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6/f. before Mr Duncan's visit please

6.10.80

ICI PLANT PROTECTION DIVISION

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PARAQUAT

1 Emetic Policy

2 Solid Paraquat

3 Small Plant Technology

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ITEM 1.

PARAQUAT & THE EMETIC : FUTURE POLICY

1. Background

It was realised early in 1976 that PP796 added to paraquat would induce vomiting if the product was swallowed, and should, therefore, reduce the number of deaths following swallowing of paraquat formulations, at least in cases where the amount swallowed was fairly small. The required rate of addition of PP796 was determined to be 0.5g per litre of 'Gramoxone', ie the paraquat/PP796 ratio is 400:1.

PPD's original policy was to register and introduce emeticised paraquat products into all markets as soon as possible (EDC meeting, 29th October 1976, Minute No 40/76).

It was hoped that many registration authorities would, as a result, require that paraquat formulations should contain an effective emetic agent, and in practice this ruling has been sought and obtained in some cases (see below).

The restatement of policy following an EDC meeting on 17th September 1979 was:

"It remained acceptable commercial policy to seek some form of exclusivity for emeticised paraquat, but that the emeticised product must over a period of time be made available in all markets wishing its introduction, whether or not exclusivity could be obtained." (Minute No 137/79).

2. Market introductions of emeticised paraquat

The current position on introduction of emeticised paraquat is shown in Table 1.

In West Europe Regions, emeticised prodict is on sale in all countries except Austria : it is to be introduced there in early 1981. An emetic is required for paraquat products by the registration authorities in France and effectively in the UK and Denmark, and there is a possibility that it will be required soon in Eire and Belgium. Other countries in West Europe may also make an emetic a requirement if further evidence of efficacy becomes available.

In EMA Region, PP796 will have been introduced in almost all countries by the end of 1980, a major exception being Hungary. At present only Czechoslovakia have made addition of an emetic a requirement, although there is a possiblity that Greece and South Africa will do so.

In Americas Region, PP796 has been introduced into Canada, Brazil and Venezuela. The latter has made inclusion of an emetic in paraquat products mandatory and there is a possibility that Canada will do so. Registration of PP796 has not yet been achieved in the USA, but when it is registered the EPA is unlikely to make an emetic mandatory for paraquat.

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In FEP Region, PP796 will have been introduced into Australasia, the Pacific Islands, and Papua/New Guinea and Japan by the end of 1980. In some states of Australia, and in New Zealand and Japan (for the non-industrial weed control sector of the market) an emetic is required.

In those parts of FEP and Americas Region where PP796 has not been introduced, the decision against introduction has been made for two reasons: (i) because there is no active concern by the authorities over the toxicity of paraquat which could lead to an awareness of the emetic's potential benefits; and (ii) the addition of PP796 would increase product costs and reduce ICI's competitiveness.

In two large FEP markets (Malaysia and Thailand) local competitive manufacture has recently been established, making it unlikely that a requirement for an emetic will be introduced.

3. Efficacy

The original evidence, on which we based our view of the likely effect of adding PP796 to paraquat, consisted of observations in animal experiments that the effective toxic dose of paraquat was increased at least 3-fold. It was also believed that the rapid onset of vomiting, which PP796 would cause,would,by drawing attention to cases of paraquat poisoning, help to ensure that medical attention was sought rapidly.

It was realised that it was important to obtain evidence from human poisoning cases, and attempts have been made to do this for the past two years. It was initially believed that Western Samoa, where there were known to be fairly frequent incidents of paraquat poisoning, would be an ideal "test market", and a system was set up to enable us to make observations on the effectiveness of emeticised product in saving life. Unfortunately this attempt failed because of the difficulty of making reliable observations. More recently, attention has focused on the UK and Japan where it is easier to establish suitable monitoring systems.

In recent months this monitoring has brought to light four cases of poisoning involving emeticised product (three in the UK, one in Japan) in which amounts of paraquat were swallowed which would normally have been lethal but in which the patients survived. Although the cases were all attempted suicides the amounts swallowed were relatively small (70ml or less) and cover the amounts which would be expected to be swallowed in cases of accidental swallowings. This information thus strengthens our view that PP796 will save lives following the accidental swallowing of paraquat - indeed may almost eliminate the possibility of death following such accidents - and also will save life in cases of deliberate swallowing where the amount swallowed is fairly small (up to and around 50ml): most cases of attempted suicide involve the swallowing of large quantities of the product, of course.

Monitoring of the situation is continuing. It is unlikely that statistical evidence, showing that the emetic has caused a reduction in the total number of deaths from paraquat poisoning,will be obtained, and we shall have to rely for our evidence on individual cases of lives having been saved. The information obtained so far should be useful to help persuade

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some registration authorities that emeticised paraquat is to be preferred over non-emeticised product, and it should also help to re-inforce the views of those authorities who have already taken the view that paraquat products should contain an emetic. It is probable that the most recent case of survival in the UK will be published, and this will provide useful external support for the emetic.

4. FAO specification

Early in 1980 ICI submitted a new specification for paraquat to FAO, in the hope that the existing FAO specification would be tightened to take account of our information on impurities in competitive paraquat products. We did not suggest that an emetic should be included in the specification.

FAO in their response to the suggested revision refused to include the information on impurities. However, to our surprise, they propose that the specification should now include the following statement:

> "The product shall contain an effective emetic and an effective and persistent stench agent."

FAO have asked us for our comments on the proposal by the end of September, although it is by no means certain that they will take account of any comments which we make, and it is considered likely that FAO will publish their proposed revised specification in an unamended form. It is not known when the specification will be published, but it is unlikely before mid-1981.

It is worth noting the ways in which FAO specifications are used:

1 Some organisations (eg large estates) use them to specify product for business put out for tender.

2 Some countries (mainly developing countries) adopt them in the absence of any other specification. In addition, they probably have some wider influence on registration authorities in some more developed countries.

3 FAO staff use them when asked to advise about quality of individual products.

In replying to FAO, we could oppose the inclusion of an emetic and stenching agent in the specification. However, in view of our belief that PP796 reduces, to some extent, the effective toxicity of paraquat, it would be difficult for us to challenge FAO's desire to include a requirement for an emetic in their specification. In any case West Europe Region believe strongly, and EMA Region to a more limited extent, that the inclusion of an emetic in the specification will be a valuable influence in preserving the exclusive positions we have and perhaps in creating some new ones. FEP & Americas Region believe that the FAO specification will probably not help significantly in this way.

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However, we believe that we should oppose the inclusion of a stenching agent in the FAO specification, on the grounds that addition of an emetic is a more positive measure to take than addition of a stenching agent and there is a possibility that stenching the product may inhibit use of the product. (There is some evidence of this.)

It is, therefore, proposed that Dr B Johnen should reply to FAO supporting the inclusion of an emetic but requesting deletion of the requirement of a stenching agent.

5. Competition

Some companies selling competitive paraquat have included emetic agents in their product or are reported to be investigating such additives. Those on which we have information are:-

(i) Sodium antimony tartrate

Included in Taiwanese paraquat sold in Japan by Otsuka. This compound is believed by us to be environmentally and medically less acceptable than PP796 as an additive for paraquat, but has nonetheless been approved by the Japanese authorities.

(ii) Emetine (the active ingredient of the natural product ipecac).

This has been included in Taiwanese paraquat sold by Cillus in Denmark. The levels detected in the product are, we believe, too low to induce vomiting. The level of additive needed to induce vomiting would lead to a very high additional cost (about £1.50/l of 'Gramoxone'.)

Toxicological investigations with emetine are apparently being carried out in the USA on behalf of a New Zealand company.

6. Production

The Organics Division plant for PP796 has a capacity of 36t, i.e. sufficient PP796 to add to a total of 14,000t of paraquat (or paraquat and diquat) at the currently recommended level of addition. The plant was commissioned in July of this year and production in 1980 will be about 4t of PP796, the smallest amount which could be made to commission the plant.

Required production, forecast offtake and stocks until end-1982 are shown in Table 2. Stock was very high at the beginning of 1980. As a result of this, if no further introductions of PP796 are made beyond those planned, no production of PP796 will be required during 1981 and 8t will need to be manufactured in 1982. Table 2 also shows the production, offtake and year-end stocks if PP796 were introduced into all paraquat by 1982. Since offtake of PP796 would then be much higher, some PP796 would need to be made in 1981 and 25t would be manufactured in 1982.

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The transfer price to PPD of PP796 reduced with offtake as shown in Table 3. Because of the high stocks of the more expensive PP796 from previous production at Pharmaceuticals Division the cost reductions will only be partially applicable during 1981 and 1982.

Table 4 shows the effect that increased offtake would have on the cost to PPD of adding PP796 to 'Gramoxone', assuming that all the PP796 required was actually made on the Organics Division plant in 1980. Based on the tonnage of PP796 required for the introduction of PP796 made by the end of 1980, the added cost would be 2.8p/l; if PP796 were included in all paraquat, the cost would be 2.1p/l. If other uses were found for PP796 to enable the plant to be operated at full capacity, this cost would reduce to 1.7p/l. (All these costs are based on the 1980 transfer price of PP796 from Organics Division.)

Other possible uses for PP796 are discussed below.

Possible alternative uses of the PP796 plant for the synthesis of other compounds are being investigated.

7. Cost/Benefit

An obvious benefit from PP796 that has accrued so far has been to help it has given in protecting the high-priced paraquat markets in W Europe, Australasia and Japan, since without the emetic, these markets would have been more vulnerable to Taiwanese competition. Profit would have been reduced by several million pounds as a result of lowered prices and loss of volume.

Table 4 shows that the addition of PP796 to paraquat in the markets in which it has been introduced will cost £550,000 in 1980. This is not in fact the actual cost to PPD, since the cost of PP796 is handed on to overseas companies or distributors. (In the case of Japan, PPD makes a large margin on sales of PP796 to TAL). The cost also includes a return to Organics Division for profit, to reward their capital and contribute to overheads. However, it does give an indication of lost potential margin to the Group.

If PP796 were to be added to all paraquat, except the USA, the cost of addition at transfer price would be £790,000 in 1980. If the USA is included the cost becomes £860,000. Thus the cost of including PP796 in all paraquat additional to those markets where it is already included is £240,000 (excluding USA) or £310,000 (including the USA).

8. PP796 and other toxic chemicals

PP796 is included in 'Weedol', in some paraquat cols for W Europe and in 'Reglone' for Israel (to overcome the need to supply PP796 to Makhteshim for addition to the mixed paraquat/diquat product sold there).

So far PPD's policy has not been to seek other outlets for PP796, at least until clinical evidence for the efficacy of PP796 has been obtained (EDC Minute No 137/79). Although some evidence is now available, it is not considered that this is of a nature which could be used to support the inclusion of PP796 in any other pesticides. In any case it is not believed that any other pesticides would have their toxicity characteristics modified sufficiently by PP796 to justify the development, by ICI, of special emetic-containing formulations. It would only be possible to obtain further information on this subject by discussing it with manufacturers of particularly toxic compounds, and with registration authorities.

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To date there are no strong candidates although Zoecon have asked us whether we could supply PP796 for addition to a fly-attractant. There was interest in South Africa in the addition of PP796 to methylated spirits to help overcome the "meths drinking problem", but interest in this now seems to have waned and it seems unnecessary for PPD to attempt to revive it.

Occasional enquiries have been made about the supply of PP796 as an emetic for use by the medical profession. Pharmaceuticals Division, who would market the product for this use, do not wish to sell PP796 for such outlets.

9. Other safety additives for paraquat

'Gramoxone'containing pyridine bases as stenching agents is on sale throughout West Europe, except Italy. It is also sold in Australia and New Zealand and is to be introduced in Papua/New Guinea (with emetic also) soon. The cost of stenching with pyridine bases is 0.5p/l, ie £25 per tonne of paraquat ion. A blue dye is also included in'Gramoxone'sold in Eire and Belgium. The cost is 3.3p/l (£165/tonne paraquat ion).

Valeric acid has been approved by the EPA as a stenching agent for paraquat, but Chevron are not yet selling paraquat containing it because of reluctance from some of their production and marketing staff.

10. Policy options

The important policy option to be decided is whether or not PP796 should be included in all paraquat even in markets in which registration authorities have not made the inclusion a requirement.

The case for including PP796 in all paraquat rests on the following:

(i) We now have some good indications that the addition of PP796 to paraquat can contribute to the saving of life, at least when the product is swallowed accidentally.

(ii) We are otherwise maintaining a double standard, even though we have evidence referred to in (i). Such a double standard can become public knowledge and might be difficult to defend.

(iii) As evidence for the effectiveness of PP796 in saving life accumulates, more authorities may require the addition of an emetic to paraquat. The revised FAO specification when published could influence attitudes to this.

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(iv) Inclusion of PP796, by effectively reducing the toxicity of paraquat, reduces to some extent toxicological pressures on the product.

(v) If the revised FAO specification, when it is published, contains a requirement for an emetic and we do not include PP796 in all paraquat we shall no longer be able to claim that ICI paraquat always meets the FAO specification. If the FAO specification also includes a stenching agent, we shall, of course, also fail to meet it unless we stench our product everywhere. A possible course of action is to delay further emetic introductions until we know whether the FAO specification includes an emetic.

The case against rests on the following:

(i) If registration authorities are not sufficiently concerned about paraquat toxicity as to require all paraquat to contain an emetic, ICI should not impose a competitive disadvantage on itself by adding PP796 to its paraquat.

(ii) Inclusion of PP796 in paraquat in markets other than those where it is already introduced will reduce potential paraquat profits by about £300,000. Most of the markets involved are those where prices are already low as a result of competition and it is unlikely that the emetic would give an exclusive position : additional costs of just over 2p/l of 'Gramoxone'(£100/tonne ion) would be incurred as a result of adding PP796.

The extra cost of adding PP796 to all ICI paraquat might perhaps be best considered as an expense to support the total paraquat business, rather than as an added cost in individual markets which is not commercially justified in those markets.

The balance of advantage and disadvantage of including PP796 in all paraquat remains difficult to determine. However the majority view in PPD, held by PMG and all regions except FEP, is that the preferred course of action is to include PP796 in all paraquat. FEP Region believe that no further introductions should be made unless registration authorities make an emetic mandatory for all paraquat.

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If it is decided that all ICI paraquat should contain an emetic, some exceptions may have to be made:

(i) In cases (eg Hungary) where quaternisation of 4,4'-bipyridyl is carried out by a non-ICI company, the present Division policy of not supplying PP796 to such companies precludes the inclusion of PP796 in the paraquat produced.

(ii) In cases where distributors are supplied with ICI paraquat (eg Montedison and other companies in Italy and distributors in C America who receive "black-drum" ICI paraquat) it is preferable to allow policy on emetic inclusion to be determined locally.

11. RECOMMENDATIONS

1. ICI should support FAO's proposal to include emetic, but oppose the inclusion of stenching agents, in the specification for paraquat.

2. PP796 should be included in all paraquat sold by ICI as soon as possible, although exceptions should be permitted as discussed in Section 10. Registration authorities should be alerted to the fact that the emetic is included in the product.

3. The recent information on the efficacy of PP796 should be made available for presentation to appropriate registration authorities when they request it.

4. Other potential outlets for PP796 should not be pursued, neither actively by PPD investigating possible markets, nor reactively when approaches are made by other companies. Investigations should continue to find alternative uses of the spare capacity in the PP796 plant for the synthesis of other compounds.

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TABLE I

Introductions of Emeticised Paraquat

	Introduced?	Emetic Mandatory
1. W Europe		
All countries except Austria	Yes	France UK Denmark
Austria	Early 1981	No
2. EMA		
Czechoslovakia	Yes	Yes
Rest of E Europe (except Hungary*)	End 1980	No
Greece	Yes	Possible
Israel	Yes	No
Turkey	End 1980	No
Rest of Middle East	Most by end 1980	No
Ivory Coast	Yes	No
South Africa	Yes	Possible
Rest of Africa	End 1980	No
3. Americas		
USA	Registration awaited : likely to be slow	Unlikely
Canada	Yes	Possible
Brazil	By end 1980	No
Colombia	No	No
Venezuela	Yes	Yes
Rest of S America	Not planned	No
C America	Not planned	No
Cuba, Caribbean	Not planned	No
4. FEP		
Australia	Yes	Yes (some states)
New Zealand	Yes	Yes
Pacific Islands	Yes	No
Papua/New Guinea	End 1980	No
Japan	Yes	Yes (except for industrial weed control uses)
Rest of FEP	Not planned	

* Introduction in Hungary is inhibited by the Division policy of not supplying PP796 to outside the ICI Group.

+ In no case has PP796 itself been specified as the required emetic.

TABLE 2 Production, usage and stocks of PP796

	Assuming no further PP796 introductions			Assuming all paraquat contains PP796 by 1982		
	Production t	Usage t	Year-end stock t	Production t	Usage t	Year-end stock t
1980	4 (Plus 23t stock at end-1979)	10	17	4 (Plus 23t stock at end-1979)	10	17
1981	nil	11	6	2	17	2
1982	8	12	2	25	25	2

TABLE 3

Variation in PP796 transfer price from Organics Division to PPD with offtake+

t PP796	1980 Cost to PPD*(£/kg)
10	55
15	45
20	41
25	36
35	33

(Variable cost £26/kg)

+ Assumes plant produces at these levels. In 1980–1981 this will not be the case because of previous stock of Pharmaceuticals Division product.

* May be lower once plant is in full operation, and process development work could lower it further.

TABLE 4.

Cost of adding PP796 to paraquat formulations

In 1980 £s, and at 1980 transfer price, assuming all PP796 requirements made at Organics.

	t PQ ion (1980 likely out-turn)	t PP796	PP796 added to paraquat only: Total cost of adding PP796 to paraquat (£m.)	PP796 added to paraquat only: Cost of emetic p/l of Gramoxone	If remainder of PP796 used for other products (ie plant at full capacity): Total cost of adding PP796 to paraquat (£m.)	If remainder of PP796 used for other products (ie plant at full capacity): Cost of emetic p/l of Gramoxon
Markets to which introduced and those planned by end-1980	3900	10	0.55	2.8	0.33	1.7
All markets (excluding USA)	7400	19	0.79	2.1	0.63	1.7
All markets	8900	22	0.86	1.9	0.73	1.7

ITEM 2

PARAQUAT TOXICITY - JAPAN

1. INTRODUCTION

There were over 100 fatal suicide attempts with paraquat in Japan in 1979, about the same number as in 1978. Although this number is small in comparison with the total number of suicides (over 21,000 in 1979) there is pressure from the Japanese authorities on ICI Japan and our distributors to take action which will reduce the number of paraquat suicides "significantly". This pressure is likely to increase with the introduction this autumn of 'Roundup' which will be seen as a safer product, and could increase further if a competitor introduced an apparently safter form of paraquat. Asahi Chemical are carrying out trials with a solid formulation of paraquat/diuron, which may be seen by the authorities as a safer product.

2. POSSIBLE ACTIONS

2.1 The emetic formulation was introduced in 1979, and is now fully approved : the requirement for effective emetic agents is blocking the full approval of at least two competitive paraquat products.

However, although it is believed that the inclusion of PP796 in 'Gramoxone' will reduce the number of deaths resulting from accidental swallowing of the product, it is not likely that this measure alone will reduce the number of successful suicides with 'Gramoxone' to the extent required by the Japanese authorities.

2.2 Following approval by the PPD Executive, preparations for the possible introduction of a product diluted approximately three-fold have been made as the next line of defence : the necessary trials work has been done and an application for registration could be made at any time. Dilution of 'Gramoxone' (which would still contain the emetic) will increase the percentage of survivals following the swallowing of paraquat. Provided the number of poisoning incidents does not increase significantly, the number of fatal poisonings should therefore be reduced. The extent of the reduction is difficult to quantify with any accuracy, but it is possible that the numbers of successful suicides may be reduced by up to one-third. It is not certain that such a reduction will be sufficient to satisfy the Japanese authorities.

In addition, marketing a dilute product would be expensive and inconvenient. It has been estimated that a tnree-fold dilution of 'Gramoxone' would result in additional formulation, packaging, transportation and warehousing costs amounting to £2500/t paraquat ion.

Alternatives are therefore being considered, and are discussed below.

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2.3 Trials work with Paracol (the 1:1 paraquat/diuron col product) and a paraquat/diquat mixture is in progress in Japan. These products could displace some Gramoxone from part of the present market, although the extent of the displacement has not been quantified. This could lead to some reduction in the number of suicides with Gramoxone once the sales of Paracol or mixed paraquat/diquat have become significant. However, fatal poisonings would still be expected with these mixtures, and so the total number of suicides with paraquat products may not be significantly reduced, following introduction of the mixtures.

2.4 Other methods of reducing the number of Gramoxone suicides have been considered and rejected : these include introduction of formulations containing stenching agents, bittering agents and colour as deterrents, and of thickened formulations.

In a new initiative, Takeda and Nihon Nohyaku are carrying out research to devise intrinsically safer paraquat formulations, and Nihon Nohyaku claim to have produced a paraquat complex which has a lower acute toxicity, and which requires addition of an "activator" to the spray tank to restore herbicidal activity which is otherwise also lowered as a result of the complex formation.

A joint PPD/CTL meeting is to be held at the end of September to discuss this and any other possible new approaches to overcoming the paraquat poisoning problem. It should be recognised, of course, that a very large effort has already been expended by ICI in the attempt to overcome the problem, and the chances of success for any new approach must be very small. In particular, new formulations of the type envisaged by Nihon Nohyaku would need considerable development before they can be registered and sold.

2.5 An alternative to dilution long-favoured in Japan is a solid formulation. The rest of this paper reviews the advantages and disadvantages of solid paraquat products.

3. SOLID PARAQUAT

3.1 Background

There is a strong belief in Japan, shared by some in ICI Japan, our distributors and some key officials in the Ministry of Health, that there would be fewer attempts at suicide, and therefore fewer deaths, with paraquat if the product were a solid rather than a liquid, because, it is alleged, Japanese people are less likely to attempt suicide with solid products. Hard evidence on this point is difficult to obtain : there are no other pesticides with the mix of properties possessed by paraquat - viz high acute toxicity, and high water solubility. In addition, there appears to be no evidence that a change of formulation from liquid to solid with other pesticides has led to fewer suicide attempts with those products. Further attempts should be made in Japan to assemble evidence on this crucial point by examining the records of suicides with solid products of all kinds, not pesticides only.

However, we know that Asahi Chemical have been carrying out trials with a solid paraquat/diuron product - though not as far as is known with

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solid paraquat itself. Successful introduction of such a product could lead to further pressure on us. There is thus a strong view in Japan that sooner or later a solid paraquat product will be demanded by the authorities. ICI Japan, FEP Region and PMG therefore consider that it is prudent to make the necessary preparations to respond to such a demand if it arises. Part of the preparations would include an assessment of the economics and the practical problems involved, which would assist in the decision as to whether introduction of a solid product would be a more desirable course of action then introduction of diluted Gramoxone.

3.2 Characteristics of a solid product

Various solid formulations can be envisaged :

- paraquat alone
- paraquat and diquat mixed
- paraquat plus residual herbicides

A solid paraquat/diquat mixture or solid paraquat/residual mixture could have the advantage over solid paraquat alone in that they could be launched alongside liquid 'Gramoxone' and maintain or even increase total paraquat sales, and at the same time lead to a gradual reduction in sales of the liquid product, which would be seen as an advantage by the authorities. Such a gradual approach would also be preferable to switching completely from liquid 'Gramoxone' to solid paraquat in that it would enable an assessment to be made of the extent to which solid formulations inhibited suicides with paraquat products, before a full commitment to solid products was made.

It is assumed that a solid product should have the following characteristics :

1 It should contain no more than 20% paraquat ion or a mixture of paraquat and diquat, since it seems likely that a formulation stronger than the current one could not be registered.

2 It should contain PP796.

3 It should dissolve easily in water.

4 It should not lead to major new hazards in manufacture or use.

3.3 Availability of technology

3.3a Fluid-bed drying

Solid paraquat formulations have been considered in depth several times, and detailed investigations were carried out in 1968/69 and 1975/76. By 1976, with the US market in mind, a solid product based on sodium chloride as a carrier, and containing 25% paraquat ion (the same strength as the liquid paraquat product sold in the USA), had been produced by PPD by fluid-bed drying on a pilot-plant scale. Limited toxicological investigations were carried out (see Section 3.4).

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Field work showed that the herbicidal performance of the solid product was the same as that of the liquid product. It was easy to handle, dissolved readily and was not friable - a desirable attribute if dust hazards are to be minimised. Samples of the product examined recently appear not to have deteriorated.

It is assumed that a plant for making solid paraquat would be sited in Japan. The fluid-bed drying process would be suitable for use on the scale required in Japan (up to 1000 tonne of paraquat ion per annum). More work would need to be done with this process to establish its suitability for preparation of paraquat mixtures and for the inclusion of surfactants and PP796. The fluid-bed drying plant at Yalding could be used for these investigations and to prepare tens of tonnes of product for evaluation in Japan.

3.3b Other processes

Other possible processes for producing a solid product can be envisaged and are listed in Appendix 2. One such is the'Weedol'process in which paraquat concentrate is mixed with anhydrous magnesium sulphate and the mixture is extruded. This process seems less suitable than fluid-bed drying. Capital cost of a plant is likely to be at least as high as for fluid-bed technology, and the product would be friable and would dissolve with difficulty.

No other process for preparing solid paraquat has been taken beyond a laboratory scale and if it is agreed that a programme of work on solid paraquat is to be carried out, a first task would be to carry out a re-examination of some of the processes listed in the Appendix and any other new ideas for solid formulations : this re-examination might require limited laboratory investigations. However, there is no reason to think that the choice of process now would be any different from the choice of fluid-bed drying made in 1976.

3.4 Costs

An estimate of the costs likely to be incurred if fluid-bed drying were used to produce a solid paraquat product are given in Appendix 1. These costs are current in the UK, and so can only be a guide as to likely costs in Japan.

The capital costs of a drying and packing plant, and a building for it, is estimated to be £1.5m.

The additional operating cost for production of a solid paraquat product compared to the costs of formulating liquid 20%'Gramoxone'is about £490/t paraquat ion, ie the cost of sodium chloride and of drying and of maintenance of the drying plant, and depreciation and interest add a further £150/t and £225/t respectively.

This figure excludes depreciation and interest on capital, assumes that labour costs associated with packing are the same as those associated with packing liquid 'Gramoxone', and also assumes that the costs of the pack for a solid product would be the same as that for liquid 'Gramoxone', per kg of paraquat ion.

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It is possible that a solid paraquat product could be produced by toll manufacture in Japan : this would remove the need for capital investment, at least until some sales of the product had been made and its effectiveness in reducing the suicide problem measured.

3.5 Toxicology

It is obviously vitally important that if a solid paraquat product is introduced into the Japanese market with the sole aim of reducing suicides, it must not result in any new toxicological hazards in manufacture or use. We have no field experience of the toxicoligical characteristics of a solid product containing 20% paraquat. The solid product 'Weedol' (2½% paraquat, 2½% diquat) has been used by gardeners in the UK and elsewhere for many years without ill-effects of any kind being recorded, although occasionally workers in the 'Weedol' manufacturing plant at Yalding experience nose bleeds; however the experiences with 'Weedol' are probably not relevant to those which might be expected with a more concentrated product.

It is likely that any potential hazards in manufacture could be eliminated by suitable design of the drying and packing plant. Potential hazards in use could not be so easily contained, and a programme of work will be required to establish that a solid paraquat product can be used safely. This would include an assessment of the amount of small particles in the product and the extent to which they are increased during transport, studies on skin and eye irritation, and an inhalation study. Preliminary discussions have been held with CTL, but a detailed protocol cannot be drawn up, since the work programme can only be defined in collaboration with those in Japan who can judge how a solid product would be handled (and mishandled) in the field in that country. A tentative estimate for the cost of the work is £50,000 - £100,000.

Some toxicological studies were carried out with the sodium chloride-based, 25% paraquat solid prepared in 1976 (see Section 3.2a).

Acute oral toxicity, 24-hour dermal toxicity and skin irritations were measured with aqueous solutions of the formulation.

Determinations were made of the amount of respirable particles in the product, both before and after subjecting the samples to attrition in a dust generator. The produce contained only a small amount of respirable particles and the amount was increased ten-fold after the attrition process. However it was decided that without further investigations it was not possible to draw any firm conclusions about the actual risks likely to arise in handling the product.

Apart from 'Weedol', the other possible solid products listed in Appendix 2 have not been subjected to any detailed toxicological investigations.

3.6 Packaging

A suitable means of packing a solid product needs to be devised : hazards to users could be minimised if the right package were chosen. Possibilities include small unit packs and water-soluble sachets. Detailed discussions are required with ICI Japan and Takeda and

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Nichino on this subject and it is possible that the package development work would be best carried out in Japan.

3.7 Solid and diluted paraquat compared

Although a higher initial capital investment would be required (present estimate £1.5m for a 1000tpa plant) additional variable costs of a solid paraquat formulation are low compared to the added costs involved in marketing a diluted paraquat formulation. Unfortunately, it is not possible easily to compare their attractiveness as a means of reducing the paraquat suicide problem.

Dilution of the product will lead to a reduction in the number of deaths following from suicide attempts, although the size of the reduction is difficult to quantify. Introduction of a solid product depends largely upon a belief in Japan that it would be less likely to be used for suicide attempts. A dilute product would cause no extra user hazards, of course, whereas careful study will be required with the solid product to ensure that new hazards do not arise.

4. CONCLUSIONS AND RECOMMENDATIONS

4.1 Although preparations have been made for introduction of a diluted product into Japan, it is not certain that dilution of the product would have the desired effect on the numbers of paraquat suicides. ICI should therefore commit some further effort to the evaluation of a safer formulation for the Japanese market. Close collaboration is required between PPD, CTL, ICI Japan, Takeda and Nichino.

4.2 Ideas for a novel formulation could arise from forthcoming CTL/PPD discussions or from the research currently being conducted by Takeda and Nichino. However the only "safer" formulation available at present as an alternative to diluted Gramoxone is a solid form of paraquat. Further evaluation of this is required as a joint activity by PPD, ICI-Japan and Takeda and Nichino. Any commitment to the Japanese authorities that the formulation will be introduced must be avoided.

4.3 Part of the evaluation will include a further attempt to obtain evidence that a solid paraquat product will reduce the number of deaths from suicide attempts.

4.4 The most promising technology for the preparation of solid paraquat is fluid-bed drying. However, some PPD resources (1-3 man months)should be devoted to re-examining alternative processes for producing solid formulations.

4.5 Once a decision is made on the most appropriate technology, samples of product should be prepared for detailed toxicological investigation to enable potential hazards in manufacture and use to be identified, and for field assessment (but not official trials) in Japan. This work should be taken to the stage where a solid product could be introduced into Japan at short notice, should this be required.

Note : This paper has been prepared in collaboration with FEP Region and ICI Japan.

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Cost of solid paraquat by fluid-bed drying

M Blackford, Yalding, has recently estimated the capital cost and operating costs for a fluid-bed drying plant.

The assumptions made were :

1. The capacity would be 1000t paraquat ion per annum.
2. The product would be based on sodium chloride and would contain 20% paraquat ion. Starting material would be paraquat concentrate (36% w/w ion).
3. The plant would operate on 4 shifts, 24 hours per day, 5 days a week.
4. Product would be filled into plastic tubs each containing 250g of paraquat ion.

Costs are current UK rates.

Capital cost

	£m
Drying plant	0.5
Filling & packing plant	0.25
Building, site work, services etc.	0.75
TOTAL	1.5

Operating costs

	£/t paraquat ion	
Sodium chloride	140	(ex Mond, delivered Yalding)
Energy cost	150	
Labour : Drying plant	150	
Maintenance	50	
	490	

These costs exclude the cost of the package, which might be about the same as that of the existing pack, and the cost of surfactants, which will be the same as for liquid Gramoxone and also exclude depreciation and interest on capital. Assuming full occupation of the plant, 10-year depreciation and 15% interest, depreciation adds £150/t and interest adds £225/t to this figure.

SOLID PARAQUAT TECHNOLOGY

APPENDIX 2

Process	Product	How far developed	Comments
Evaporation - fluid bed	PQ + sodium chloride (PQ + magnesium sulphate rejected as inferior).	Pilot plant scale	Easy to handle product, not friable, easy to dissolve.
Absorption	1. PQ + $MgSo_4$	Weedol (2.5% PQ, 2.5% DQ) Product is extruded Up to 20% paraquat would be possible.	Product friable, difficult to dissolve.
	2. PQ + cellulose	Lab-scale (Mikasa, Japan)	Product light & dusty. Residue in spray tank.
	3. PQ + silica	Lab-scale	Residue in spray tank.
	4. PQ + polyethylene glycols(eg Carbowax)	Lab-scale (Chevron) Some drying also required.	Liable to cake, poor solubility. Shown to be inferior to PQ/NaCl solid from fluid bed.
	5. PQ + acrylic polymer	Lab-scale. Some drying also required.	
Precipitation	PQ + urea) PQ + thiourea) PQ + metal salts)	Lab-scale. Some drying and granulation would also be required.	Could be difficult to dissolve in small volume of water.

ITEM 3

SMALL PLANT TECHNOLOGY

1. Introduction

The ability to build small, efficient, low capital cost plants is an important weapon for the defence of paraquat, particularly in preventing our exclusion from significant markets by competitive local manufacture.

At Mond Division, considerable progress has been made on the development and simplification of the cyanide processes and, during July/August, Mond Division personnel visited Mexico and Brazil to examine the cost profile of these processes in the context of specimen less developed economies. Their findings are incorporated in this paper.

The work of A G Jacklin and J A Orr of Mond Division is particularly acknowledged as essential to the preparation of this paper.

2. Capital Cost Estimates

The fixed capital costs for the water and ammonia cyanide processes are shown in Table I below. These figures are based on typical engineering costs in Latin America.

TABLE I

Capital Cost: Cyanide Process Plants

Capacity Te/Yr	Water cyanide $USm	Ammonia cyanide $USm
200	1.2	2.0
500	2.1	3.5
1250	3.7	6.2

In simple terms, the capital cost of the water cyanide process is only 60% of that for the ammonia cyanide route because there is no requirement for solvent recovery and dimerisation is carried out at atmospheric pressure.

These capital costs should be understood in the context of the following:

(a) Grade C estimates (ie $\pm$ 30% accuracy) in mid-1980 $s.

(b) Assumed construction on an established chemical works. The estimates cover on-plot equipment together with steam and cooling water supplies but exclude the costs of land, roadways, offices, amenities, laboratory, electrical supply installation and any special provision for effluent treatment.

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(c) The definition of capacity assumes 24-hour working and 85% plant availability.

(d) In practice, of course, total capital costs will vary from site to site and country to country depending on, for example, local equipment and construction costs, local effluent treatment standards, the extent of off-plots required and any possible use of existing quaternisation plant. The cost of construction on an established site in the Far East has not yet been investigated but should be no higher than in Latis America.

(e) Consideration of current and previous cost estimates for cyanide process plants indicate that ICI would be strongly advised to seek out an established chemical works as the site for any local plant.

3. Manufacturing Cost Estimates

A comparison of the variable and full costs for the water and ammonia cyanide processes is shown in Table II below:

TABLE II

Production Cost Summary: Variable Cost

	Cost per tonne of material	Water cyanide		Ammonia cyanide	
		usage	$/te ion	usage	$/te ion
Pyridine	$ 3750	1.35	5051	1.01	3788
Methyl chloride	$ 1720	.87	1493	.70	1211
Sodium cyanide	$ 2275	.59	1345	.16	357
Others	-	-	1052		742
Total raw materials			8941		6098
Services			471		984
Variable			9412		7082

The above figures are based on Latin America meterials and services costs.

The ammonia cyanide process has a variable cost advantage of over $2,3000 per tonne ion,mainly due to a higher pyridine efficiency (85% compared with 65%) and lower sodium cyanide usage.

4. Economic Analysis of Cyanide Process Plants

4.1 Choice of plant for particular markets

The trade off is between the lower capital cost of the water cyanide process and the lower variable cost, better long-term competitiveness and greater protection from pyridine price increases of the ammonia cyanide process.

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Although the ammonia cyanide process requires higher levels of fixed expenses,overheads and depreciation, it still retains a cost advantage at full cost levels at full and half capacity.

If a 20% return on capital employed at these plants is added to the full cost, then the ammonia cyanide plant retains a cost advantage at full capacity for 200,500 and 1250 tonne plants. At half capacity the advantage is extremely small at 500 tonnes and disappears at 200 tonnes. These detailed calculations are displayed in Appendix I.

Incremental cash flow analysis of the two plants confirms these results and also indicates the sensitivity of the plant choice to the capital allowance position in the country in which the plant is to be constructed.

TABLE III

Incremental Cash Flow Analysis

	200te/yr		500te/yr		1250te/yr	
	Full Capacity	Half Capacity	Full Capacity	Half Capacity	Full Capacity	Half Capacity
After Tax with CA $000 NPV	+234	-205	+1113	+14	+3634	+886
Yr of payback	2	-	2	3	2	2
After Tax without CA $000 NPV	-99	-539	+529	-568	+2592	-155
Yr of Payback	4	-	3	-	2	4

Cash flow analysis compared the additional capital cost of an ammonia cyanide plant with it lower running costs. A positive NPV is favourable to investment in ammonia cyanide.

For modelling purposes 10% inflation, 50% taxation lagged year and 100% capital allowance have been assumed. The investment is discounted over 5 years after tax at 20%.

From these calculations it can be seen that:-

(i) the ammonia cyanide plant is better at 500 and 1250 tonnes capacity,even if capacity is only half utilised in the early years,providing there is some form of capital allowance.

(ii) at 200 tonnes water cyanide is to be preferred if there is early under utilisation of capacity and/ or poor capital allowances.

(iii) water cyanide always limits the Group's capital exposure in any sensitive market.

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It is worth noting that it should be possible to start local production with a 200tonnes/year water cyanide plant and later expand and convert to an ammonia cyanide plant of increased capacity by adding an ammonia recovery unit and changing the dimeriser. Mond are exploring these possibilities.

Analysis not shown in this paper indicates that the methanol cyanide process would not be our preferred process at any of the capacities under review.

The comparison of the preferred cyanide route plants with new scaled down local LTS plants also clearly indicates the superiority of the former. Although less efficient in the use of pyridine, (ca $300 per tonne ion) lower costs for services and other raw materials make a 500 tonne ammonia cyanide plant under Brazilian conditions slightly better at the variable cost level. Cheaper services and lower depreciation increase this advantage to $1000 per tonne ion at the full cost level. However, the most important advantage is that the capital cost per tonne of ammonia cyanide ($7,000) is $\frac{1}{3}$ to $\frac{1}{4}$ of that for a local LTS plant on the Bayport or Mihara design.

4.2 Comparison with existing capacity

The variable cost of supplying a Latin American market with paraquat a) from a local 500te per annum ammonia cyanide plant and b) from Bayport are shown below.

TABLE IV

Variable Cost Comparison - Bayport and Ammonia Cyanide

Raw Materials	Ammonia Cyanide $/te	Bayport $/te
Pyridine	3788	2976
Others	2310	973
Services	984	622
Transport	-	750
	7082	5321

When this cost disadvantage is added to $375,000 incremental fixed expenses and an additional $3.5m fixed investment at a time of overcapacity,it is easy to see that ICI should not voluntarily build any new cyanide process plants while there is spare capacity on the LTS plants. For the present this technology only represents a defensive weapon which can be used to prevent our exclusion from important markets or to overcome major duty penalties.

4.3 Competitiveness with local HTS plants

An ammonia or water cyanide plant should be able to compete successfully with a local "Taiwanese technology" HTS plant behind tariff barriers. It is believed that the cyanide process would enjoy a variable cost advantage over the competitive plant. (See Table V overleaf.)

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TABLE V

Comparison with local Taiwanese production

	Ammonia Cyanide 500te/yr Latin America $/te	HTS 360te/yr Latin America (ca) $/te
Pyridine	3788	6375
Other raw materials	2310	2294
Services	984	100
	7082	8769

This assumes 50% pyridine efficiency. Other efficiency assumptions are as for the Chia Thai plant in Thailand.

In the above comparison it has been assumed that the Taiwanese could purchase pyridine ex US at the ICI price. In practice, pyridine prices to the local HTS producer are likely to be higher. If the local producer paid the US list price of $4.05/kg FOB for pyridine then ICI's variable cost advantage would increase by another $935/te of ion.

Furthermore, when the capital cost information we have on the Chia Tai/ San Yuen plant in Thailand is adjusted for local costs and regulations in, say, Brazil, it is believed that it would cost nearly $5m for a 360te/yr plant which is considerably more than for a 500te/yr ammonia cyanide plant ($3.5m). ICI's ammonia cyanide plants are basically simpler than Taiwanese HTS plants (7 reaction and separation vessels as against 60) and should, with the same steel and construction cost and the same safety regulations,have a lower capital cost.

5. Mexico and Brazil

(a) The estimated capital cost for a 200 tonne/year water cyanide plant in Mexico (Canamex site) is ca $1m. This assumes no use of the existing quaterniser but does assume use of the existing steam boiler and effluent disposal arrangement. The absence of capital allowances and under-utilisation in early years make a water cyanide plant almost certainly the preferred choice for Mexico.

(b) The estimated capital cost for a 500te/year ammonia cyanide plant in Brazil (Paulina site) is ca $4m. This assumes that expenditure for solar evaporation of the effluent is cancelled out by the use of the existing quaternisation plant.

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The cyanide processes have been discussed by Mond Division with local personnel in Mexico and Brazil, who supported in general terms the above estimates and commented favourably on the simplicity of both processes.

6. Product quality and process safety

The cyanide processes produce paraquat of similar total impurity content to the product of the LTS process. The level of other isomers (2:4 and 2:2 bipyridyl) and terpyridyls are exceptionally low. One additional impurity is cyanide ion at a level of 25ppm maximum, but it is believed that this will not effect the toxicological or biological properties of the product.

Information on the toxicology of the processes is under review. Present indications are that the product, intermediates, and effluent should not exhibit any mutagenic activity but further work is required to confirm this.

It is worth noting that the cyanide routes do not have 4,4'-bipyridyl as an intermediate and, therefore, provide a possible alternative should there be any toxicological problem with the existing LTS route.

7. Patent position

ICI patents on the cyanide process in the main European countries will expire in 1988/89. They expire in Malaysia/Singapore in 1989, Mexico in 1985 and Brazil in 1994. There are no patents in Taiwan. Competitors anywhere are free to operate the uneconomic published water cyanide process (pyridine efficiency ca 20%) and it would be virtually impossible to prove that ICI patented improvements were being incorporated.

In view of our comparative weak patent position, it is essential that (1) we exercise care in using this process as a weapon to deter competition and (2) we maintain the highest level of secrecy about the unpatented know-how and engineering details of our processes.

8. Project organisation and resources

Mond Division are currently preparing a design package for a 500te/yr ammonia cyanide plant which should be completed by November 1980. This will be followed by a design package for a 200te/yr water cyanide plant which should be ready early in 1981.

If a small plant was required, the local company would need to complete the detailed engineering design using a contractor or hiring contract engineers as appropriate. The local company would also be responsible for the sanction estimate, procurement, cost control and commissioning, but Mond Division would provide assistance during commissioning and would be available throughout for consultation and advice.

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9. Conclusions and Recommendations

(1) ICI should not build any local small plants unless there is an imminent and serious threat of exclusion from valuable markets.

(2) If a local plant is necessary ICI should construct an ammonia cyanide plant for 500 tonne (eg Brazil) or 1250 tonne (eg Malaysia, Thailand) markets. In some circumstances in a 200 tonne market (eg Mexico) water cyanide is likely to be better.

(3) These plants can compete on capital and variable product cost terms with local HTS technology.

(4) At this time, there appear to be no process safety or material purity problems associated with these processes.

(5) The detailed design and commissioning of such plants would be under local direction. Mond have sufficient resources to provide back-up. Basic design packages will be available from 1981.

(6) ICI's patent position on these processes is not strong and we should be careful about disclosure to potential or existing competitors.

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APPENDIX I

[redacted]AQUAT SMALL PLANT COST SUMMARY

			WATER-CYANIDE				AMMONIA-CYANIDE		
CAPACITY (T/YEAR)			200	500	1250		200	500	1250
CAPITAL			$M	$M	$M		$M	$M	$M
FIXED			1.2	2.1	3.7		2.0	3.5	6.2
WORKING			1.4	3.4	8.0		1.4	3.4	8.0
TOTAL			2.6	5.5	11.7		3.6	6.9	14.2
COSTS AS FULL LOAD	PRICES $	USAGE	$/T	$/T	$/T	USAGE	$/T	$/T	$/T
RAW MATERIALS (T)									
PYRIDINE	3750	1.347	5051			1.01	3788		
METHYL CHLORIDE	1720	0.868	1493			0.704	1211		
SODIUM CYANIDE	2275	0.591	1345			0.157	357		
CHLORINE	300	1.109	333			0.753	226		
CAUSTIC SODA	480	1.393	669			0.970	466		
OTHERS			50				50		
			8941	8941	8941		6098	6098	6098
SERVICES (T)									
NITROGEN	100	0.85	85			0.53	53		
STEAM	36	3.5	126			17.9	644		
OTHERS			260				287		
			471	471	471		984	984	984
VARIABLE COST			9412	9412	9412		7082	7082	7082
OPERATING COST			975	400	173		1110	470	205
MAINTENANCE			240	168	120		400	280	198
PLANT COST			10627	9980	9705		8592	7832	7485
DEPRECIATION 10%			600	420	296		1000	700	496
OVERHEADS 100% LABOUR SUSPENSION			1005	433	205		1180	535	265
FULL WORK COST UNFORMULATED			12232	10833	10206		10772	9067	8246
COSTS AT HALF LOAD									
PLANT COST			11842	10548	9998		10102	8582	7888
DEPRECIATION			1200	840	592		2000	1400	922
OVERHEADS			2010	866	410		2360	1070	530
FULL WORKS COST			15052	12254	11000		14462	11052	9410
FULL CAPACITY FULL COST PLUS 20% RETURN ON CAPITAL EMPLOYED			14832	13033	12078		14172	11827	10518
HALF CAPACITY FULL COST PLUS 20% R.O.C.E.			18852	16654	14744		19862	16572	13954