

IMPERIAL CHEMICAL INDUSTRIES LIMITED  
CENTRAL TOXICOLOGY LABORATORY

721.01/19

MINUTES OF CHEVRON/CTL LIAISON MEETING

8-9 September 1976

Present : Dr J N Ospenson ✓  
Dr R D Cavalli  
Mr A W Waitt  
Dr M H Litchfield  
Dr M S Rose  
  
Dr L L Smith )  
Dr G T Steel ) part-time  
Mrs I A Whitaker )  
Dr I F H Purchase )

CHEVRON CHEMICAL CO. ORTHO DIV. R & D DEPT.	
OCT 11 '76	
File	Index
1	J. N. Ospenson
	J. Abell
	E. V. Dearman
3	A. G. Franke
	R. Hawkes
	Hillmann
	Hedus
4	B. F. Quisenberry
2	K. Stazari
	R. Vasick
5	V. P. W.
6	J. C. W.
R & D FILES	

ACTION

Emetic Formulation

The results of experiments carried out at CTL and Huntingdon were discussed, as was the summary of available toxicological data on PP 796. The toxicology of PP 796 was seen to be divided into 2 categories -

- 1) work to show the efficacy of the new formulation and
- 2) toxicology to demonstrate the safety of the additives

It was agreed that the information required might include :

- a) LD50 (oral) of emetic alone in dog and monkey.
- b) LD50 of the formulation in the rat (to show that the combination of the emetic and paraquat was not more toxic than paraquat alone) - already carried out. CTL
- c) LD50 of the formulation in the dog (to demonstrate that the emetic formulation is less toxic than the existing formulation) - at present being carried out. CTL
- d) LD50 of the formulation in the monkey (as (c)) - at present being carried out. CTL
- e) Skin absorption studies on PP 796 in the presence and absence of paraquat - to be carried out. CTL
- f) Inhalation studies on the emetic alone (using large droplet size, non-respirable aerosol), to assess the risk of vomiting following exposure to mists of PP 796 - to be carried out. CTL
- g) Ames test - to be carried out. (Pharmaceuticals Division may have to carry out such tests as part of the work required by the Safety and Health Act - MS Rose will contact). Some of the above work will have to be carried out with the US formulation with and without stench. CTL/PPD

ACTION

It was agreed that once the final formulation was decided upon ie emetic alone, emetic plus stench, emetic plus stench plus colour, oral and dermal toxicity studies would be required. It was agreed that Dr Litchfield would review the toxicology which had been carried out on PP 796 by Pharmaceuticals Division and recommend further work required for registration. It was agreed that copies of the data would be passed to Chevron for them to carry out an assessment. Chevron expressed the view that the submission to EPA would be for an "inert". This would not require long term studies or mutagenicity. However, it was felt that it was unlikely that the first submission to EPA would be successful and further work would be required.

MHL

AWW

Solid Formulation

Chevron had decided that the formulation of choice would be the ICI NaCl based material but that further development of solid formulation should be brought to a suitable stage and then "frozen" and the product held in reserve as a "fall back" formulation. It was felt that the new emetic formulation would supercede safer formulations based on solids.

Stenched Formulation

Chevron has submitted to the EPA for clearance of n-valeric acid as an "inert". The toxicology data for the n-valeric acid stenched formulation (1% valeric acid) which had been carried out by Chevron was reported :

oral LD50 ♂ rats 107 mg PQ<sup>2+</sup>/kg body weight

oral LD50 ♀ rats 63 mg PQ<sup>2+</sup>/kg body weight

dermal LD50 rabbits (occluded) : stenched formulation 117 mg PQ<sup>2+</sup>/kg  
non stenched formulation 66 mg PQ<sup>2+</sup>/kg

Rats exposed to "saturated vapour" from the formulation showed no effects.

Inhalation (aerosol) experiments are still to be completed at spray dilution and twice spray dilution.

Chevron

EPA - RPAR

Chevron reported that it is extremely unlikely that any action will be taken by EPA on the date originally set (October 1st) as the list of compounds has now been increased from 42 to around 180. Chevron are continuing to gather information which will be useful, including obtaining endorsements of the value of the product. Information on deaths due to other products and the availability of treatment is also being obtained. There had been no response (none being expected) to the "effective treatment" paper sent to EPA.

Chevron

A preliminary "redraft" of the paraquat label is being considered, including information on treatment.

Chevron

ACTION

NIOSH

There has been no response to the submission on teratogenicity.

Chevron

Laboratory Accreditation

It was agreed that PPD would request from Chevron a list of all data which had been submitted on paraquat and diquat in order that CTL could "authenticate" it. Dr Ospenson pointed out that contract laboratories used by Chevron had been requested to examine all past studies critically and some of them would concern these products.

AWW

Chevron

Treatment of Poisoning/Research

There was discussion of the value of reduced oxygen in treatment. CTL repeated their view that low oxygen would increase the perfusion of lung by blood and thus would expose the lung to more paraquat if blood levels were not extremely low. Experimental studies in rats gave increased mortality when low oxygen was used after oral dosing of paraquat. If oxygen could be lowered without increasing cardiac output (PEEP ventilation) then this form of treatment might be acceptable. However, this type of therapy involves curare which will reduce the efficacy of gut lavage and will also be contraindicated. A copy of the paper which summarizes this view and which was given at Iowa was given to Chevron.

Dr Cavalli described the poisoning case involving Mr Collins. The blood paraquat levels during the first day of poisoning were 1.9 ppm indicating this to be a very serious case. Treatment involved repeated dosing with bentonite and purgatives (and later with Dowex cation exchange resin as he was unable to keep the bentonite down), haemodialysis, and, at a later stage, lowered oxygen (following advice given by Dr Ken Fisher). Plasma paraquat was seen to fall rapidly over the first few days and although the patient developed renal failure, pulmonary complications did not develop and he was eventually discharged in good health. A complete case history would be sent to CTL as soon as possible. It was agreed that Chevron would approach Ken Fisher to explore his reasons for continuing to recommend lowered O<sub>2</sub> despite the CTL work of which he is aware. CTL will then consider whether to approach him directly with a view to collaborating on experiments designed to decide the rôle of low O<sub>2</sub> in paraquat treatment.

RDC

RDC

The work carried out by Chevron on the use of adsorbents and cathartics was then summarized. It was clear from this work that cathartic alone would not work and that although bentonite was the best adsorbent, Dowex cation exchange resin could be quite effective. Activated charcoal was not very effective but was better than no treatment at all. It was agreed that the detailed results would be reported to CTL when in a suitable form.

RDC

Chevron expressed satisfaction with the quarterly research summaries they had received and only a brief resume of the current position was necessary. CTL is concentrating its research efforts into 4 major areas: 1) examining the efficacy of some putative therapeutic agents such as antioxidants, low oxygen, free radical scavengers; 2) examining the factors involved in the uptake and efflux of paraquat from lung; 3) examining the sequence of reactions involved in the mechanism whereby paraquat damages the lung; and 4) examining the rôle of renal failure in paraquat toxicity. The subject

ACTION

of fibrosis was discussed and it was agreed that Chevron will explore the possibility of examining the efficacy of some antifibrotic agents if a suitable dosing regime for producing fibrosis can be set up. CTL is involved in a collaborative study with Trent Polytechnic and Pharmaceuticals Division on fibrosis, and will keep Chevron fully informed of progress.

RDC

MSR

Dr Cavalli reported on the interests of a clinical group in the USA to use ultrafiltration of blood as a way of removing paraquat. This was discussed and it was agreed that few advantages could be seen for such an approach, as haemodialysis and haemoperfusion should be as effective and were much more readily available. However, although CTL would not be prepared to recommend funding such work, it was agreed that it should not be discouraged.

RDC

Carcinogenesis Studies

Chevron reported on the EPA response to the submission of the mouse study, report number HO/IH/P/21. This report was not considered satisfactory as there was insufficient raw data presented for an independent assessment of the conclusions to be made. It was agreed that CTL would re-examine this study with a view to rewriting the report if the data was adequate or recommending a new study if necessary. The view was expressed by Dr Purchase that the rat carcinogenesis study carried out in the early 1960's by Biotest was not satisfactory and would not stand up to scrutiny by today's standards. He felt that it might be necessary to carry out a new rat study. (See page 5 under "Haematological effects of paraquat"). Dr Purchase reported that the mutagenicity study in Salmonella had been redrafted. It was agreed that when this draft had been finalised, it would be sent to Chevron.

IFHP/MHL

IFHP/MSR

Information Exchange

Mrs Whitaker reported on the computerization of cases of poisoning and Dr Cavalli reported on Chevron's compilation of cases. Certain modifications were suggested to the CTL system which were agreed. The need for good follow-ups to cases of poisoning was stressed, particularly to establish the degree of impairment to health.

IAW

KH

Litigation USA

The 4 cases involving litigation against paraquat were summarized by Dr Cavalli. Two of these involved haematological disorders and 2 generalized organ damage. Chevron believe that more work should be carried out on the effects of chronic exposure to paraquat to help in the defence of these actions. Two approaches were seen to be possible - experimental (see page 5 under "haematological effects of paraquat"), and epidemiological.

Legionaires Disease

Paraquat was not involved in this incident. The clinical course of poisoning never involved renal problems. Paraquat analysis of post-mortem tissue samples and urine samples taken during the course of illness were negative.

Haematological Effects of Paraquat

Lautenschlager (Dtsch med Wschr 99 2348-2351 1974) reported haematological changes and bone marrow changes in 5 cases of paraquat poisoning. In 2 of the patients who recovered, these changes returned to normal. Rat studies carried out recently at CTL confirm these changes and confirm that they are reversible in those rats that recover. Dr Sanderson disagrees with the interpretation of the findings of Lautenschlager and does not believe that the defect is a pure red cell aplasia. He expressed the view that the data cannot be interpreted without more experimentation and believes this to be unnecessary as the effects in his opinion are transient and probably of little toxicological significance. CTL have agreed to send details of the CTL experiments to Chevron when they are in a suitable form. On discussion of this data, it was felt that more work should be carried out on the bone marrow changes as these must be understood in order to refute any claims with respect to haematological changes in man. It was felt that other laboratories might investigate this aspect of paraquat poisoning and then ICI and Chevron would be in a very weak position in attempting to assess the significance of any new published findings. It was agreed that further acute work should be carried out at CTL and that a study might also be carried out by Chevron. It was felt that a combined 90 day study might be carried out by Chevron and used to check if haematological changes occurred with this type of exposure. Similarly, any new carcinogenic studies in rats might be used to study both haematological and bone marrow changes as well.

MSR/JS

MSR  
RDC

Epidemiology

It was reported that Dr Keir Howard was attempting to find a suitable population of spray workers on which to carry out a survey (probably in India). It was agreed that an important aspect of such studies would be adequate medical supervision. Preliminary information on the 2 epidemiological studies in the USA were given by Dr Cavalli. There are no results to report as yet.

It was felt that Dr Howard should also examine with Dr Rose and Dr Browne of Mond, the possibility of looking at workers involved in handling paraquat in the manufacturing and packing area.

MSR/KH/  
DB

Analysis of Paraquat

Dr Steel reported on progress in developing a fast accurate assay for measuring paraquat in plasma. CTL agreed to send details of methods to Chevron. Dr Cavalli discussed the problems of analysis in the USA, particularly those related to the analysis of paraquat in urine by doctors in small towns where supplies of dithionite are not readily available. CTL/PPD undertook to look into commonly available alternatives.

MSR/GTS

AWW/MSR

Communications

No problems had been encountered in the last year with the exchange of information. It was noted that from 1 September 76, ICI USA would be involved in the paraquat area and, therefore, all communications between CTL and Chevron would have to be copied to Dr D C Walker, ICI USA.

RDC/MSR

Circulation:

Those present at the meeting

- Dr A Calderbank
- Dr J T Brauholtz
- Dr K Howard
- Dr T D Browne
- Dr A A B Swan
- Dr J H Sanderson