plots have been cultivated and consequently no longer useful to make our point - however, the data from these plots is available).

The other potential triggers discussed in Caniglio's report are:-

Toxicity to hares/rabbits

Caniglio was 'very vocal' on this matter had has been in touch several times with Mlle Lavoir (Versailles). Copies of two recent publications, indicating the problem in France has receded, are presently being translated into English to send to Chevron/EPA.

Hatchability

Concern for pheasant eggs in fields. Evidence that PQ spray could penetrate egg shells and affect hatchability. Potential hazard to endangered species.

Mutagenicity/teratogenicity

Little concern now in this area (more for fecundity rather than mutagenicity). Problem of teratogenic effects now thought to apply to DQ rather than PQ. (Paper by Dr Clegg of Health, Protection Branch, Canada).

Medical Treatment

There was some philosophical discussion in the report as to what was meant by adequate treatment. Caniglio's report has interpreted the information on this subject that adequate treatment would generally not be available in the time frame. Therefore the criteria was exceeded (triggered). Dr Cavalli saw the summary of this statement, disagreed with it, and was invited to take it away and submit a revised version to Caniglio. Some further case histories of successful treatment are also now available.

2 yr Dog Study

This was the IBT two year dog study. One lung adenoma was detected (most unusual) and had raised concern, with recommended re-investigation (ICI has already seen a internal EPA memo on this subject).

Drift

Problems of drift from aerial application are also highlighted as a potential trigger.

Dr Ospenson informed us that Chevron were setting up a high level group to act on RPAR/IBT problems for Chevron (all products). ICI said they would arrange a small group to deal with the PQ/RPAR situation as a top priority and to liase closely with those nominated at Chevron.

We emphasised that it was important that ICI should have direct contact with EPA (Caniglio) and it was agreed that representation should be at the technical level from both Companies.

2 Status of Long term Toxicology Studies

Two studies were carried out on PQ (2 yr dog and 2 yr rat) by IBT.

(i) 2 yr Rat : Microfiche of all the IBT data is now held by Chevron. They believe this fairly complete, with the exception of pathology notes.

The repeat 2 yr rat study is scheduled to start at Life Sciences Laboratory in April 1978. Final reports have been promised no later than March 1981.

Dose levels have yet to be selected based on results of preliminary feeding study (pathology complete by mid March). A copy of the full protocol will be sent to Chevron. MSR

(ii) Mouse carcinogenic study : Started October 1977 at CTL.

Dose levels 12.5, 37.5 and 100 ppm. Top dose level is not showing expected effects on growth rate and may need to be revised upwards. This is under investigation at CTL. Copy of full protocol, suitably signed should be sent to Chevron. MSR

Rehash of old mouse study is in progress and a report should be available about mid 1978. Any evidence which could be provided that the animals were actually fed the test substance (PQ) would be most valuable.

(iii) Rat multigeneration reproduction test

New study scheduled to start 21 March 1978 at CTL. Chevron had objected to strain of rat used which was subject to up to 2% imperforate vagina. Agreed to change to another strain of rat (Charles River) which would delay the start by 6 weeks to early May.

It was agreed that the old three generation reproduction study should be 'rehashed' by CTL as an interim measure and possibly to help the RPAR situation. AC/MSR

(iv) 2 yr Dog Study : Carried out by IBT.

One lung adenoma was seen which has caused comment from EPA (see comments under RPAR).

Microfiche of raw data for the addendum report has been received by Chevron. They are still awaiting microfiche of raw data from the main study.

The raw data will need to be evaluated before a decision is taken on whether or not it is necessary to do a new dog study (3 or 6 month

would probably be adequate) to obtain a "no effect" level in a 2nd species.

Chevron who submitted the PQ petitions to EPA are responsible for validating the IBT studies. The original date (August 1978) scheduled for doing his has now been put back by 3 months to November 1978.

Dr Cavalli is responsible for evaluating all the IBT raw data for Chevron. If ICI do not obtain copies of microfiche direct from IBT, Chevron will either get copies for us or lend us theirs. AC to follow up as necessary

Chevron said that since they would be submitting the new reports and hence responsible to EPA, it was essential that they audit the repeat studies at CTL and Life Sciences Lab. Some suitable system for doing this would be agreed by Dr Rose and Dr Cavalli. MSR

3 Safer Formulations (Stench, colour, emetic)

Chevron expecting to introduce valeric acid stench into paraquat as soon as facility is available (mid June 1978 at earliest). Meanwhile Chevron are carrying out a small test market survey among aerial applicators in the Fresno area.

Chevron are not interested in colour.

No further information on progress with the emetic submission was available. Approaches have been made to EPA by Chevron's Don Dye in October and December 1977 and in January this year to enquire about progress. Chevron felt that a stronger approach to EPA should not be made until we had clear evidence that the emetic was saving lives.

Chevron felt that the present new information from W Somoa was probably not sufficiently clear cut.

We said we would re-evaluate the data from W Somoa, together with other new information on gastric emptying and consider whether we had an adequate case on which to pressurize EPA. Otherwise we would await new cases coming to hand which would support our cause. MSR

Status/Restricted Use

PQ is now on the Federal restricted list for all uses (except the Home and Garden), published in the Federal Register 9 February, 1978. Chevron believe this will have no significant effect on sales. The mechanics involved is basically a revision in label. Chevron have 60 days (from Feb) in which to submit the revised label to EPA, and the product must show the new label within 270 days (ie by November/December 1978). By 1 June all advertisements will have a statement that PQ is in the Restricted Use Category.

Herbi Sprayers

Chevron (Art Assad) will write to Herbi saying that use of PQ in Herbi equipment would not be legal, since it is not in the label registration and we have no efficacy or residue data from this type of application.

Marijuana

All telephone calls are being referred to Dr Hawks, Chemist in the Federal Laboratory for Drug Abuse, responsible for investigating the PQ/Marijuana problem (See Science article, Appendix 2).

Dr Hawks has been analysing marijuana samples for PQ. Information after our meeting was received to the effect that 21% of samples analysed contained PQ, ranging from 3 to 2264 ppm, with an average of 452 ppm. Marijuana artificially spiked at 10,000 ppm and burned apparently produced bipyridine and a small unquantified amount of PQ. Further tests on smoke are continuing but suggestions are that 50 to 250 nanograms of PQ can be expected to be present in smoke from single joint contaminated with 450 ppm PQ. Chevron did some work a few years ago burning grass (real grass not 'pot') containing 200-800 ppm PQ and allegedly detected 0.01 to 0.02 ppm PQ in the smoke.

Head of Federal Health Education and Welfare (Mr Califano) issued a press statement (12 March) warning that marijuana contaminated with PQ could lead to permanent lung damage for users. The National Organisation for the Reform of Marijuana Laws (NORML) has announced its intention of filing suit against the US Government further participation in the spraying program. NORML also alleging PQ is a carcinogen and mutagen. No action has been taken to rebut these statements.

Some concern about the danger of inhalation is believed to have arisen through the contact of Hawks with Dr Zavalla (see above under RPAR) who is being used as a consultant by the Department of Drug Abuse.

Goat and Rabbit alleged teratogenic effects

This incident arose as a result of pasture, on which pregnant goats were feeding, being sprayed by air with PQ. The pasture was adjacent to cotton.

Some of the goats are alleged to have died and others aborted; a number of goats have been born with missing hind limbs or lower jaws. A lady owner of pregnant rabbits housed nearby also claims effects on her rabbits.

The goat man (Mr Adams) is now suing the spraying contractors, and is having analysis done by the University of Texas. Meanwhile Chevron can get no further data - on residue levels in the pasture or animal tissue. [PQ was clean in laboratory teratology studies on rabbit, rat and mouse.]

Epidemiology

No further information is available from the Californian study, which should be complete in Summer 1978. Reference to it was not included in the Canilgio RPAR document. Dr Cavalli will try to elicit more information.

ICI plans for a cross sectional/follow up studies in Malaysia - subject to Board approval - were discussed with Chevron. Once it is decided the studies will go ahead then copies of the protocol will be forwarded to Chevron.

Competitive Paraquat

The ship (Pindar) allegedly carrying Taiwanese PQ for Aceto has docked at two ports in the USA without apparently discharging any PQ. Chevron and ICI Americas are keeping watch on the situation and will continue to leak information to EPA as necessary.

Nothing further is known (progress or otherwise) of the long term feeding studies on PQ arranged at IBT by Otsuga. The validity of the data will be questionable since pure white crystalline material was used. Source of information to Chevron has now dried up.

It was suggested that the ideal time for ICI to propose a new specification for our PQ to EPA would be when we submit results of the ICI repeat long term studies in about 3 years time.

Drift Reduction

Little new information from 1977 trials. Nalcatrol does reduce drift from aerial spraying by 70-80% (cotton). With alfalfa and other leafy crops X77 spreader is needed and the benefits of nalcatrol are then reduced (see notes of last liaison meeting).

The significant piece of new information which could be quite helpful to the RPAR potential drift trigger is that official complaints of drift from use on cotton in California have gone to zero since -

(i) Dept of Agric of California issued instructions that Nalcatrol must be used for aerial spraying of PQ on cotton in California.

(ii) An educational program by Chevron Marketing Support R & D personnel to aerial applicators, distributors etc.
Chevron said that the State Agricultural Commissioners would testify to the greatly improved situation in California.

Oleoresin Project

Chevron effort now reduced to 10% of one man.
Label submitted August 1977.
EPA interim review November 1977 of efficacy data OK but would like more specific use directions. Rest of package has not been reviewed.
Revised label resubmitted to EPA January 1978 (see Appendix 3).
The Experimental Use Permit has been extended for 1 year. Bill Hogan, previously running this project, has been replaced by Alan Wooldridge.

Registrations

Field Work - label Expansion

Field work to expand several of the existing registrations and to support pending registrations (see Appendix 4) are planned for 1978.

Hydrogen Evolution/PQ and Al

Chevron are concerned that an accident might arise from explosion/fire arising from the reaction of aluminium or other metal containers or equipment in contact with strong paraquat solution. Apparently there is a warning on the 'Roundup' label which warns against the use of that product in galvanised spray equipment.

Paraquat concentrate reacts with aluminium very readily giving off hydrogen and the reaction is enhanced in the presence of X77 wetter. (An incident was reported from the field in which an aluminium coupling was dropped accidentally into a spray tank containing paraquat concentrate and bubbles of gas were noted). Chevron have since established that there is no reaction of 1% paraquat solution with Al powder.

It was agreed that Chevron would investigate the matter further and establish the strength of PQ solution at which reaction occured and to compare the same reaction with glyphosate solutions. They would then be able to decide whether, for their own legal protection, they needed to add a warning to their label.

DIQUAT

1 Water Weed Petition

DQ has now had a temporary tolerance (water) for almost 5 years. Problem of establishing a full tolerance because of the difficulty of controlling a particular body of water for 10-14 days after treatment. Chevron still have no idea when (or if) this internal EPA problem will be resolved. However EPA's Ed Johnson has recently proposed that tolerances should not be used to control the use of a product in water, but to leave that to the label. DQ label changes were made to this end by Chevron last year.

At this time however it seems unlikely that EPA will convert a temporary to full tolerance without re-reviewing the long term toxicology. One of the early studies (2 yr rat) was done by IBT (see below).

The WRO work with DQ and alginate systems was described to Chevron. They will consider the commerical and registration implications as well as inform their field man (successor to Bill Hogan) of this new development.

2 Potato Petition

Chevron have decided to submit the petition in April 1978 (One or two applications of 1 pint/acre). Efficacy data available. Residue data almost complete. Requested tolerance, probably 0.2 ppm.

It is proposed to submit the new 2 yr rat cataract study. Revised report needs to be forwarded to Chevron. AC

Chevron still concerned about storage rot and a new trial is being set up in 1978 to get more storage data. ICI stressed the importance of assessing rot in tubers as harvested as well as after storage.

Assuming a tolerance is established then Chevron marketing will decide whether or not they wish to enter this market with diquat. It seems doubtful however that a full tolerance will be established because of inadequacies in the 2 yr rat feeding studies (see below).

3 Nitrosamine Analysis

Results of nitrosamine analysis on PQ samples should be available shortly. Chevron will forward samples of diquat with the next batch, after the data from the Company doing analyses on the first batch have been evaluated.

4 Cereal and Rice Desiccation

(a) Efficacy : 10 trials were carried out last year on rice, wheat and sorghum. PQ was used as a standard with untreated controls. DQ was generally equal to or slightly inferior to PQ. Thus PQ probably satisfactory at $\frac{1}{4}$lb/acre whereas DQ may need $\frac{1}{2}$lb/acre.

Residue data : Rice after 8 days ($\frac{1}{4}$lb/acre) 2 ppm PQ, 0.5 ppm DQ

Wheat after 7-8 days ($\frac{1}{2}$lb/acre) Up to 2 ppm PQ, 2.0 ppm DQ in one test

(only limited amount of data available)

(b) Photoproducts : ICI described the progress made in this in this area, which is regarded as most satisfactory.

(c) Dichloride availability : ICI indicated that a process (not very efficient) was available, but because of capital investment etc it was likely that the price to Chevron would be at least as high as the new DQ price.

Because of the indifferent efficacy results, the probable need of the higher rate (½lb/acre) and consequently reduced market, and the uncertainties in registration (long term toxicology), it was decided jointly to recommend that this project be shelved.

It could be resurrected and the data reviewed should circumstances change in the future.

5 Long term toxicology

CTL have carried out a preliminary assessment.

(a) 2 yr Rat

Two studies were carried out. One by CTL, reported 1964 and one by IBT, reported 1965. The IBT study was started when it was apparent that large numbers of animals in the CTL study were dying from respiratory infection. Both studies have been submitted to EPA, viz

CTL Reports (TR375
(TR35 supplement
(P253

IBT Report 227/65

Both studies used dichloride salt and both are considered inadequate in terms of study design, too few animals, respiratory problems etc.

A 'modern' 2 yr rat study - for evaluating the no-effect level for cataract formation is now available, but will not meet EPA needs regarding "no effect" on other parameters and as a carcinogenic study.

A new 2 yr rat study may be needed to establish full tolerances for DQ in water and potatoes. However the first step will be to 'validate' the IBT study and then to establish whether a combination of both old studies might meet regulatory needs.

(b) Mouse carcinogenic study

Done by Life Sciences Research. This seems adequate, with no major problems and has been submitted by Chevron to EPA.
Dr Purchase will evaluate the study in detail.

(c) Rat 3 generation reproduction study (Reported 1972)

This seems fairly reasonable but has not been evaluated in detail.

One problem is that no diet analysis was done. It will be reviewed more critically by CTL as soon as possible.

(d) 2 yr dog study

This was done at CTL and reported in 1966. Inadequate in study design and in the details reported. Appears to be an effect on body weight - not mentioned in the report. The "no effect" level is in question. Opinion is that it would not pass an EPA critical review.

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