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PJ21/76/2C

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DEVELOPMENT

PROJECT TEAM REPORT

PARAQUAT : REDUCTION OF HAZARD

November 1976

Full Edition

Editor : D M Foulkes

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1 3

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CONTENTS		PAGE	NO.
	Summary and Recommendations	i	
1	PP796 Development	1	
1.1	Policy	1	
1.2	Animal model studies	1	1
1.3	Inclusion rate of PP796	1	×
1.4	Formulation	2	
1.5	Formulation and packing Widnes Works	3	
1.6	Field Trials (including solid formulations)	4	
1.7	User trials	5	
1.8	Metabolism and residues	12	e e
1.9	Patent status	15	
1.10	Registration	16	
1.11	Policy on Safer Formulations	17	• •
2	Hazard reduction : General	18	
2.1	Summary of CTL work	. 18	
3	Patents	20	
3.1	Status of Safer Formulations Patents	20	
4	Alternative Formulations	24	
4.1	Liquid encapsulation	24	
4.2	Current policy	25	
4.3	Solid Formulation	26	
4.4	Valeric Formulation Storage	27	
5	Toxicology and Poisoning	28	
5.1	Incident Review	28	
6	Registration Status	29	
	Appendix I		
	Appendix II		

Appendix III

- 123

PARAQUAT : REDUCTION OF HAZARD OCTOBER 1976

SUMMARY

The salt-based, fluid bed solid paraquat formulation is preferred by Chevron and I.C.I. to the carbowax formulation explored by Chevron. It is proposed that the technical case for the I.C.I. formulation be written up and this project be indefinitely shelved.

There have been ten fatalities through paraquat ingestion reported since May 1975. There is no evidence that stenched formulation was involved.

An extensive programme to develop an emetic formulation of paraquat has been undertaken. This is now capable of technical realisation and is the subject of the major part of the report. It is proposed that we seek our first registration, in the U.K., through submission to the P.S.P.S. in November, followed thereafter by introduction in Europe and other territories as soon as possible.

RECOMMENDATIONS

- 1. The technical support for the inclusion of PP796 in all paraquat containing formulations should be sustained as high priority.
- 2. Soil leaching and plant uptake of PP796 should be examined.
- 3. Work on previously explored techniques for hazard reduction by formulation should terminate with a watching brief maintained on alternative ideas which may arise.
- 4. The P.P.D./Mond evaluation of solid formulations should be carefully written up and filed for any future reference.
- 5. Patents on alternative approaches to safety should be maintained but reviewed following our future experience with PP796 containing formulations.
- 6. The U.K. user trials of stenched emetic v. non-emetic "Gramoxone" should be completed as planned and reported separately.
- 7. Future work at C.T.L. on understanding the mechanism and control of paraquation toxicity should be kept under review.

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PP796 Development

1.

Emetic Formulations

No major difficulties have yet arisen in the development of the emetic formulation. The animal work at CTL to confirm previous results on the efficacy of the product should be completed very soon, and there have been no problems with the formulation of the emetic agent (PP796) into paraquat formulations in laboratory tests. Preparation of stenched emetic "Gramoxone" on a plant scale is feasible since PP796 can be added to "Gramoxone" in a solution in pyridine bases, and work is in progress to find the best means of incorporating PP796 into unstenched "Gramoxone" and paraquat concentrate.

1 -

Results from user trials are expected to confirm that there will be no adverse effects on users of the new formulation and the trials will also confirm previous evidence that PP796 does not reduce paraquat's herbicidal effectiveness. Work on the environmental and crop residue behaviour of PP796 is in progress. It is the intention to register the emetic formulation worldwide as soon as possible. Discussions are taking place at present with Regional Departments to determine the strategy for the timing of its introduction

The development of coloured, thickened and stenched paraquat formulations has reached the position of being able to provide stable formulations with all these deterrent properties either alone or in combination. The emergence of an emetic formulation together with the absence of any other obvious deterrent approach has led to the reduction of effort in this general area. It is proposed that active deterrent research be minimal pending our feedback from the marketing of an emetic formulation which, in any event, is likely to be stenched.

1.1 The rationale for the inclusion of PP796 in "Gramoxone"

This is summarised in CTL report 390 (Appendix I)

1.2 Animal Model Studies

Studies on the combination of PP796 with paraquat in animals are described in Appendix I.

1.3 Inclusion rate of PP796

After consideration of human and animal exposure to PP796 and the data from animal studies referred to in Section 1.2 of this report the level of inclusion of 0.05% PP796 in "Gramoxone" is proposed. The reasoning supporting this proposal is displayed in Appendix II.

1.4 Formulation

C. Barris P. C.

Since the last project team report an analytical method (PAM 551) has been developed to determine low levels of PP796 in the different paraquat formulations. This method has been used to show that formulations of "Gramoxone" U.K., Export and S containing 500 mg/litre of both pure and and 90% purity PP796 stored for in excess of 3 months at 25, 37, and 50 °C, show no chemical breakdown in any samples measured.

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A method for incorporating 500 mg/litre PP796 into "Gramoxone" U.K. (stenched) JF 6044 by dissolving the PP796 in pyridine base at 5%. (The solubility of PP796 in pyridine base at 0°C 4.4% w/v; 10°C 5.5% w/v; 25°C 6.3% w/v) was investigated and sufficient of this intermediate (JF 5986) to prepare the 8000 litres required for the U.K. trial was prepared at Jealott's Hill and incorporated into the paraquat by Mond Division. Physical tests on crystallisation temperature of this intermediate indicated no crystallisation of PP796 even at temperatures close to freezing.

Problem of analysis was encountered by Mond Division but these anomalies are being investigated by both Mond Division and P.P.D.

The solubility and stability of PP796 in paraquat concentrate has been investigated in order to facilitate the possible incorporation of PP795 via this concentrate. The solubility of PP796 was always in excess of 0.4% at 10°C and 20°C, and chemical stability investigations on two paraquat concentrates (40.2% w/v and 36.5% w/v paraquation concentration at pH 2.2 and 3.25 respectively) containing 2.6% w/w. PP796 indicated no significant breakdown after 6 weeks at 50°C or 1 week at 90°C. No crystallisation of PP796 from these concentrates has been observed after 6 weeks at temperatures dow to $-5^{\circ}C$.

The approximate solubility of PP796 in a number of different solvents with a view to incorporation via a solution, has been looked at, and at present the most interesting solvent for toxicological and processing consideration is propylene glycol in which PP796 has an approximate solubility of 4.0% w/w at $20^{\circ}C$

1.5 PP796 Formulation and Packing - Widnes Works

A 9,000L batch of the formulation was produced and packed at Widnes Works to provide material for field trials. The emetic compound was introduced in solution in pyridine base so that the resulting concentrations in the final formulation would be 1% pyridine base and 0.05% emetic compound. No difficulty was experienced in obtaining a uniform blend by mixing with pump recirculation. No problems arose on packing.

- 3 -

The present system for addition of pyridine stench is unsatisfactory on safety and environmental grounds, and prior to the introduction of the emetic an improved system was being considered. This improvement is now even more desirable and is being pursued urgently with the aim of having it available by the beginning of 1977. With the proposed modifications the plant should be capable of producing the required amounts of stenched PP796 in bottles, but at the moment there is no system for producing a stenched or unstenced PP796 formulation of concentrate in drums.

1.6 Biological Testing of Solid and Emetic Paraquat Formulations

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Four sets of trials have so far been completed during 1976 on the above subject. The series coded PFA and PFD were both carried out in early spring using the metre box. They studied solid paraquat formulations and PP796/paraquat mixtures respectively, and compared them with standard Gramoxone U.K. as a perennial ryegrass sward killer. The PFC series was carried out in April/May and looked at activity of solid paraquat formulations and a PP796/paraquat mixture on potato weeds with the same Gramoxone U.K. standard. The PFB series was a similar set of trials but on perennial ryegrass. They were carried out in the June/July period. The results are summarised in Graphs I - VI. Wetter concentration for a given paraquat rate was constant for all treatments.

PP796

The inclusion of the emetic agent PP796 in no case had any significantly adverse effect on the biological activity of paraquat on the species tested, even when the rate was increased from 500 mg to 2000 mg PP796 per litre of Gramoxone U.K.

Solid Formulation

CC 5989 was the outstanding formulation, on some occasions being significantly better than Gramoxone U.K. particularly at the lower rates. The performances of PPD MS11 and MS21 were more variable, they both appeared to give slightly lower initial activity than Gramoxone U.K. but then recovered. In general their activity was slightly inferior to Gramoxone U.K. with MS21 being slightly inferior to MS11.

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1.7 User Trials

新闻》:"你们没有 韩全国的公司,你们

The possibility of spray operators, in U.K. conditions, encoutering side effects as a direct consequence of the presence of PP796 is, based on knowledge of lack of volatility and minimal uptake through skin, a remote possibility. Nevertheless, in order to detect any unexpected response and, in addition to gain further information on the biological performance of the new formulation a series of operator trials have been undertaken.

The trials were designed to compare U.K. stenched "Gramoxone" with the stenched emetic formulation in the following manner.

- A further 60 operators ½ day spraying with emetic "Gramoxone" (3 pints in 10 gal/acre).
- 3. 10 operators 2 days continuous spraying with emetic "Gramoxone" (3 pints in 10 gal/acre).

The trials are being undertaken through U.K. Development Department whose development officers are using a market research questionnaire to gather individual responses.

The information from these trials is still being received and will be the subject of a separate review document. Preliminary indications show that the only adverse response encountered is linked to the presence of the stench in the formulations.

Trials PFD/1-3/76

Comparison of scorch indeces over a five week period after spraying of Gramoxone UK (YF 6583) and Gramoxone UK (YF 6583) plus three rates of inclusion of PP796 as a tank mix.



Fig. II. Trials PFB/2-6/76

Comparison of scorch indeces over a five week period after spraying of Gramoxone UK (YF 6583) and Gramoxone UK (YF 6583) plus 500 mg/l PP796 as a tank mix.



Comparison of scorch percentage of weeds on a potato crop treated with Gramoxone UK (YF6533) and Gramoxone UK (YF6583) plus 500 mg/l PP796.







Comparison of scorch indeces over a five week period after spraying of Gramoxone UK (YF 6583) and three solid formulations

10





Comparison of % weed scorch one week after spraying of Gramoxone UK (YF 6583) and three solid formulations on emerging potato crops.

g/ha paraquat 600 1200 600 1200 600 1200 600 1200 cation CC 5989 MS21 YF 6583 MS11 Gramoxone UK 20090351

1.8 <u>Metabolism and Residues</u>

Soil Studies

Results of the treatment of four soils with ten and a hundred-fold levels of the propyl-labelled PP796 are now available for five weeks after treatment.

The volatile radioactivity (other than ¹⁴CO₂) trapped has not amounted to more than 0.01% of the original activity. The ¹⁴CO₂ evolved (after 5 weeks) varies from 2.2% of the low-rate dose to 0.1% of the high-rate application. This suggests that the "undesirable" propyl labelled molecule is, in fact, fairly resistant to microbial attack of the propyl group.

After 5 weeks, the percentage of applied radioactivity recovered by somhelet extraction for 24 hours with methanol has decreased to 70%

Day	's after	applicat	ion :		0	10	18	38
% ∈	xtractal	le with	MeOH	:	100%	85%	80%	68%

A further 12 - 14% of the activity may be extracted from the Day 38 soil sample with water/méthanol and water treatments leaving 20% strongly bound. As yet no data has been obtained on this residue.

Of the extractable material, radioscanning reveals > 80 - 90% of the radioactivity is due to parent material.

The results from all four soils have been broadly similar (including an experiment in the presence of paraquat).

Plant Studies :

In a preliminary experiment with bean plants, PP796 was applied in methanol at a rate approximately 2000 times the field rate. Methanol extraction gave quantitative recovery from day 0 and 1 leaves whilst on day 14, 80% was extractable. > 90% of all extracts was unchanged emetic. Unfortunately at this rate the bean plants died with curling of the leaves; thus a realistic assessment of the degree of exposure of the leaves to the sun is impossible.

In a current experiment PP796 has been applied to cotton leaves in a greenhouse under lamps at 400 x field rate. Data is at present available for the first 14 days of the study. These follow the same general pattern as the first experiment with no significant metabolism. There are some base-line radioactive compounds present on chromatography, but at present these are regarded as artefacts.

Water Studies :

pH Hydrolysis

In a simple pH 5, 7 and 9 hydrolysis study of 5 ppm solution of PP796 in the dark, samples have been taken and analysed for a period of 26 days.

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The results indicate that the radioactivity in solution remained constant over the four week study and no metabolism has been found in any solution.

River Water Hydrolysis

Samples of Thames and Blackwater (containing relatively high levels of ATP, <u>i.e.</u> micro-organisms) have been treated with 5 and 50 ppm of PP796 (including Gramoxone in one case). The solutions have been aerated and samples have been taken and analysed over a period of 28 days.

The results indicate that the emetic is not removed from the solution (only traces [] < 0.01%] of 14CO2 have been evolved) as incubation time increases. There also appears to be little absorption onto the sediment. Autoradiograms for Day 1 to 14 reveal no metabolism to have taken place.

Photodegradation in water

5 ppm solutions of PP796 have been allowed to stand in sunlight under a polythene cover for 28 days.

Analysis and extraction reveals that the level of radioactivity presents in the solution does not change, but the emetic degrades rapidly (halflife - 4 days) to a multitude of compounds (the majority of which are more polar than PP796). The presence of Gramoxone does not affect the rate of degradation of parent material but does appear to change the route of degradation.

The presence of acetone in the photodegradation solutionalso appears to have this effect.

Anaylsis

A provisional analytical method has been developed which allows quantitative determination of PP796 in crop samples in the presence or absence of paraquat. The limit of detection for this method is 0.01 ppm.

In summary, the method involves initial extractions of the compound using methanol followed by column chromatographic cleanup. Final quantitative determination of residues is by gas liquid chromotography utilising a nitrogen specific detector. Additional confirmation of the identity of the residue is possible using the alternative detection techniques of mass fragmentography and fluorimetry.

Preliminary results obtained from ryegrass samples which had been treated with 6.0 1/ha of "Gramoxone" and PP796 (500 mg/l) i.e. Formulation JF5862 indicated the 0 day residues of 0.25 ppm of pp796 fall to 0.02 ppm after 7 days.

Results of analysis of potato tubers, harvested 6 weeks after treatment of the plants with 6.0 1/ha JF5862 indicated no detectable residues (re 0.01 ppm) of PP796.

Further samples of ryegrass and potatoes will be analysed and the results reported for P.S.P.S. registration

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It has been agreed to send details of the provisional analytical method together with the results obtained to the Chevron Chemical Company, U.S.A.

Taint tests in fresh and canned potatoes harvested following spraying with 1 g/l PP796 "Gramoxone" formulation (i.e. twice proposed concentration were negative.

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1.9 Patent Status

1. PP796

U.K.

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I.C.I. Case PP 28720 - filed 15th April 1976; and updated

I.C.I. Case PP 29810 - filed 19th August 1976.

I.C.I. Case PP 28720 has been filed in the following countries:

Taiwan - June 1976 U.S.A. - September 1976 Colombia - Sept/October 1976 South Korea - October 1976

It is worth making the point that the "content" of the patent specification relating to PP796 bipyridylium composition varies from country to country.

2. Other Emetic Compositions

I.C.I. Case PP 28924 : PQ + selected, known emetics

28926 : PQ + amidines

29827 : PQ + aminoguanidines

29825 : PQ + 1.5(C) pyrimidines

All the above cases were filed 19th July 1976.

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<u>U.K.</u>:

Limited clearance has been obtained for the use of 10,00 litres of "Gramoxone" formulation JF 6044 on about 2,000 hectares of stubble and other normal, cleared, "Gramoxone" outlets. The Ministry consider that clearance is (except in the safety sense) a minor formulation change that is not expected to present any hazard to spray operators. The clearance is valid until 31st July, 1977, and is unconditional except that it in no way commits the Ministry to agree to any other use of the product. A new notification should be submitted at least two months before further clearance is required. If an application for commercial clearance of the emetic formulation cannot be submitted by the end of October, a request for extension of clearance of YF6690 (stenched) must be made to cover the period from 1st January, 1977. This would still take two months but should be a formality provided that we can express our intent to proceed with JF 6044.

The ACAO has granted permission for the current "Gramoxone" label to be used during the period of limited clearance, Full details of tests and results are required before the emetic formulation becomes commercially available.

Overseas :

No formal presentation has been made to any overseas authority. Views of West European agents have been sought at a meeting on 12th October, when they were briefed on all aspects of the compound.

Our hope is that the submission will be accepted, as in the U.K., as a minor formulation change. If this is correct, a massive experimental programme will not be needed and re-registration could be effected in about 6 - 9 months.

1.11 Policy on Safer Formulations

"Deterrent" Formulations

The pyridine-base stenched formulation is being sold in U.K., Eire, France, and Germany and it is planned that it should be introduced into most of the remaining countries of Western Europe in 1976/77. The registration authorities now require its introduction as soon as possible in Malaysia and New Zealand and it is intended to introduce it to Australia also. In the U.S.A. Chevron are carrying out the necessary work to enable n-valeric acid-stenched paraquat to be sold in the U.S.A. from late 1977/early 1978.

- 17 -

Before stenched product is introduced more widely it is intended that some consumer research should be carried out to determine whether valeric acid or pyridine base stenched material has any adverse effects on users and/or is deterrent to use of the product.

2. Hazard Reduction : General

2.1 <u>Summary of CTL work</u>

1(a) Inhibition of paraquat uptake into lung

Attempts to reduce the amount of paraquat accumulated into rat lung in vivo following the subcutaneous administration of a variety of compounds shown to be very effective in inhibiting paraquat accumulation into lung in vitro have not proved successful. The failure of compounds which inhibit the in vitro accumulation to work in vivo is not understood. Some compounds given in vivo (promethazine, cysteamine, spermine, and 1 - 6 hexa diamine) possibly reduced the clearance of paraquat by the kidney by either damaging the kidney or competing with paraquat for its site of secretion by the kidney. This results in elevated plasma paraquat levels and subsequently elevated lung paraquat levels when compared to paraquat dosed, saline treated rats. With lysine, putrescine and decane diamine there was no effect on the plasma paraquat levels but no inhibition of paraquat into the lung. At present, studies are being undertaken in an attempt to understand more fully the factors important in the uptake of paraquat into the lung <u>in vivo</u> and perhaps explain the failure of agents such as lysine and putrescine to inhibit paraquat accumulation. However, it appears unlikely that blocking uptake is a vlable therapeutic approach.

1(b) Treatment of fibrosis

Following recent discussions with representatives of Huntingdon Research Centre and the Poisons Unit, London it has been decided that the cost of carrying out survival studies on the use of antifibrotic agents on beagle dogs cannot be justified. However, it is possible that as appropriate facilities become available within CTL, studies directed towards the development of a suitable fibrotic model in rats will be undertaken.

2(a) Biochemical changes in the lung

The effect of paraquat on several biochemical pathways in the lungs of treated rats has been investigated. Also in vitro studies have confirmed that paraquat will inhibit various metabolic pathways. At present several agents (e.g. free radical scavengers, superoxide dismutase, sodium lactate) are being investigated using the inhibition of fatty acid synthesis as an indirect measure of the toxic action of paraquat on the lung. It is hoped that in this way a clearer understanding of the precise mode of action of paraquat toxicity can be obtained and that the efficacy of potential antidotes can be rapidly screened. To date only sodium lactate (a compound with therapeutic properties in the treatment of oxygen toxicity) has been investigated and this did not afford protection to paraquat treated rats nor reduce the inhibition of fatty acid synthesis in lung slices treated with paraquat.

2(b) Relationship of oxygen to paraquat toxicity

Recent studies have shown that rats given an oral LD100 dose of paraquat then placed in 10% oxygen : 90% nitrogen die more rapidly than rats given the same dose of paraquat then placed in ambient air. We have also shown that the increased toxicity in 10% oxygen treated rats is associated with a more rapid accumulation of paraquat into the lungs such that by 6 hours after dosing, the concentration of

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paraquat in the lung of 10% oxygen treated rats is similar to that of air treated rats at approximately 24 hours. This increase in lung levels of paraquat cannot be explained by elevated plasma paraquat levels in the 10% oxygen treated group. However, it is possible that there is an increase in cardiac output, together with an increase in the surface area of lung perfused by blood due to hypoxia, thus exposing more lung alveoli to paraquat. At present, experiments are being undertaken to investigate this effect further and also to study the effect of hyperoxia in paraquat poisoning. It is clear from the data at present available that the use of lowered oxygen therapy in cases of paraquat poisoning should only be undertaken (if at all) when plasma paraquat level is very low.

2(c) The effect of paraquat on the kidney

Paraquat damages the kidney in both man and experimental animals. Current work is aimed at elucidating the mechanism by which this damage occurs, with a view to finding ways of protecting the kidney. The mouse was chosen as a suitable model as it is susceptible to kidn@g/ damage by paraquat (Eckers, Hook and Gibson, 1975) and as slices of renal cortex have been shown to accumulate paraquat to several times the concentration present in the incubation medium (Eckers, Gibson, and Hook, 1975). However, to date we have been unable to repeat the observation of Eckers showing that mouse renal slices accumulate paraquat, giving slice/medium ratios of about 4 - 5 by 180 min at 37°. The best slice/medium ratios for paraquat uptake we have obtained is about 1.4 despite extensive experimentation. Under these conditions (i.e. small paraguat uptake) the base N'-methylnicotinamid® is accumulated by mouse renal slices giving slice/medium rations in agreement with other published data. At the present time we are unable to explain our inability to repeat Ecker's observations, but it remains possible that this is due to strain differences in the mice used.

Current work is aimed at measuring renal function in the rat after paraquat, in order to assess whether the rat is a suitable model for studying kidney damage.

Work on young rats (approximately 50 g body weight) has confirmed that these are more resistant to paraquat than adult rats (approximately 200 g body weight). This has been explained previously by other workers as being comparable to the resistence of young animals to oxygen toxicity and higher levels of superoxide dismutase present in lung etc. We have now shown that the plasma paraquat levels in young rats (given the same dose orally/kg body weight as adult rats) is considerably less at 24 - 48 hours and consequently lung levels are considerably less. This is considered to be a renal effect i.e. the kidney of young animals appears more resistant to the effect of paraquat. Research into this observation is continuing.

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3.1 Status of Safer Formulations Patents

PP 24119/24665

This case relates to aqueous formulations of paraquat containing a gelling agent to convert the formulation into a thixotropic gel. The claims as filed were broad enough to cover all conventional gelling agents. Those mentioned by name include water-soluble polysaccharides e.g. "Kelzan" and cellulose derivatives, finely divided silica and alumina, and china clay. There is a certain amount of prior art in the form of publications disclosing thixotropic formulations of herbicides, and patentability is likely to be difficult to establish in countries (e.g. U.S.A., Germany) where patent applications are rigorously examined. In such countries it will be necessary to restrict the claims to the types of gelling agent specifically named in the patent. The complete specification was filed on 26 June 1972 and applications were also filed in the following countries :-

20 -

Australia Hungary Belgium Israel Italy Brazil Canada Japan Chile Jugoslavia Columbia Mexico Cuba New Zealand Czechoslovakia Peru Denmark Poland Eire Philippines France Russia Germany South Korea Germany East South Africa Holland Spain

Switzerland Taiwan Uruquay U.S.A. A & M. U. Bulgaria Costa Rica Egypt Greece Nicaragua Portugal Sweden Nigeria

PP 24933

This case relates to aqueous paraquat compositions containing an odourant comprising one or more alkypyridines (e.g. pyridine base). Patentability is difficult to assess; the application was rejected in Bulgaria but a U.S. patent has been granted. The complete specification was filed on 15 March 1973. Corresponding applications were filed in the filowing countries :-

Australia	Holland	Sweden
Belgium	Hungary	Taiwan
Bulgaria	Israel	U.S.A.
Canada	Italy	Philippines
Czechoslovakia	Japan	South Korea
Denmark	New Zealand	Malaya
Eire	Spain	Singapore
France	South Africa	Sarawak
Germany	Switzerland	Sabah
U.K.		

PP 26695

This case relates to ULV formulations of paraquat comprising an emulsion in which droplets of an aqueous solution of paraquat

are dispersed in an oil in the presence of an emulsifier. This case was filed basically because of the interest in ULV application of paraquat, but there has been some interest in the compositions as possible safer formulations of paraquat in view of their viscous nature. Patentability is considered doubtful; the United States application has been rejected on the grounds that such formulations are well known in pesticide technology, and the application is now at the stage of appeal. The complete specification was filed 13 December 1974. Corresponding applications were filed overseas as follows :-

Germany

Holland

Hungary

Israel

Italy

Japan

Mexico

Argentine Australia Belgium Brazil Canada Cuba Czechoslovakia France New Zealand Russia South Africa Spain Switzerland Taiwan U.S.A.

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PP 26865

This case relates to aqueous formulations of paraquat made viscous by incorporation of polyacrylamide. Interest in this formulation as a safer form of paraquat was not very high at the time when completion of the patent application fell due (February 1975). Patentability was considered and the prospects of obtaining overseas patents poor. It was decided to complete the U.K. application only. However, I.C.I. Australia requested filing in Australia and New Zealand and this was also carried out.

PP 27971

AL LON

This case relates to a process for preparing solid granular formulation of paraquat, comprising injecting an aqueous solution of paraquat into a heated fluidised bed of a particulate carrier (e.g. salt granules) so that the aqueous solution evaporates and deposits the paraquat on the particulate carrier to form granules. The complete specification was filed 25 May 1976. Corresponding applications were filed in the following countries :-

Australia	Hungary	Mexico
Belgium	Israel	West Malaysia
Brazil	Italy	Russia
Canada	Japan	Roumania
Denmark	New Zealand	Taiwan
Eire	Holland	U.S.A.
France	Luxembourg	South Africa
West Germany	-	

PP 28492

This case exists at present only as a provisional specification filed in the U.K. It was filed on 20 January 1976 and relates to aqueous paraquat formulations containing an odourant comprising valeric acid or certain analogues thereof. Consideration must be given to overseas filings of this case by November 1976.

PP 28703

This case exists at present only as a provisional specification filed in the U.K. It was filed on 12 April 1976 and covers aqueous paraquat formulations containing an odourant selected from a list of named compounds. Consideration must be given to overseas filings of this case by early February 1977.

PP 28628

This case exists at present only as a provisional specification filed in the U.K. It was filed on 19 March 1976 and covers aqueous paraquat formulations containing an odourant comprising tetrahydrothiophene. A decision as to the completion and overseas filing of this case must be taken by mid January 1977.

For completeness, in addition to the above cases, there are three patent cases relating to solid complexes formed from paraquat and various complexing agents. These cases date back some years. They were filed partly because the complexes were thought to have increased biological activity compared with paraquat, and partly because the complexes seemed to be a possible convenient way of making solid paraquat. The cases were as follows :-

PP 20007

Argentina	Holland	New Zealand
Australia	Hungary	Pakistan
Canada	Israel	South Africa
Denmark	India	Phodesia
Eire	Italy	South West Africa
France	Japan	Spain
Germany	Mexico	U.S.A.
J.K.		

PP 20361

This case covers complexes of paraquat with aromatic compounds bearing one or more hydroxy, amino, or mercapto groups (e.g. Paminophenol). The complete specification was filed in June 1968. The overseas filing list was as follows :•

Australia	Holland	New Zealand
Canada	India	Pakistan
Denmark	Israel	Rhodesia
Eire	Italy	South Africa
France	Japan	Spain
Germany	Mexico	U.S.A.
I.K.		

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PP 20376

This case relates to complexes of paraquat with a range of metal salts (e.g. cobalt chloride, ferrous chlordie). The complete specification was filed in June 1968. The overseas filing list was as follows :-

Australia India Pakistan Rhodesia Canada Israel Denmark Italy South Africa Eire Japan South West Africa Mexico Spain France New Zealand U.S.A. Germany U.K. Holland

- 23 -

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4.1 Liquid Encapsulation

Following the last project team report recommendation, we have investigated the idea of producing a stable water in oil emulsion which would not break on ingestion, but readily invert on dilution and/or addition of an emulsifier. So far we have tested the "Comb" stabiliser of Paints Division, and the "Span 80". The former was unsuccessful, contrary to prediction whereas the latter produced a stable water in oil emulsion but very difficult to invert on dilution. The preliminary experiments showed that these ideas are not easy to achieve, unless a major effort is devoted to them, and in view of the promise presented by the emetic formulation it was decided to terminate this project in early July.

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4.2 <u>Current Policy</u>

The development of coloured, thickened and stenched paraquat formulations has reached the position of being able to provide stable formulations with all these deterrent properties either alone or in combination. The emergence of an emetic formulation together with the absence of any other obvious deterrent approach has led to the reduction of effort in this general area. It is proposed that active deterrent research be minimal pending our feedback from the marketing of an emetic formulation which, in any event, is likely to be stenched.

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Solid Formulations

4.3

Both the ICI fluidised bed salt based product and the Chevron carbowax formulation appeared to be generally acceptable in the Spring field trials, although the rate of solution of the ICI product received adverse comment. Both formulations have a high hygroscopicity and are more corrosive to aircraft alloys, and therefore require a suitable package and corrosion inhibitors to overcome these problems. Preliminary order of cost estimates by ICI and Chevron indicated that the capital cost of a 5000 T/yr plant would be £4M, and the additional production cost about 30 cents/lb, or £370/T active ingredients at 1976 prices. Such a project would take about 3 years to completion of commissioning from sanction with normal priority, or 2 years with the highest priority and with some risk of an extended start-up.

The ICI fluidised bed salt based product was produced on small scale plant equipment which could be scaled up with reasonable degree of certainty. The Chevron product was produced in the laboratory and their efforts to produce an acceptable product, using available process equipment which could be scaled up, have failed. They have concluded that the ICI product and process is to be preferred and is the one to be recommended for possible future emergency introduction.

The ICI magnesium sulphate formulation was abandoned earlier in the year as being the least promising product for further development.

A status report of the project will be prepared to allow ICI and Chevron to agree formally that sufficient work has been done for the present.

4.4 Valeric Acid Stenched Formulation

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The results obtained from the accelerated package storage tests showed that the valeric acid formulation can be satisfactorily packed in the intermediate density polythene bottles. There was no evidence of excessive permeation of odour through the container walls.

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5 <u>Toxicology and Poisoning</u>

5.1 Incident Review

The statistics for poisoning incidents are shown in Appendix III. There have been ten fatalities caused by accidental ingestion of paraquat since May 1976, eight are shown in the statistics and a further two have been reported to us subsequently.

Only one of the cases was in the U.K., and there is no evidence to implicate the stenched product. Four of the cases occurred before 1975, but have only recently come to light.

There have been a few deaths following dermal contact with concentrated paraquat solution.

Registration Status

<u>U.K.</u>:

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depair out the

Nothing to report.

West Europe :

Registration of pyridine-base stenched "Gramoxone" has now been completed in Switzerland. The Belgian authorities have requested colour as well as stench; if the position cannot be reversed, this will be introduced in February, 1977, at the same time as new standards of labelling necessitated by 1975 legislation.

Other Countries :

Data have been sent to register stenched "Gramoxone" in Hungary.

Following several poisonings in New Zealand, it will shortly be a legal requirement for paraquat to be stenched in that country. Data has been sent to the authorities to assist with the drafting of the legislation. The stenched product will simultaneously be introduced into the Pacific Islands, notably W. Samoa and Fiji, where the incidence of poisoning is causing official concern.

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APPENDIX I

REPORT NO: CTL/R/390

THE CONCENTRATION OF PP 796 REQUIRED TO PRODUCE EMESIS IN EXPERIMENTAL ANIMALS AND AN ESTIMATION OF THE EMETIC DOSE IN MAN

M S Rose

October, 1976

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SUMMARY

From the limited evidence of clinical trials and data from experimental animals, it is concluded that PP 796 should be added to paraquat formulations at a level of 5 mg in 10 ml (0.05%). It is estimated that the majority of those ingesting 10 ml of this formulation will vomit within an hour.

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The ICI development compound ICI 63197 produced by ICI Pharmaceuticals Division is a phosphodiesterase inhibitor (Farrell, 1970, Vol II) which has been shown to have a potent emetic action (Bayliss, 1973). This compound has been reclassified by ICI Plant Protection Division as PP 796.

When PP 796 is included in a paraquat formulation in amounts that will cause emesis within 1 hour in dogs and monkeys, the toxicity of the formulation to these species is reduced (Rose, 1976). In order to reduce the toxicity of the paraquat formulation to man, therefore, it will be necessary to add sufficient PP 796 to cause emesis, in a volume of paraquat concentrate that would normally be lethal if ingested. A volume of 10 ml of the 20% w/v paraquat concentrate is considered to be the smallest volume containing a possible lethal amount of paraquat to man (Fletcher, 1974). The question that remains to be answered therefore, is what amount of PP 796 should be added to this volume of formulation?

An emetic response in dogs, monkeys and pigs has been obtained with PP 796 over the dose range 0.1-1.0 mg/kg body weight (Table 1). On this basis a dose of 2 mg/kg was chosen as one that would clearly ensure vomiting in dogs and monkeys, and this dose was, therefore, used for studying the effect of emesis on paraquat toxicity in these species (Rose, 1976).

Studies in dogs using intravenous infusion have suggested that the emetic effect may be a response to the <u>rate</u> of increase in plasma concentration of PP 796 rather than due to a critical plasma concentration being reached (Hepworth, 1971). Certainly, the relationship between dose and emetic effect is steep (Table 1). 3

Clinical studies (Bayliss, 1973) have indicated that man is more sensitive to the emetic effects of PP 796 than the experimental animals studied, emesis being seen with doses in the range 0.03-0.11 mg of PP 796/kg body weight (equivalent to total doses in the range In the first human study involving 12 healthy volunteers 2-8 mg). (average body weight 70 kg), 1 was given 0.25 mg, 1 was given 0.5 mg, 2 were given 1.0 mg, 3 were given 2 mg, 2 were given 3 mg, 2 were given 4 mg and one was given 8 mg. Of these, the volunteer given 8 mg vomited as did one of those given 4 mg. Nausea was a marked effect reported by almost all of the volunteers. It can be seen that when the blood levels of PP 796 in the 2 volunteers given 4 mg are compared, the one that vomited absorbed the compound more quickly than the other (Table 2). This suggests that, as with dogs, the rate of absorption might be critical in determining whether vomiting will occur. After this first volunteer study, one conclusion reached was that "The agent was poorly tolerated at doses above 1-2 mg. Nausea, vomiting, dizziness, sweating and flushing were complained of". As a consequence of this, all further studies were carried out with a maximum dose of 2 mg. Of those who took 2 mg, approximately 10% vomited and 60% complained of nausea.

From the limited data available in man, therefore, it can be argued that a dose of 5 mg should certainly cause nausea and ought to induce vomiting in the majority of those ingesting it (Table 1). It should be noted that the clinical studies were carried out using PP 796 in tablet form. This will have led to an inevitable delay in absorption (Farrell, 1970, Vol. I). When present in paraquat formulations PP 796 will be in solution and may, therefore, be more readily absorbed. An additional factor that should also be considered is the irritancy of the paraquat concentrate, which causes nausea and vomiting (albeit after a delay of many hours).

In conclusion, the addition of PP 796 to formulated paraquat at the rate of 0.05% (5 mg emetic to 10 ml formulation) should be sufficient to ensure that most people ingesting 10 ml will vomit. Inspection of the statistics of paraquat poisoning incidents reported to ICI shows that most cases involve ingestion of quantities in excess of 20 ml, many suicides involving 50 ml or more. Under these circumstances, and considering 1) the irritant nature of the formulation, and 2) the fact that PP 796 will be in a soluble, dispersed form, it seems highly likely that vomiting will occur within an hour, with a consequent reduction in the amount of paraquat available for absorption.

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The emetic action of PP 796

	Dose	Nos. Vomiting	% Vomiting response	<u>Total dose (mg)</u>
Dog*	0.5 mg/kg 1.5 mg/kg	3/8 6/8	35 75	
Pig**	0.25 mg/kg 0.5 mg/kg 1.0 mg/kg	0/8 3/8 5/8	0 35 63	
Monkey ⁺	0.1 mg/kg 0.2 mg/kg 0.5 mg/kg	4/19 6/16 4/5	21 38 80	•
Man ⁺⁺	0.015 mg/kg 0.03 mg/kg 0.06 mg/kg 0.11 mg/kg	0/2 4/37 1/2 1/1	0 11 50 100	1 2 4 8

×	Data	from	Farrell (1970) Vol.	II.
*	Data	from	Broome (1972)	
÷	Data	from	Davies and Hepworth	(1969)
÷	Data	from	Bayliss (1973)	

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TABLE 1

*Comparison of blood concentrations of PP 796 in 2 volunteers given 4 mgs in tablet form

TABLE 2

	microg	'96/m1		
Hours after dosing		2		1990-990
Volunteer No 10*	180.0	0.041	0.034	
Volunteer No 11	0.045	0.056	0.044	

- * Vomited after 30 minutes
- + Data from Bayliss (1973)

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Bayliss, P.F.C. (1973) A summary of clinical results of the phosphodiesterase inhibitor ICI 63197 in a variety of disease states. Report No: PH20992B.

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APPENDIX II

REPORT NO: CTL/R/391

THE EFFECT OF ADMINISTRATION OF AN EMETIC (PP 796) ON PARAQUAT TOXICITY IN DOG AND MONKEY

M S Rose

Contributors : G R Parkinson W J D Laird

November, 1976

Summary

When paraquat was administered orally to dogs (20 or 30 mg of cation/kg body weight) or monkeys (100 mg of cation/kg body weight) together with a potent emetic (PP 796), the animals vomited. Dogs that vomited within the first hour of dosing survived an approximate LD75 dose of paraquat. Monkeys that vomited within the first hour of dosing survived an otherwise lethal dose of paraquat. The concentration of paraquat in the plasma of animals administered both paraquat and emetic was markedly lower than that of animals given paraquat alone. The toxicity to monkeys of paraquat formulated in the presence of an emetic dose of PP796 was estimated to be lowered by a factor of approximately 5.

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INTRODUCTION

Death from paraquat poisoning has occurred in man as a consequence of both accidental and deliberate ingestion of paraquat formulations (Fletcher, 1974). The LD50 in man has been estimated to be approximately 30 mg of paraquat cation/kg body weight which is equivalent to a volume of 10-15 ml of the 20% (w/v) paraquat concentrate to an adult man.

The addition of stenching agents to the formulation is currently being carried out as a possible way of reducing the risk of accidental ingestion. However, in order to increase the chances of preventing accidents or suicidal ingestion, it would be desirable to reduce the toxicity of the formulation. The addition of an effective emetic agent might be one way of achieving this, but such an emetic would have to be a) potent following oral administration b) of low toxicity c) stable in a mixture with paraquat and d) effective as an emetic in the presence of paraquat.

An ICI Pharmaceuticals Division compound, ICI 63197 [2-amino-6-methyl-5oxo-4-n-propyl-4,5-dihydro-s-triazolo(1,5-a)pyrimidone] which was developed as a phosphodiesterase inhibitor with anti-bronchoconstrictor effects, was shown after clinical trials in man to have a potent emetic action (Bayliss, 1973). This compound, which has been reclassified as PP796 by ICI Plant Protection Division, appears to have the necessary spectrum of properties required for an emetic that could be added to the paraquat formulation.

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In the work to be described here, this emetic, together with paraquat has been administered to dogs and monkeys in order to assess the effect on paraquat absorption and toxicity.

METHODS

<u>Animals</u>:

Male cynomolgus monkeys (Macaca fasicularis), body weights in the range 3.5-5 kg were used. Male beagle dogs, body weights in the range 9-12 kg were used.

Experimental:

In the case of monkeys, the paraquat dosing solution consisted of the appropriate volume of "Gramoxone" (formulation no. JF1423/A) diluted into a total volume of 20 ml such that animals received 100 mg paraquat cation/kg body weight. This dosing solution also contained 10 g Complan (Glaxo-Farley Foods Ltd, Plymouth, Devon) in an attempt to reduce the irritancy of paraquat to the stomach. The emetic (PP796) when added was present such that the animals received 2mg/kg body weight. In the case of dogs, the total dosing volume was 50 ml containing 6 g "Complan" and the required volume of "Gramoxone" (formulation no. JF1423/B) such that animals received either 20 mg or 30 mg paraquat cation/kg body weight and either 2 or 3 mg of emetic/kg body weight.

Animals were dosed by stomach tube with paraquat either with emetic or without, and the animals were then observed and the time taken to vomit recorded. 3.

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Blood samples (approximately 5 ml) were taken at intervals from a jugular vein (dogs) or femoral vein (monkeys). Paraquat was measured in these samples using the gas chromatographic method of Draffen et al (1976).

Two experiments were carried out in each species, each experiment involving 8 animals.

The LD50 to monkeys of paraquat formulations containing wetters (10%) stench (1% pyridine bases) and an emetic dose of PP796 was determined by dosing undiluted formulations followed by 100 ml water via a stomach tube, using pairs of animals at each dose level.

RESULTS

Monkeys dosed with 100 mg of paraquat cation/kg body weight died within the first few days of dosing, despite vomiting between 3 and 5 hours of being dosed (Table 1). Most of the monkeys dosed with the same amount of paraquat containing PP796 vomited within an hour and these animals survived (Table 1).

The concentration of paraquat in the plasma of monkeys dosed with paraquat plus emetic was considerably less than that in the plasma of monkeys dosed with paraquat alone (Table 2).

None of the dogs dosed with either 20 or 30 mg of paraquat cation/kg body weight vomited and 3 out of a group of 4 died between 4 and 8 days after dosing (Table 3). All dogs dosed with these levels of paraquat containing PP796 vomited within one hour of dosing and survived (Table 3).

The concentration of paraquat in the plasma of dogs dosed with paraquat plus emetic was considerably less than that in the plasma of dogs dosed with paraquat alone (Table 4).

The LD50 of paraquat formulated with 10% wetting agent, 1% pyridine stench and an emetic dose of PP796 was in the range 250-500 mg/kg body weight in monkeys (Table 5).

DISCUSSION

PP796 [2-amino-6-methyl-5-oxo-4-n-propyl-4,5-dihydro-s-triazolo (1,5-a)pyrimidine] has been shown to have emetic properties in experimental animals (monkeys, dogs and pigs) and in man (Tables 1 and 3; Farrell, 1970; Davies and Hepworth, 1969; Broome, 1972; Bayliss, 1973).

2-3 mg of PP796/kg body weight is clearly an emetic dose to monkeys and dogs, usually causing vomiting within an hour of dosing (Tables 1 and 3) and this action does not appear to be affected by the presence of a large excess of paraquat (between a 15 and 50 fold excess).

As a consequence of vomiting, the absorption of paraquat is considerably reduced (Tables 2 and 4) and animals survive an otherwise lethal dose of paraquat.

The administration to monkeys of paraquat formulation (containing no added emetic) also resulted in vomiting after a delay of many hours (Table 1), but this did not lead to the survival of the animals. Thus, for emesis to be effective, it must occur within an hour of

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administration of the paraquat.

The LD50 of paraquat to monkeys has been shown to be approximately 60-70 mg/kg body weight (Purser et al, 1975). The presence of an emetic dose of PP796 raises this value to 250-500 mg/kg body weight, thus reducing the toxicity of paraquat by a factor of approximately 5.

In conclusion, therefore, it is clear that the inclusion of an emetic dose of PP796 to a formulation of paraquat reduces the absorption of paraquat and thus significantly reduces the toxicity of the formulation.

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*Survival of Monkeys

	Animal no.	Time to vomit (hours)	Time to death (days)	Survival
Expt. 1	63) 95) 293)paraquat 295)	3.75 5 6 4.5	2 0.3 1 2	0/4
•	297)paraquat 299)paraquat 301) + 303)emetic	0.9 0.5 0.4 7.5	Survived Survived Survived 14	3/4
	e Paris			
Expt. 2	313) 315)paraquat 317) 319)	5 5 5	0.25 1 1-3 2	0/4
• •	305)paraquat 307)paraquat 309) 311)emetic	0.3 4.75 0.3 0.4	Survived 2 Survived Survived	3/4

* This work was carried out at the Huntingdon Research Centre, Huntingdon, England under the supervision of Dr D Purser and will be described in detail in a subsidiary report.

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			· .	6 9		_						
Mon	keys			Plas	ma	Paraqu	iat C	oncent	<u>rations (</u>	mic	rogra	ms/ml
· .				*								
	Hour	· .		Par	aqu	at			Paraqu	at 4	- Eme	tic
	1.0			8.6	+	4.0	(4)		1.5	±	0.5	(4)
	2.0			13.4	<u>+</u>	8.6	(4)		1.1	<u>+</u>	0.7	(4)
	3.0			15.0	<u>+</u>	6.2	(4)		1.4	<u>+</u>	1.2	(4)
Expt. 1	4.0			18.1	<u>+</u>	13.7	(4)		1.6	±	1.3	(4)
	6.0			12.8	<u>+</u>	13.9	(4)		1.5	±	1.0	(4)
	8.0			3.2	<u>+</u>	2	(3)		1.4	+	1.0	(4)
	10.0			3.2	+	1.7	(3)		0.8	<u>+</u>	0.6	(4)
•		-										•
	• •											
				·							, *	
•	1.0			4.3	<u>+</u>	1.5	(4)		1.5	<u>+</u>	0.8	(4)
	2.0			8.0	+	3.0	(4)		2.7	+	2.3	(3)
	3.0			9.6	+	6.0	(4)		1.0	+	2.4	(4)
Expt. 2	4.0		÷	7.5	+	2.7	(3)	•	1.1	+	0.9	(4)
	6.0			4.0	+	0.4	(3)		0.9	<u>+</u>	0.9	(4)
	8.0			2.3	+	0.8	(3)		1.0	<u>+</u>	1.4	(4)
	10.0			3.0	+	2.7	(3)		0.8	· +	1.6	(4)

Values are expressed as means \pm standard deviation with the number of determinations in parentheses.

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TABLE 3

Survival of Dogs

	<u>Animal no</u> .	Time to vomit (hours)	Time to death (days)	Survival
Expt. 1	20) 93) 990) 986)	8. 67 93	4 4 7 Survived	1/4
	86) 936) 21) 95)emetic	$\begin{array}{r} 0.2 - 0.5 \\ 0.2 - 0.5 \\ 0.2 - 0.5 \\ 0.2 - 0.5 \\ 0.2 - 0.5 \end{array}$	Survived Survived Survived Survived	4/4

27)	ت	8	1/4
92)	به	6	
611)paraqua	ت	5	
9)	ه	Survived	
28) 51)paraqua 91) 626)emetic	t $0.1 - 0.2$ 0.1 - 0.2 0.1 - 0.2 0.1 - 0.2 0.1 - 0.2	Survived Survived Survived Survived	4/4

Expt. 2

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TABLE 4

D	ogs	Plasma Paraquat Concen	trations (micrograms/ml)
	Hour	Paraquat	Paraquat + Emetic
	0.5	4.3 + 3.4 (4)	**
· · · ·	0.75		2.9 + 3.0 (4)
Expt. 1	2.5	8.9 + 2.8 (4)	2.4 + 2.6 (4)
Ministration and a second s	5.0	1.9 + 1.3 (4)	0.6 + 0.5 (4)
	7.0	0.9 + 0.6 (4)	0.5 <u>+</u> 0.4 (4)
	:		
•			
· .	0.5	1.3 <u>+</u> 2.0 (4)	0.3 <u>+</u> 0.2 (4)
	1.0	5.6 + 4.4 (4)	0.3 <u>+</u> 0.3 (4)
Expt. 2	2.0	8.3 + 5.8 (4)	$0.3 \pm 0.4 (4)$
	4.0	6.2 <u>+</u> 3.3 (4)	0.2 + 0.3 (4)
	6.0	$2.8 \pm 2.1 (4)$	N D*

* ND = none detected

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Values are expressed as means \pm standard deviation with the number of determinations in parentheses.

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T	Ά	В	L	E	5

	emetic dose	of PP796		
Dose:	<u>Animal no.</u>	Died	Survived	Total survival
100 mgPQ ²⁺ /kg	351			
• • •	353	.	1	2/2
250 mgPQ ²⁺ /kg	363	~		•
	365	war .	1	2/2
500 mgPQ ²⁺ /kg	377	· · · · ·	-	
	379			0/2

^{*}Survival of monkeys given paraguat in a formulation containing an <u>emetic dose of PP796</u>

This work was carried out at the Huntingdon Research Centre, Huntingdon, England under the supervision of Dr D Purser and will be described in detail in a subsidiary report.

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PARAQUAT PATALITIES IN U.K. 1964 - 1976

TABLE 1

	1964	1965	1965	1967	1966	1969	1970	1971	1972	1973	1974	1975	to 1/11/76 1976	TOTAL
·						-								
CRIMINAL	-	~	~	-	~	-		~		3	1		-	2
ACCIDENT		-	1	2	2	6	6	. 5	4	. ا	3	3	2	38
SUICIDE	-	-	1	2	4	7	2	6	10	15	26	37	21	131
UNKNOWN	-	-	~	~ '	-	2	-	2	3	10	8	8	5	38
		·												
TOTAL	-		2	4	6	15	8	13	17	30	38	48	28	209

MORLD PARAQUAT PATALITIES (INCLUDING U.K.) 1964 - 1976

TABLE 2

	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	1975	to 1/11/76 1976	TOTAL
CRIMINAL	× _	~	-			-		•	1	1	1	· · · · · · · · · · · · · · · · · · ·	-	4
ACCIDENT	з	2	з	6	11	12	16	20	24	16	1 8	13	12	156
SUICIDES	1	-	6	7	11	14	17	62	• 79	69	46	96	33	441
UNKNOWN	-	-	-		3	5	3	3	9`	21	28	17	8	96
STORAGE Incident	~	-	-	-	-	-	1	-		27	· -	11	-	38
TOTAL	4	5	9	13	25	31	- 36	85	112	133	93	138	53	735

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APPENDIX III

TABLE 3

	1964	1965	1966	2967	1968	1969	1970	1971	1972	1973	1974	1975	to 1/11/76 1976	TOTAL
CRIMINAL	-	-			-	~	-		-		-	3	-	3
ACCIDENT	-	. .	4	-	5	4	6	9	9.	6	3	· 4	1	51
SUICIDE	-	2	-	1	-	4	1	3	8	23	19	· 21	7	89
UNKNOWN	-	-	-	-	· -	•	-				-	2	6	8
TOTAL	-	2	. 4	. 1	5	8	7	12	17	29	22	30	34	151

MORLD PARAQUAT RECOVERIES (INCLUDING U.K.) 1964 - 1976

TABLE 4

	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973	1974	1975	to 1/11/76 1976	TOTAL
CREMINAL	-	~		~	-	-				~		3	1	4
ACCIDENT	1	-	6	3	11	10	11	18.	21	10	7	18	6	130
SUICIDE	-	2		3	2	6	. 5	5	14	33 '	24	31	8	13
UNIKNOWN	1	-	-	· -	· .	-	~	-	з	з	11	12	7	37
STORAGE INCIDENT	-		-	- 1	-	-	~	10	-	11		2	~	13
TOTAL	2	2	6	6	13	16	16	23	38	65	42	66	22	317

Japanese figures missing

APPENDIX III

APPENDIX III

Paraquat fatal accidents reported between 14/4/76 and 1/10/76.

Country	Number	of cases
England		1
Falkland Islands		1
Hungary		1
New Zealand		3
South Africa		1
USA		1
Jugoslavia		2

Case No.		Source/ container	Stenched Material
141/73	Falkland Islands (farmworker)	Beer laced with "Gramoxone"	No
130/74	Hungary(Man aged 50)	Wine Bottle	No
131-132/74	Jugoslavia (married couple (67))	"Gramoxone, source unknown	No
196/75	New Zealand (Boy aged 2 years)	Coca Cola Bottle	No
34-35/76	New Zealand (woman & man)	Whiskey Bottle	No
68/76	USA (farmer aged 61)	Coke Bottle	No
84/76	England (woman aged 75)	Container unknown stored in kitchen	Probably No
117/76	S. Africa (Boy aged 17)	Coke Bottle	No

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