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Contains original Report by ms Rose as appendix.

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EMETIC FORMULATION OF PARAQUAT:

PROPOSED STRATEGY FOR INTRODUCTION WORLDWIDE

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SUMMARY

The technical development work with emetic formulations of paraquat is nearly complete and provides assurance that the formulation is less likely to cause death if swallowed and will not result in any additional hazards to users, consumers of treated crops or the environment. The formulations and the emetic agent PP796 have very strong patent protection.

Production of PP796 at Pharmaceuticals Division is proceeding very satisfactorily and regular supplies can be provided from March 1977. Registration of the new formulations is believed to be possible for some key countries in 1977, with virtually all others following in 1978. A publicity announcement about the new formulation is unlikely to be necessary before early in 1977.

The implications of adding stenching agent to paraquat for all markets are examined and the need to assess possible market reactions to a stenched product prior to launch in less advanced markets is discussed.

RECOMMENDATIONS

1 The action outlined in the report should be taken to enable the emetic formulation to be marketed worldwide as soon as possible - by early 1978 in most countries.

2 The registration petition should be submitted to the UK authorities at the beginning of November.

3 Other countries where introduction should be sought in 1977 are all the countries of Western Europe, Australia, New Zealand, Malaysia, Indonesia, Japan, Brazil and South Africa. Immediate introduction in Western Samoa should be arranged, with existing stocks of Gramoxone in the country being reclaimed as far as possible.

4 PP796 should be incorporated into Weedol, Pathclear and paraquat mixtures with residuals as soon as practicable.

5 Overseas companies not yet fully informed about the emetic formulation should be briefed about it as soon as possible.

6 Overseas companies should commence discussions with registration authorities as soon as it is appropriate with the objective of seeking to ensure that the emetic is the sole paraquat formulation allowed to be sold.

7 Pharmaceuticals Division should be requested immediately to begin production of PP796 at the rate of approximately 1 tonne per month from March 1977.

8 Discussions with Pharmaceuticals Division about the price of production quantities of PP796 should take place at the end of November.

9 As far as possible, PP796 should be added to paraquat formulations and concentrate at Mond Division (or Yalding). However there will be many exceptions to this general rule; for patent reasons overseas formulations will be worthwhile in many cases.

10 The cost of PP796 to PPD should be passed on to the overseas companies, but efforts should be made to prevent further mark-ups being made on the cost by our agents.

11 A publicity statement about the new formulation should be prepared as soon as possible with a view to releasing it in the UK and Eire at the time of launch. No publicity announcement would be made outside those countries.

12 User trials with stenched product overseas and investigation of the possible permeation of stenching agent through non-ICI packs should be carried out by early 1977 to enable recommendations to be made about countries in which the emetic product should also be stenched.

THE TECHNICAL CASE

Although the addition of an emetic agent to Gramoxone has been considered in the past as a means of safening the product it had not been pursued because it was believed that no suitable emetic agents were available. The situation has changed dramatically this year with the discovery of PP796 which seems to have all the properties needed in an emetic agent to be added to paraquat formulations.

These properties are:

i That it will produce rapid and effective vomiting in man at low concentrations and with no adverse side effects. It is believed that this will greatly reduce the risk of death following ingestion of paraquat.

ii That it is stable and will not affect the physical or chemical stability of paraquat formulations.

iii That it will not adversely affect the herbicidal action of paraquat.

iv That it will not give rise to any adverse toxicological or environmental effects.

v That it will not result in too great an increase in the cost of Gramoxone.

PP796 was developed by Pharmaceuticals Division between 1968 and 1972 as a potential drug for the relief of asthma. Toxicological studies in mammals were completed to the satisfaction of the UK Committee for the Safety of Medicines, which granted a Clinical Trials Certificate. On the basis of this Certificate, trials on humans were carried out in the UK. It became clear from these trials and from data generated in monkeys and dogs that PP796 was an effective and reliable emetic agent of considerable potency.

The rapidity of action and acceptable toxicological characteristics of PP796 give it an advantage over other known emetics and it was chosen, in January 1976, as a likely candidate for addition to Gramoxone. Since then, a programme of work has fully confirmed the preliminary hopes, and is satisfying all the criteria necessary for the acceptance of PP796 as an additive to Gramoxone on a commercial scale and to meet the demands of registration authorities of any country in which it is decided to sell such a product. A summary of the important results obtained to date and of work in progress and projected are set out below.

1 Level of Addition

It is clearly crucial that PP796 should be added to Gramoxone at the right concentration. We are fortunate that results of exposing people to the compound are available from the clinical trials which enables this

level to be set. The concentration that has been selected is 0.05% w.v, ie 5 mg in 10ml of Gramoxone. This is expected to produce vomiting within 1 hour in the majority of those ingesting such a quantity, which is the approximate minimum lethal dose of Gramoxone in man. In fact most paraquat poisoning cases result from the swallowing of 20ml or more and many suicide cases drink 50ml or more.

The use of a 0.05% concentration has the full support of Dr M S Rose of CTL and [redacted] of the Clinical Research Department, at Pharmaceuticals Division. A paper by Dr Rose summarising the evidence for this rate of addition appears as Appendix 1.

Consideration has been given to carrying out additional work with humans to establish with greater certainty that the chosen concentration is the correct one. It has been concluded that this is neither practicable nor necessary.

2 Effectiveness in the presence of paraquat

Animal experiments have demonstrated the effectiveness of PP796 in the presence of paraquat. Dogs were dosed with paraquat at a level that killed three out of four animals within four days. All animals in a second group, given the same dose of paraquat plus PP796, vomited within 1 hour and paraquat blood levels were reduced. There were no deaths. Similar results were obtained with monkeys.

Further work has substantiated these findings. The toxicity to dogs of paraquat in the presence of an emetic dose of PP796 has now been estimated to be lowered by a factor of 5, and to monkeys also by a factor of 5, compared to paraquat alone.

3 Toxicology of PP796

Extensive toxicological work was done by Pharmaceuticals Division including acute oral and intravenous toxicity in rats, mice and rabbits, 90 day tests in rats and dogs, teratogenic studies in rats and rabbits and dermal studies in rabbits and guinea pigs and in man.

Further observations have since been made, including toxicity to fish, and acute oral, dermal, irritation and inhalation studies with the pyridine base stenched emetic formulation are in progress. PP796 is rapidly absorbed, metabolised and excreted in rats, dogs, monkeys and man.

4 Formulation

Paraquat concentrate, Gramoxone (stenched and unstenched) and Gramoxone S can be formulated with PP796 and storage tests show that there will be no physical or chemical problems with these products. PP796 can be added to appropriate formulations in pyridine bases, valeric acid (for stenched products) or propylene glycol (for unstenched product or concentrate)

although work with the latter is incomplete. Systems can therefore be devised for the addition of PP796 to any paraquat product. Stability work and animal studies with paraquat mixtures with residuals, and formulation work with Weedol and Pathclear to enable emetic Weedol to be made at Yalding are in progress or are to be started shortly.

5 Herbicidal Activity

PP796 has been shown, in glass house tests, to have no herbicidal properties.

It is virtually inconceivable that the addition to Gramoxone of PP796 at the low rate of 0.05% would have any adverse affect on the herbicidal activity of the product. This has been confirmed in a series of field tests, in which rates of addition of PP796 of up to 0.2% were examined.

6 Possible hazards to operators

PP796 is not absorbed through intact skin and has low volatility. It has a very short persistence in man. These facts, coupled with the extremely low level of PP796 in spray-strength material virtually eliminates any risk of operator hazard. Observations are now being made in the field on farm workers in the UK spraying stenched or stenched emetic product as part of the large-scale development. The results obtained so far have not shown any adverse effects from the emetic, although some operators have claimed some minor ill effects from the stenched formulation.

Consideration has been given to carrying out trial work overseas to ensure that no side-effects occur when the new formulation is applied from a knapsack sprayer under tropical conditions for several days continuously. Dr Howard, the Division Medical Officer, has concluded after considering all the available data, and taking into account the negative results from the UK trials, that such work will not be necessary.

7 Possible environmental and food residue hazards

When Gramoxone containing PP796 is used in agriculture only about 2g of the compound will be applied per hectare. This low rate of application provides a fair degree of assurance that its residues will not be detectable in food crops and that no environmental hazards will ensue. Work is in progress to confirm this.

A residue method sensitive to 0.01ppm has been developed and has been used to demonstrate absence of residues of PP796 in potato tubers harvested after haulm desiccation with the emetic formulation, and to show that PP796 is degraded on the surface of leaves (probably photochemically

Preliminary results indicate that the compound is not degraded to any significant extent in soil in periods up to 5 weeks, although it is broken down by sunlight in water.

Work on environmental degradation of PP796 is continuing and an assessment of the significance of its apparent soil stability is being made.

Taint tests with potatoes harvested after spraying with the new formulation were negative.

PATENTS

A UK patent application, disclosing emetic herbicidal compositions comprising a bipyridylium herbicide and PP796 or a close analogue, was filed on 15 April 1976. This case will be completed in the UK and filed in most countries overseas early in 1977, claiming priority under the International Convention. Foreign filings have already been made in the USA (to serve as a basis for claiming priority in some South American countries not members of the Internation Convention), Taiwan, South Korea and Columbia.

These patents, when granted, should prevent manufacture, import, sale or use of the patented formulations by competitors.

PP796 is protected as a new compound per se by the Pharmaceuticals Division original filing on the compound (UK patent priority 13 September 1968) which also protects the processes of manufacturing. This patent is filed in 24 countries.

The prospects of preventing competitors selling emetic formulations of paraquat seem good, since there will be very few places where they would be free to sell the product without challenging ICI's patents (China, Indonesia, Thailand are the most significant exceptions). There are provisions in the laws of many countries that patents which are not "worked" locally may lapse, or be the subject of compulsory licences. However, in the present case, it should be possible to "work" the invention by local formulation in significant countries.

The prospects of our competitors discovering suitable emetic agents as alternatives to PP796 must be very remote. In any case we have filed patent applications in the UK on mixtures of paraquat with known conventional emetics such as ipecacuanha and mixtures of paraquat with other active emetics discovered by Pharmaceuticals Division. A case covering other pesticides mixed with PP796 has also been filed. A decision to proceed with these cases has not yet been made.

STENCHED FORMULATIONS

The decision was made recently that as a general policy Gramoxone should be stenched, although if a suitable case could be made, individual countries could be exceptions to this general rule.

Discussions have taken place with Regional Marketing Departments on the implications of this decision. It has been concluded that a necessary preliminary to its implementation should be a field evaluation of the presently favoured stenching agents to determine possible adverse reactions amongst field workers in less advanced countries. The form and possible location of suitable trials are being considered as a matter of urgency. A second point which also requires resolution before stenched formulations are used more widely is the possibility that the stenching agents might permeate through the Gramoxone packages used by some local repackers, which are believed to be inferior to UK packs (known to retain the stenching agents). If the stenching agent were to permeate through container walls it is believed that this could also lead to consumer resistance.

It is hoped that results of these investigations can be available early in 1977 to enable recommendations to be made on the markets where stenched product will not be introduced.

Evidence on consumer reactions in the UK to pyridine base stenched Gramoxone is being accumulated as a result of the user trial with the emetic formulation (which also assessed reaction to the stench) and from some of the 1976 market research. Results from the user trial indicates some adverse reaction (and the suggestion of some health side effects) to the stenching agent. However the market research seems to show that this has not been translated into unwillingness to use Gramoxone. These findings have not yet been fully analysed and any judgement on their implications must await such analysis.

GENERAL REGISTRATION STRATEGY FOR THE EMETIC FORMULATION

To expedite registration of the new formulations it is hoped that registration authorities can be persuaded that addition of PP796 to paraquat products is a minor formulation change. At the same time we also hope to convince them that the new formulation is a major advance in our attempts to overcome the paraquat poisoning problem, because it effectively reduces paraquat's toxity. We believe that we shall very shortly have a package of information which should amply satisfy most authorities on both these counts. We hope that as a result of the registration of the new formulation less safe formulations of paraquat will no longer be permitted.

The approach to registration authorities will therefore need to be made with these points in mind. In general the initial approach will be an informal one by our agents to acquaint the authorities with the background to the development, stressing in particular the unique nature of the formulation and the low level of addition of PP796, from which the general inference can be drawn that there are on theoretical grounds unlikely to be any hazards arising from the use of the new formulation. Wherever possible these initial approaches by agents should also involve a visit by a CTL toxicologist to explain the toxicological background to the development. Submission of our full dossier of information on efficacy, toxicology and environmental studies would follow shortly afterwards.

Such a process will, it is believed, obviate the need for us to submit toxicological and environmental information on the compound and the formulations as if PP796 were a pesticide, with the addition work that would be involved. However, we cannot exclude the possibility that some authorities will require additional pieces of information not provided in our initial package.

As a preliminary to the approaches to registration authorities, overseas companies who have not been told in detail about the development of a safer formulation should now be fully briefed about it. A suitable document has been prepared for this purpose.

PROPOSED TIMETABLE FOR INTRODUCTION OF THE EMETIC FORMULATION

Pharmaceuticals Division's production plan for PP796 will allow emetic formulations of paraquat to be introduced into all countries by about mid 1978. However, in some countries (notably the USA) it is possible that registration procedures will delay the introduction until early 1979 or later.

It is proposed that the new formulations should be marketed in some countries in 1977 if registration procedures permit. These countries are:

UK, most countries in Western Europe, Australia, New Zealand, Western Samoa, Malaysia, Japan and possibly Brazil, Indonesia and South Africa.

The case for introduction on an area basis follows.

UK

There is clearly a strong case for early introduction of the new formulation in the UK. The paraquat poisoning problem has been under more severe scrutiny in the UK than in any other country and the registration authorities expect us to be doing more to overcome the problem. Because of the attention given to it in the past and our close relationship with medical people concerned with paraquat toxicity we could expect fairly rapid feedback as to the efficacy of the emetic formulation.

As part of the development programme with the new formulation the UK authorities were informed about its nature in July to enable us to obtain clearance to carry out a series of field trials with co-operating farmers. The present timetable shows submission of information to the authorities to enable sales to begin early in 1977. Early registration in the UK could be a useful tool to use to persuade some other authorities to permit registration.

Western Europe

The toxicity of paraquat has also been of concern in many countries of Western Europe and any introduction of a safer formulation in the UK must be closely followed by its introduction into the rest of Western Europe. Stenched product is already being marketed in some European countries (Eire, Germany, France and Finland) and it is planned to introduce it elsewhere in the Region in 1976-1977.

At a meeting with representatives from the overseas companies in Eire, France, Germany, Belgium, Holland, Denmark, Italy and Spain on 12 October, it was agreed that everything possible should be done to introduce a stenched emetic formulation in Europe in 1977. It is believed that in most cases (an exception could be Italy because of delay in obtaining registration), sales could begin in the last quarter of 1977.

In Belgium it may be necessary to introduce the new formulation in May 1977 as a possible means of overcoming the official requirement for a stenched coloured product to be introduced.

It is proposed that a summary of available data should be sent to the overseas companies to support an informal approach to registration authorities within the next month or so. This should be followed by a more formal submission shortly afterwards. It is hoped that a representative from CTL and PPD will attend early discussions with the authorities since it will be important that the novel aspects of the formulation and the lack of hazards from it are fully understood by the authorities.

North America

Chevron, ICI US and PPD agree that the new formulation should be introduced into the USA as soon as possible. The best strategy is considered to be to get PP796 (at the level of inclusion in 20% paraquat of 0.05%) classified as in "inert" (which is defined by the EPA as a non-pesticidal substance). Chevron are at present reviewing the available information on the compound to determine whether sufficient is available for them to submit it later this year for clearance as an inert. Chevron's recently reported view is that if such clearance is obtained, efficacy and residue trials will be required and these can be carried out in 1977 and approval of the new formulation could be obtained in early 1978 to enable sales to begin in late 1978. Failure to obtain clearance as an inert may mean that PP796 has to be registered as if it were a pesticidal ingredient with the consequent need for a full programme of long-term toxicity studies which could delay introduction of the new formulation for at least three years.

It is proposed that submission of the formulation to EPA for clearance as an inert should be a process independent of any approach to the EPA relating to the decision currently being considered as to whether paraquat's registration should be presumed against. The original deadline for such a decision was to have been 1 October: no firm information is available as to when the decision will now be made, but it is expected in early 1977. A decision by the EPA committee to put paraquat into the rebuttable presumption category might mean that we should draw the committee's attention to the emetic agent immediately.

It is planned to introduce valeric acid stenched product into the USA by early 1978: unless this introduction is delayed, it will not be possible to introduce stench and emetic simultaneously.

In Canada it is considered that an initial approach to the registration authorities must be made soon after any submission to the EPA. Clearance of the formulation could be obtained fairly quickly, but since there is no pressing need for early introduction in Canada, sales should begin in early 1978.

No decision has yet been made about introduction of stench in Canada.

Australasia

In New Zealand and Australia there has been increasing concern about paraquat toxicity and we are required to introduce a pyridine base stenched product in New Zealand by June 1977. The decision has also been taken to introduce stenched product in Australia in 1977.

The fact that there is increased pressure on paraquat in these countries means that they should both be candidates for early marketing of the emetic formulation. In addition there are good contacts between the registration authorities in UK, New Zealand and Australia so that introduction of the emetic formulation in the UK would quickly be known in New Zealand and Australia. There is therefore a strong case for introducing stenching and emetic simultaneoulsy. Registration of the emetic is not thought likely to be time-consuming, so that a late 1977 launch could be possible, causing perhaps a few months' delay in incorporation of the stenching agent.

It has been suggested that Western Samoa would be a good place for a very early launch of the emetic formulation. Suicides using Gramoxone there have increased markedly recently and the medical authorities are concerned about the problem. Dr Glass, the ICI New Zealand medical adviser believes that it would be possible to obtain information about the efficacy of the emetic very quickly; it should be possible to reclaim at least some of the existing Gramoxone in the market to allow a swifter response to the new formulation. It is therefore proposed that the pyridine base stenched emetic formulation is launched in Western Samoa early in 1977 (January if possible).

Central America

Registration of an emetic formulation should be straightforward with a minimum of formality, although we shall wish to draw the attention of the authorities to its unique nature. Introduction is not believed to be a matter of urgency so that although registration authorities should be approached early in 1977 with information about the formulation and notice of our intent to register it, marketing should be delayed until 1978.

South America

It is believed that the package of registration information being prepared for the authorities in the UK should also satisfy those in South America. Following briefing of the overseas companies there should be an approach to registration authorities within the next few months. In general, marketing should begin early in 1978. An exception to this is Brazil, where 1977 marketing is more appropriate.

Far East

In Japan there is increasing pressure on paraquat because of large numbers of suicides with the product. Nichino, one of our agents in Japan, have recently been asked by a toxicologist on the registration committee to investigate the possibility of introducing a solid formulation to minimise the risks from paraquat. It is believed that registration of such a "safer" formulation would exclude the use of other "unsafe" formulations of paraquat. Since the emetic formulation is potentially a much more positive contribution to safety than a solid formulation, its introduction in Japan must have high priority. Informal approaches to the registration authorities are proposed within the next 1-2 months with a view to early marketing, although this is felt to be unlikely to be permitted before 1978.

In other countries of the Far East, introduction has lower priority: discussions with authorities should take place early in 1977, in the hope that marketing can begin in 1978. (In some countries efficacy trials may be requested).

Pacific

In Malaysia, we are required to introduce a pyridine base stenched formulation by March 1977 because of concern about paraquat toxicity. It is proposed that the emetic should be introduced at the same time as the stench (possibly leading to a slight delay in introduction of the latter). Registration procedures are negligible at present.

Recently pressure on paraquat appears to have increased in Indonesia and there may be a case for introduction of stenched emetic product in late 1977. Registration would be assisted by the knowledge that the product was registered in the UK or any other sophisticated market.

In the Philippines registration is straightforward, and should take place during 1977 to enable marketing to begin early in 1978.

The other countries of the area should also commence marketing the emetic formulation in 1978.

Africa

The emetic formulation will be introduced into Africa in 1978. The only exception to this could be South Africa where it may be possible and desirable to introduce it in late 1977.

E Europe

Discussions with registration authorities should begin early in 1977 (shortly after the approaches to Western European authorities). It is believed that registration should take about 1 year and the emetic formulation will therefore be marketed in 1978.

Mediterranean

There is no pressing need for introduction of the new formulation in 1977. An approach should be made to authorities in some of the Mediterranean countries (Israel, Greece and Yugoslavia) early in 1977 with a view to marketing in 1978. In many of the countries (Greece, Egypt, Algeria and Morrocco) registration should be straightforward, taking only a few months to complete.

Mixtures

It can be expected that in most countries in which paraquat mixtures with residuals are sold, we shall be required by registration authorities to include PP796 in these formulations also. The technical work with mixtures (stability and emetic efficacy) is not yet complete, but it is considered unlikely that any difficulties will arise. It is therefore proposed that PP796 should be incorporated into paraquat mixtures at the same time as introduction of emetic Gramoxone or as soon as possible afterwards.

Weedol and Pathclear

Significant numbers of paraquat poisoning cases occur with Weedol and in the UK annual deaths from suicide using the product are now at a fairly high level (7 in 1975, 3 in 1976 so far). It is therefore important to incorporate PP796 into Weedol and Pathclear as soon after completion of the technical work as possible.

PRODUCTION PLANS AND PRICE

Pharmaceuticals Division have devised a four-stage process for the synthesis of PP796. The first one tonne production batch is expected to be produced by January 1977: process development work has been going on simultaneously with production of the compound. Existing plant will be used to make the compound. Jealott's Hill Chemists have examined the production process and have been unable to suggest improvements to it.

The present plant for production of the compound has a capacity of 12-16 tpa (sufficient for 4800-6400 t of paraquat). This rate of production (1-1.25 t per month) can be achieved at any time in 1977 provided 4 months notice is given. From the end of 1977, the scale of manufacture can be increased to double or treble the initial rate. Supplies of PP796 will therefore be sufficient to meet all PPD's requirements for the addition to paraquat formulations globally.

The price at which Pharmaceuticals Division are to sell the first tonne of PP796 to PPD is £130/kg which will add 6.5p to the cost of a litre of Gramoxone (£325/tonne ion). The price of £130/kg includes approximately 30% ROC to Pharmaceuticals Division. The plant used to make the first tonne of product will be used for subsequent production: Pharmaceuticals Division will sanction capital to replace the plant used as its use reduces the flexibility for making sales range drugs.

We are assured by Pharmaceuticals Division that the cost of producing PP796 will be decreased by process improvements to be implemented when full production commences and we shall be discussing this with them when details of the process have been finalised (late November).

Forecast production of Gramoxone for the markets in which it is proposed that the new formulation should be introduced in 1977 is shown in Appendix 2. It is expected that in all these markets pyridine base stenched emetic product will be the one to be introduced. Production of the new formulation will not begin for any particular market until registration has been obtained: the most likely times when production can begin are also shown in Appendix 2.

Sufficient PP796 will be available for these introductions to be made and for stocks of the compound to be built up for 1978 use. If the new formulation is registered in some countries (eg Japan and Italy) more rapidly than expected, sufficient PP796 will be available for early introduction.

Suggested quarterly production of PP796 and emetic Gramoxone in 1977 (assuming introductions made as indicated in Appendix 2):-

End of quarter	1	2	3	4
Max production of PP796 (t per quarter)	2	3	3	3
Suggested production (t per quarter)	1	1	2	2
Sufficient to formulate paraquat (t)	400	400	800	800
Likely actual production:				
(1) Begin for W Europe in October (t)	145	382	346	691
(2) " " " " July (t)	145	382	475	691

Elsewhere, as in Appendix 2)

Stock of PP796 at end of year Case (2) 1.75 t

Appendix 2 also shows where it is intended to add PP796 to Gramoxone for the 1977 introductions, although these are preliminary intentions and the details have not been worked out. Where the pyridine bases are to be used as stenching agents addition of PP796 can be made in a solution in the pyridine bases, and it is proposed that initially for France, Australia, New Zealand, Malaysia and Indonesia pyridine base plus PP796 is added locally. The alternative, supplying of concentrate containing PP796 (for all except France) would cause some difficulties at Mond: it is not in fact a feasible alternative for Malaysia who will be receiving some concentrate from TAL in 1977. However once all markets receiving concentrate have switched to the emetic formulation it could be preferable to add PP796 to concentrate at Mond, although the implications of this on the customs duty paid on concentrate in some countries have still to be fully assessed. The question of local addition of PP796 to paraquat formulation also needs further consideration because of its possible value as a means of ensuring patent cover is obtained as a result of working the invention.

The cost of PP796 to PPD should be handed on to the overseas companies, although the effect on paraquat price will be hard to assess at a time when the price may need to be reduced for other reasons. However every effort should be made to prevent mark-ups inflating the cost of paraquat to the farmer as a result of the addition of PP796.

PUBLICITY

So far the development of PP796 has been treated as a Company Secret and, as far as is known, no information has been passed to the outside world, with the exception of a few individuals in registration authorities, who have been given the information in strict confidence.

During the next few months, the possibilities that the information about the project will become known to the public must increase. "Leaks" could occur in several ways.

a) Co-operators involved in the user trials in the UK may pass on the small amount of information they have received about the new formulation.

b) Officials in registration authorities may discuss it publicly.

c) The process workers at Mond, who are to be informed about the nature of the new formulation before production begins early in 1977, and those at Pharmaceuticals Division may discuss it publicly.

d) Poisons Centres and some members of the medical profession will be told about the new formulation prior to launch because it will modify the symptoms of paraquat poisoning and could affect the approach to treatment.

e) In general it is believed that no label changes will be needed for the new formulation (with the exception of a clear distinguishing mark on the label for identification purposes), although a few countries (notably France) may require that PP796 is identified on the label.

f) The patents will be published in Belgium and South Africa in October 1977.

We shall therefore require to prepare ourselves to explain to the public the general nature of the new formulation. Publicity is in many respects desirable. We can justifiably claim to have made an important and novel advance in overcoming paraquat toxicity. We shall be in a position to respond to the adverse publicity which paraquat receives in the press (principally in the UK). However, any publicity about the new formulation carries dangers. First it will alert the competition. Second we may raise over-optimistic hopes that we have overcome the paraquat toxicity problem, and if significant numbers of poisonings occur in the future we may find our publicity rebounding to our discredit. Third we cannot be certain that farmers will not be alarmed at the prospect that the new formulation could lead to vomiting when used normally, in spite of our evidence that this is not a problem.

Since paraquat poisoning has only attracted press coverage on a significant scale in the UK and Eire, publicity about the new formulation should be limited to the UK and Eire. It is proposed that a carefully worded press brief should be produced during the next month or so. Release of this to the press should coincide with the launch of the new formulation in the UK and Eire (probably April-May). In the meantime it can be used should any premature leaks about the new formulation occur. (A brief document was prepared on this subject in August to deal with any press enquiries should there have been a leak as a result of the UK field trials with the new formulation.)

See CTL/390, 1976

Appendix 1

Summary

From information following 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 ~~about 70%~~ the majority of those ingesting 10 ml of this formulation will vomit within an hour.

Introduction

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 rate 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).

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 PP796/kg body weight (equivalent to total doses in the range 2–8 mg). In the first human study involving 12 healthy volunteers (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 2mg. 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 ~~approximately 70%~~ 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 thus much more readily absorped. 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.

MSR:SDL

18 Oct '76

TABLE 1

The emetic action of PP 796

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

• Data from Farrell (1970) Vol. II.
•• Data from Broome (1972)
+ Data from Davies and Hepworth (1969)
++ Data from Bayliss (1973)

TABLE 2

+Comparison of blood values of PP 796 in 2 volunteers given 4 mgs in tablet form

	micrograms PP 796/ml		
Hours after dosing	1	2	3
Volunteer No 10*	0.081	0.041	0.034
Volunteer No 11	0.045	0.056	0.044

* Vomited after 30 minutes

+ Data from Bayliss (1973)

References

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

Broome, A. W. (1972) — Acceptability and emetic activity (of 63,197) in the diet of fattening pigs. Report No: CPRA14/16

Davies, G. E. & Hepworth, W (1969) — Emetic effects (of 63,197) in monkeys and marmosets. Report No: CPR095/14

Farrell, F. G. (1970) — ICI 63,197 Submission of evidence to the Committee on Safety of Drugs (Vol. I Chemistry and Pharmacy; Vol. II Pharmacology and Biochemistry; Vol. III Toxicity and Proposed Clinical Trials). Report No: PH18987C

Fletcher, K. (1974) — in Forensic Toxicology, ed. by B. Ballantyne, published by John Wright and Sons Ltd., Bristol.

Hepworth, W. (1971) — Infusion studies on emetic effects (of 63,197). Report No: CPR095/20 168A

Rose, M. S. (1976) — The effect of administration of an emetic (PP 796) on paraquat toxicity in dog and monkey. Report NO: CTL/R/391 (in preparation)

Appendix 2

PROPOSED PRODUCTION 1977

Country	Production to begin*	Tonnes paraquat by end of year*	Where added
UK	March 77	688	UK
Belgium	October 77 (April 77)	6 (12)	UK
Denmark	October 77 (July 77)	3 (3)	UK
Eire	March 77	65	UK
France	October 77 (July 77)	97 (139)	France
Germany	October 77 (July 77	11 (11)	UK (inc. stench)
Holland	October 77 (July 77)	12 (21)	UK
Italy	October 77+	46	Italy
Spain	October 77 (July 77)	9 (38)	UK
Rest of W Europe	October 77 (July 77)	20 (35)	UK
Australia	October 77	18	Australia
Indonesia	October 77 (July 77)	34 (68)	Indonesia
New Zealand	October 77	35	New Zealand
Malaysia	April 77	520	Malaysia
	Totals	1564 (1699)	

+ If registration is obtained

* Dates and production in parentheses assume registration is obtained by May-Une 1977 (March in the case of Belgium)