

File 152.31
Pg

Present:

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

PARAQUAT

- 1 Industrial Biotest Laboratory - 2 year rat and dog studies ACTION

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 and had sent a standard validation form for completion (copy attached as appendix). Since Chevron submitted the data to the EPA they were legally responsible although PPD were the customer. It was agreed that Chevron complete the form with the help of ICI where needed. Dr Franke will let Dr Calderbank have copies of all relevant data.

HGF

Legally, people are waiting to see what happens to products whose studies cannot be validated. Chevron did not expect cancellation of registrations but it was unlikely there would be new registrations until the studies have been evaluated and either validated or repeated.

2 Status of long term studies:

(a) 2 year rat study

The draft protocol for the 2 year rat 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 US 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 for individual housing and the costs involved. The contract laboratory must also 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.

MHL

RDC

MHL/AC

(b) Mouse carcinogenicity study

IFHP made the following comments on the previous study:

the tumor data had been handled in an unsophisticated fashion,
the staff who carried out the study were no longer employed at CTL,

ACTION

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; eg 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 (ie the tissues should be re-read to ensure that tissues not mentioned in the original report were indeed normal). 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

- 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, Chevron will write to EPA informing them that we will be implementing an in depth review and critique of the study.

ACTION

Dr L Stelzer will be asked to frame a suitable reply to EPA in answer to their 6 June letter.

HGF

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 replicated 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 US and Chevron before visiting the EPA in October.

RDC

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 Franke to check the delay.

HGF

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

MHL

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) Effects of paraquat on bacteria - soil nitrification. (BGJ 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 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.

AC

MSR

Restricted use category

It is likely that paraquat will be placed in the restricted use category on the basis of prejudices. Chevron now believe 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 US plant to come on stream before introducing to the market valeric acid based stench product. Blue stench formulation is being marketed by ICI in Belgium and will possibly be marketed in Ireland as well, as a result of pressure from the authorities there.

(b) Emetic

The FDA have not yet reviewed the data (26 August). The emetic formulation has been on sale in Western Samoa since June and it is hoped that we may soon be able to demonstrate benefit from a suicide case.

This would be of considerable help in speeding up acceptance through the EPA machinery. Information on the emetic is likely to become public at the end of this year but there are no plans for voluntary publicity. CTL reported that it is possible to analyse for the emetic in both blood and urine, and details will be passed to Chevron and ICI US shortly.

MSR

5 Status of Paraquat Registration:

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

The Status of Registration Petitions and Registration Programs is given in Appendices B & C.

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. Maddy's boss had also written a retraction letter to EPA.

(b)

RDC had already dealt with Medical World News article.

(c)

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

AC

(d)

The publication by Carere of his Ames' test results on a number of pesticides, including paraquat and Captan was pointed out. CTL have obtained negative results and are seeking to resolve the discrepancy with Carere.

(e)

This paper (Leahey) is with Chevron for comment.

HGF

(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.

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 - 8-10 March 1978.

AC/TH

5 October 1977

APPENDIX

To the Environmental Protection Agency:

_____ hereby certifies that:
(Registrant)

- (1) scientific personnel, whose qualifications are annexed hereto as Exhibit A, have reviewed the supporting data of the test or study summarized in Industrial Biotest Laboratory Report No. _____ (submitted in support of Registration No(s). _____ and Tolerance Petition No(s). _____);
- (2) the review was conducted in accordance with the review criteria specified in Appendix I to EPA's letter to the registrant dated July 27, 1977;
- (3) the review indicates that the test or study was performed in accordance with its protocol, except as noted in Exhibit B annexed hereto which specifies both the variances from the protocol and/or the extent to which it could not be determined from the supporting data whether or not the protocol was followed; and
- (4) Industrial Biotest Laboratory Report No. _____ accurately reflects the supporting data, except as noted in Exhibit C annexed hereto.

_____ acknowledges that this certification is being submitted to the EPA in support of Registration No(s). _____ pursuant to 40 CFR 162.8(d) and in support of Tolerance Petition No(s). _____ pursuant to 40 CFR 180.7(b) and that any false statement contained herein may be a violation of 18 U.S.C. Sect. 1001 and Sect. 12(a)(2)(M) of the Federal Insecticide, Fungicide and Rodenticide Act (7 U.S.C. Sect. 136j(a)(2)(M)).

(Registrant)

by (Name and Title of Officer)

APPENDIX I

Dates: What was the intended and actual duration of the study? Did the conduct of the study deviate significantly from plan? If so, why?

Protocol: Was the protocol written? If not, why not? Who designed the protocol? Who approved it? Did any written amendments include reasons for changes? Were there any oral amendments to the protocol? Were there any significant deviations from the protocol? What were the reasons for them and what was the name and title of the person who authorized them? What was the effect or possible effect of such deviations on the outcome or findings of the study?

Personnel: What were the qualifications of each person, professional and technical, involved in the study? Did they have the necessary training and experience for the jobs they performed? What supervision did they receive?

Test Materials and Quality Control: Was the purity of the test agent determined prior to use? If so, by whom? Were test agents checked for stability under the same conditions under which they were to be administered? Did the animals in the study receive the correct doses of the test agent(s)? How was this determined? Were there any discrepancies or errors found in the administration of the test agent?

Animals Under Test: Did the laboratory have its own colony, or did it obtain animals from commercial stocks? If the latter, from whom? What were the selection criteria as to species, strain, age of animals, sex, number of animals and health status? Were there any deviations from these criteria in the actual selection of the test population? What were the laboratory's procedures for quarantine, randomization, identification, and environment? Were there any deviations from these procedures?

Execution of Study: How frequently were the animals observed for any abnormalities? Were they palpated for tissue masses? Was the amount of food and test material consumed quantified? If so, by whom, at what intervals, and how was it recorded? What clinical laboratory tests were conducted on the animals? By whom? How were the results recorded? Were the data and records of observation, weights, food consumption, clinical laboratory tests, etc. accurate? Were any discrepancies or errors noted? What tests, if any, were run on animals that died? By whom?

Necropsies (Gross Pathology): Were necropsies performed on all animals? If not, why not? Were decomposed animals examined at least for tumors? Were examinations conducted under supervision of a pathologist? What organs were described and weighed? Who made the observations?

Were all lesions in any tissues or organ systems described? What tissue blocks and wet tissues were preserved, by whom and how identified? Where is this information recorded and where are the slides stored? Were the necropsy reports accurate? Were any discrepancies or errors noted?

Histopathology: Who examined what tissues and when were they examined in relation to completion of gross pathology? Were all tumors or other unusual findings noted on gross examination studied microscopically? If not, why not; if so, by whom? Were the histopathologic records accurate? Were any discrepancies or errors noted or were there differences of opinion among readers?

Data, Records and Reports: What was the laboratory's plan for collection of data from the study? To whom were the data sent and at what intervals? Who checked accuracy? Who determined what statistical tests were to be made? Was a life table method always used to evaluate the results? If not, what other method was used? Did the report accurately account for all animals in the study? If not, what discrepancies or errors were noted and in what part of the study? What is the potential impact of these errors on the scientific integrity of the study?

JULY, 1977

PRODUCT	USE/COMMODITY	PETITION NUMBER	DATE OF SUBMISSION	ESTIMATED DATE OF ISSUE	REMARKS
Diquat	Water	1F1101 FAP3H5022	12/18/70 10/10/70		Petition and revised label under EPA review.
Paraquat	Field Corn	5F1625	4/28/75	The RPAR status of paraquat delaying setting tolerances and approv- ing labels.	Petition amended 12/2/77
	Grain Sorghum - Harvest Aid	5F1591 6H5120	1/27/75		Petition amendment sent EPA 10/27/76.
	Pasture Reseeding	5F1639	5/30/75		Petition considered amended 9/17/76 by EPA.
	Dry Beans - Harvest Aid	7F1910	1/14/77		Petition filed 3/1/77.
	* Dry Beans (temporary tolerance)	* 5G1627	* 2/28/77		*Temporary tolerance ex- tended to 3/1/78.
	Asparagus	6E1845	8/76 (IR-4)		EPA requested addition- al toxicology data.
	Onions	?	8/76 (IR-4)		
	Strawberries	6E1853	8/76 (IR-4)		EPA requested addition- al toxicology data.

APPENDIX B

CLASSIFIED

APPENDIX C
May, 1977

TTP-temporary tolerance petition
 TP - tolerance petition
 EUP-experimental use permit
 NPA-new product application

Product & Formulation Crop or Use	Prog. & BOP No.	Program Objective	*Type of Submission	Date of Submission	Status and comments of Program and ability to meet Deadline Dates
Diquat 2 Spray Potato Harvest Aid	P-67 B18-74	To obtain residue tolerance and label.	TP	7/77	EPA letter of 9/10/76 specific data required to obtain registra- tion.
Diquat Water Weed Killer	R-61	To obtain tolerance for water and label.	TP	12/18/70	Revised label sent to EPA 6/30/75.
Diquat 2 Spray	R-101	Determine reentry hazard	LRA	1977	
Paraquat CL - Harvest Aid - Dry Beans	P-69 B19-74	Extend EUP east of Rockies for 1977 testing. Expand use to other North Central States & Colo.	EUP ex- tension LRA	1/28/77 1/78	Submission contingent upon tolerance approval
Paraquat CL-Resin Soaking in Pines	P-72	To complete testing under EUP	LRA	1977	EPA permit extension requested.
Paraquat CL-Alfalfa and Clover Dormant Use	R-52 B7-73 & B39-76	To add tank mixes. To add dormant use in East.	LRA LRA	8/77	
Paraquat CL - Mint	R-78 B35-75	Weed suppression in dormant mint. Paraquat CL alone and tank-mix with Sinbar	TP (IR-4) LRA	10/77	
Paraquat CL-Misc. Vegetable Crops	R-82 (M-142)	To register on various minor acreage crops.	TP (IR-4)	9/78	
Paraquat CL-Wheat (Broadcast)	R-94	Air label in Northwest	EUP; LRA	1978/1979	
Paraquat + valeric + emetic	R-96	To register alternate form- ula	NPA		Requires exemption for emetic which is pending with EPA.
Paraquat CL-Peanuts (Preemer- gence (ground-crack) to Postemergence (to pegging)	R-105 B49-77	To obtain tolerance & label	TP, LRA	2/80	
Paraquat CL + SURFLAN + SENCOR No-Till Soybeans Tank-Mix	R-108 B44-77	To add tank-mix label	LRA	3/78	
Paraquat CL + BLADEx + AATREX No-Till Corn Tank-Mix	R-109 B44-77	To add tank-mix label	LRA	2/78	
Paraquat CL-Rhubarb (dormant)	R-114	To obtain tolerance & label	TP (IR-4)	1978	
Paraquat CL + DUAL + Atrazine No-Till Corn Tank-Mix	R-115	To add tank-mix label	LRA	1978	

CUSA-00290569

COMMERCIAL PRODUCTS

CHANGES IN EXISTING PRODUCTS	ORIGINAL SUBMISSION DATES	LAST CORRESPONDENCE DATE	CHANGE INVOLVED	COMMENTS
Paraquat CL (Note: all major changes being held up by EPA due to RPAR candidate review.)	11/24/75		Adding grazing restriction to field corn harvest aid recommendation.	See petition.
	5/25/76	10/22/76	Removal of geographical restriction for sunflowers.	Finished label submitted 10/19/76. EPA acknowledged receipt 10/22/76.
	11/9/76	11/26/76	Remove varietal restriction from hops claim.	EPA acknowledged receipt 11/26/76.
	4/14/77	4/18/77	Add alfalfa and clover for California and tank mix with princep for alfalfa.	EPA acknowledged receipt 4/18/77.