Richmond, CA
September 24, 1976

PARAQUAT LIAISON MEETING
FALL 1976
File: 152.31 - Paraquat

MR. J. N. OSPENSON
Chevron Chemical Company

Enclosed is a copy of my notes on our September 8-10 meetings regarding paraquat toxicology. I feel that the meetings were quite constructive and that a positive program has emerged.

J. A. SPENCE

By Original Signed
R. D. CAVALLI
R. D. Cavalli

RDC:flm
Enclosure

cc: Mr. D. B. Barlow
Mr. A. P. Brown
Mr. L. F. Czufin
Mr. D. F. Dye
Mr. W. F. McCraith
Mr. R. E. Rodman
Mr. E. L. Stripling, Jr.

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MEMORANDUM TO FILE:

The Fall 1976 Paraquat Toxicology Liaison Meetings were held at the Central Toxicology Laboratories of ICI, Alderley Park, on September 8 through 10. A copy of the agenda is attached.

The meetings were attended by Drs. M. S. Rose, L. L. Smith, and M. H. Litchfield of CTL; A. Waitt of PPD; and J. N. Ospenson and R. D. Cavalli of Chevron. The situation with regard to paraquat registration in the United States was reviewed for the CTL personnel present, and the current American litigation cases were also reviewed in some detail. A fair amount of time was spent on ICI's program to prepare for an eventual EPA inspection of their laboratory records, etc. They have a program in which all the raw data from their experiments is being set out in an appropriate form and they are following the NACA and PMA guidelines to the letter. In this vein it is also important that we be sure that all data generated to date by them has been submitted to the EPA. In order to assist us with this, we have been given a complete bibliography of all internal reports generated by CTL and those which they contracted with private laboratories. A copy of this bibliography is attached to this memo.

The most significant discussion occurred regarding the new emetic formulation for paraquat. The emetic is commonly referred to as PP796. The original work on the toxicity of PP796 was done in the late 60's and early 70's in order to determine its suitability, efficacy, and safety as an anti-asthmatic drug and later as a drug for use in a topical ointment in the treatment of psoriasis. None of this work was done with the intent of using the material as an ingredient in a pesticide formulation. Because of the very pronounced emetic effect of this compound, development was stopped shortly after the preclinical human trials with it were initiated. Data was recorded on microfiche and all hard copies were destroyed. When it was suggested that PP796 might be of value as a "safening" agent in paraquat, Dr. Litchfield went to Pharmaceuticals Division and reviewed the data on the microfiche. At that time no copies were made and Dr. Litchfield's conclusions were that there did not appear to be anything in the data which indicated a serious toxic effect that would preclude its use in the paraquat formulation. He did note that there were a number of discrepancies in the data which in his opinion would have to be rounded out in order to adequately indicate the safety of the emetic in a pesticide formulation. With regard to the efficacy of PP796 in paraquat, it appears that the only studies done to date were those reported to us during the last week of August. To date no further work has been undertaken. I did obtain copies of the raw data and this is attached to this memorandum. It does appear that with the data obtained to date that the emetic formulation is effective in reducing mortality from lethal levels of paraquat in the dog and monkey, two species which can vomit, but not in the rat, a species which does not vomit. There is also some indication that the emetic formulation in the rat did cause a delay in gastric emptying with a concomitant increase in the time required for paraquat to reach its peak plasma level. A complete discussion of the data obtained from CTL will be the subject of another

memorandum. It was determined and agreed that the following studies would be performed by CTL as a minimum basis for registration of a paraquat emetic formulation.

1. Complete LD_{50} in the rat using the emetic level which will be used in the final product.

2. Complete LD_{50} in the dog using the emetic at a level which provides similar activity in the dog.

3. Inhalation toxicity of the emetic alone in the dog.

4. Complete dermal LD_{50} in the rabbit.

5. Based on the results of the above study, a sub-acute dermal study will be designed and carried out.

6. Since all of the studies done to date have used Gramoxone W with the wetting agent incorporated into it, the dog LD_{50} will be confirmed using a formulation similar to Ortho Paraquat Cl.

The solid formulation has been shelved, and no further development will be done on this product. It is most likely that development on the stenching agent and sale of a stenched paraquat will continue.

A discussion was held regarding Chevron's participation in the investigations into the Legionnaire's Disease in Philadelphia. As a result, it was decided that nothing more should be done at the present time unless something happens to reimplicate paraquat in this matter.

The next subject discussed was the treatment of poisoning. I briefly presented the results of our continued antidote program which will be issued soon as a formal report and also discussed the protocol for our upcoming dog studies. It was felt that this protocol was adequate and all concerned are looking forward to the results. With regard to the British effort in this direction nothing significant has been accomplished since the last progress report was provided. Copies of formal reports and data relating to the work done in the past year are appended to this memorandum. A discussion of their significance will be presented in another memorandum. Dr. Prescott of Edinburgh has recommended the technique of placing a nasogastric tube at the very base of the stomach and if possible introducing the tube into the duodenum. He then pumps a 7% slurry of Fuller's Earth in saline directly into the small intestine at the rate of 500 ml/hr. This apparently results in very good clearance of paraquat from the gut and this technique will be recommended to American physicians.

The work on inhibition of lung uptake of paraquat by various agents have proved to be unsuccessful in in vivo experiments. Thus, ICI is currently dropping this line of approach until they have a better understanding of the actual mechanism that they are trying to interfere with.

Research for the next 24 months will be going into two new directions because, between the successful treatment regimen presently being recommended for paraquat and the introduction of the emetic which is expected to further decrease fatality, CTL expects that there may be an increase of cases of residual fibrosis of the lung in surviving patients. Therefore they are directing a portion of their program towards the treatment of this fibrosis. However, the first problem will be to find a suitable animal model. In order to accomplish this, they are going to let a

contract to Drs. Griffin and Wynn of Trent Polytechnic, an academic institution, to try to develop such a model. We will be assisting them in this project in that a number of investigators in this country have tried to use paraquat as a model for pulmonary fibrosis. We will be contacting these people to try to determine what they have done and what direction they are taking. Once a dependable model for pulmonary fibrosis of the type caused by paraquat, i.e. alveolar fibrosis, is found, then a series of antifibrotic drugs, including POTABA, Azothioprine, and various steroid combinations will be tested against this model. The major part of their program for next year will be to determine the biochemical mechanism of pulmonary damage. Among other things they will be studying the effects on transglutaminases and other indicators of biochemical injury to the lung. A detailed protocol will be presented to us with the next quarterly report.

The next subject taken up was that of the hematological aspects of paraquat poisoning. This investigation was spurred by two personal injury law suits occurring in this country, the McKenzie case in which a small child developed a transient aplasia of the erythrocytes following an alleged slight exposure to paraquat, and the Mendez case in which a spray operator blames the contracted disease, aplastic anemia, from spraying with diquat. The first indication that hematologic injury may be associated with paraquat came from the paper by Dr. Lautenschlager, and this work represents a follow-up. Work to date was prepared by Dr. Joel Sanderson, the head of the Hematology Unit at the Central Toxicology Laboratories. The final report on this work is not completed but will be forwarded to us at that time. We do have a letter summarizing experiments written by Dr. Sanderson and that letter is appended to this memorandum. Basically, Dr. Sanderson found that after acutely toxic doses of paraquat one of the first events that occurred was hemoconcentration as a result of water loss. Other work has substantiated this, indicating that there is a rather dramatic decrease in tissue water in all organs within the first 24 hours following paraquat intoxication. The picture in the peripheral blood indicates an increase in the absolute number of erythrocytes per cubic millimeter and a decrease in the absolute number of leukocytes. Bone marrow smears that had been taken 24 hours after a toxic dose of paraquat was administered to the rat showed an increase in the white to red cell ratio. Dr. Sanderson is of the opinion that these changes are transient and thus probably not significant in acute intoxications. Personally, I cannot argue the fact that these are transient changes. Following the clinical course of our own patients, as well as those in the published literature, these changes do not appear to play a dominant role or even a significant role in acute intoxication. However, I cannot dismiss these changes as completely insignificant because of the possibility that, in cases of chronic exposure to paraquat, the mechanism of injury to the marrow may be of serious worry to us in the future. Drs. Rose and Lewis have proposed a schedule of further studies. Dr. Rose will be meeting with Dr. Sanderson in the very near future to discuss appropriate studies. We are strongly of the opinion that Chevron should initiate a 90-day study using non-acutely toxic levels of paraquat and very carefully follow parameters such as bone marrow, peripheral blood picture, cellular distribution and count, uptake of paraquat into various organs, etc.

Because time is a factor and CTL wish to perform themselves those experiments which they think will best fit into their biochemical analysis, they have asked if we can undertake this 90-day study. We expect to hear within a month the results of talks between Rose and Sanderson on this subject. However, it must be said that paraquat does apparently have an effect upon the bone marrow and the peripheral blood.

Our meeting reconvened Thursday morning and we discussed information exchanged regarding accidental or suicidal poisoning cases. We discussed ways of improving the reporting of British and European cases. CTL has gone to a computerized data retrieval system in which the cases are being filed and coded by country, patient's name, doctor's name, whether or not it was fatal and whether or not appropriate treatment was provided. This file will be constantly updated and follow-up information as

received will be added to it. We will receive the printout from this at specified intervals. This should enable us to keep an up-to-date running file on world-wide intoxication cases.

There has been essentially no progress with regard to the proposed epidemiology studies. Dr. Keir Howard, medical director of P P D, has ascertained that certain tea plantations in India and Ceylon, employ persons who may spray only with paraquat. He is investigating the possibility of utilizing these populations and we expect to hear from him within two or three months. I strongly urged that any study undertaken be carried out by British or European physicians in order to lend the appropriate degree of credibility to the work. Any protocol for the study will be reviewed and commented on by us prior to its initiation. It was agreed that this epidemiology study is a matter of the highest priority.

Dr. Litchfield commented briefly on some experimental work on paraquat that was conducted in Russia. They have done a battery of acute and subacute tests with paraquat. They have found no adverse affects from very low levels of paraquat, i.e. on the order of 1/100 - 1/1000 above the LD_{50} after one year of feeding or four months of inhalation. The Russians promised to forward reports of these studies to Dr. Litchfield and he has agreed to send them to us as soon as he obtains them. The acute toxicity of paraquat recorded in Russia was very similar to that reported by CTL and by ourselves. The parameters studied on their subacute and chronic studies included serum enzyme activities, central nervous system toxicity, behavior, histopathology, organ/body weights and histochemistry. Dr. Litchfield reported that some work done in Czechoslovakia by a fellow whose name is pronounced Rozivao has implicated paraquat as a mutagen or as a carcinogen. No references were given to Dr. Rozivao 's work and PPD through Arthur Waitt is going to try to follow this up. Additionally, we understand that further work has been done in Czechoslovakia demonstrating very conclusively that there is no carcinogenic effect from chronic administration of paraquat and again Mr. Waitt will be sending us this information. In addition, Waitt is submitting a monograph to WHO on paraquat regarding both its treatment and species sensitivity.

A note of interest is that the papers resulting from the proceedings of the clinical meeting on paraquat are now ready for printing and will be available for distribution early in the year.

Dr. Gordon Steel was kind enough to spend some time discussing with us analytical methods for measurement of paraquat. They now have a GC method using a nitrogen selective detector with which they are able to quantitate paraquat in small samples of blood. Dr. Steel's claim is that they can find 0.01 ppm in a 3 ml sample. They have done this 500 or 600 times now and feel that it is a very excellent method. It is somewhat laborious and requires anywhere from $2\frac{1}{2}$-4 hours depending on its urgency and Dr. Steel is going to be forwarding us the methodology. As we receive it, we will forward it to Jim Leary. They are continually looking for other methods. They are making some progress in a high pressure liquid chromatography system in which the paraquat is rendered soluble in organic solvent. The reaction sequence is very rapid and they feel that within 4-5 minutes they can find 0.01 ppm in 1 ml blood. This work is just starting and the method has high selectivity. However, the instrumentation for this is not readily available. They will keep us informed through Mike Rose of their progress.

With regard to the reduction of paraquat in urine, it was Dr. Steel's opinion that almost any potent reducing agent should function, providing the urine was rendered highly alkaline. He suggested trying hypochlorite solution and other common reducing agents. Dr. Litchfield has had personal experience with the dithionite method over a long period of time and has never experienced any interference other than the presence of other bipyridals such as diquat, in which the color change is more of a green color.

The subject of communications was discussed briefly and it was the opinion of all present that the communications system is working quite well for the first time. Our experience over the past 12 months has been very good. The one exception to that would be the recent fiasco regarding the emetic data. However, I don't believe that this is a result of a breakdown in communication, but rather the fact that no hard copies of the data existed. Dr. Rose had not seen any of the data on the emetic. The only information in his hands was that on the dog and rat studies using the paraquat-emetic formulation, and Dr. Litchfield, although he had reviewed the data on the microfiche at Pharmaceuticals, himself had no copies. As soon as it was possible to print these copies they were delivered to our hands.

We were asked to direct a copy of all correspondence with Dr. Rose to ICI-United States to Mr. D. C. Walker of ICI-United States in Wilmington, Delaware.

This concludes my notes on the toxicology liaison meetings. I feel that these were most productive meetings and certainly justified from both the British and American viewpoints.

R. D. CAVALLI

RDC:flm
Enclosures

CENTRAL TOXICOLOGY LABORATORY

AGENDA FOR CHEVRON LIAISON MEETING

8-9 September 1976

Wednesday, 8 September 1976

Car arranged from Mottram Hall to CTL for Drs JN Ospenson, RD Cavalli and Mr A Waitt.

Morning:

09.15 Room G.10

- Paraquat registration situation in USA
- Accreditation
- American Litigations
- New Formulations

Drs JN Ospenson, RD Cavalli, ~~IFH Purchase~~, MH Litchfield, MS Rose and Mr A Waitt

12.30 Lunch : CTL Dining Room - Drs Swan, Ospenson, Cavalli, Litchfield Rose and Mr Waitt.

Afternoon : Room G.12

14.00
- Treatment of Poisoning/Research UK
- Treatment of Poisoning/Research USA
- Haematological Aspects of Paraquat Poisoning

Drs JN Ospenson, RD Cavalli, LL Smith, MS Rose and Mr A Waitt

Dinner: Drs Cavalli, Rose, Smith and Mr Waitt - The Bridge Hotel, Prestbury.

Thursday, 9 September 1976

Morning:

09.15 Room G.12

- Information exchange re poisoning cases
- Epidemiological studies
- Russian experimentation

Drs RD Cavalli, MH Litchfield, MS Rose, Mrs IA Whitaker and Mr A Waitt

12.30 Lunch : Enzo's Restaurant - Drs Cavalli, Litchfield, Rose and Mr Waitt.

Afternoon : Room G.12

14.00
- Analytical methods for measurement of paraquat
- Communications UK/USA
- Summary

Drs RD Cavalli, GT Steel, MS Rose, Litchfield and Mr A Waitt

16.15 Car to Ringway Airport.

Copies: Drs Ospenson, Cavalli, Swan, Litchfield, Rose, Smith, Purchase, Steel, Calderbank, Mr Waitt and Mrs. Whitaker.

SDL : 3 Sep 76