

It seems likely that the emetic formulation of paraquat will be approved by the EPA shortly. It is therefore necessary to determine what our policy on introduction of PP796 in the USA should be. An important determinant of this policy is our current view on the technical efficacy of the emetic formulation, which is therefore discussed first. The commercial implications, and a suggested policy, follow.

### Technical

#### 1 Efficacy of the emetic

(These views have been endorsed by Dr T B Hart and Dr L Smith, CTL.)

ICI's view of the likely effect of the emetic in saving life in paraquat poisoning cases has, until the last year or so, been based solely on animal experiments and a belief that induction of vomiting would act as a built-in first-aid measure.

By inducing vomiting rapidly and removing paraquat from the stomach, PP796 would therefore reduce the chances of death following the swallowing of small amounts (perhaps up to 40ml) of Gramoxone. We hoped that this would virtually eliminate the few deaths from accidental poisoning by Gramoxone and also reduce the number of deaths from suicide attempts with the product where the amount swallowed was small. We did not expect that the emetic would make any significant contribution to directly saving the life of the majority of suicide victims who swallow large amounts of the product. However, the rapid vomiting caused by PP796 was expected to draw attention to the fact that a poison had been swallowed, and to make application of the treatment methods more likely. Thus there might be an indirect contribution to life-saving even in a few such suicide cases.

In the case of suicide attempts involving the swallowing of Weedol and Pathclear, we expected that the emetic would have had a proportionally greater effect on life-saving, because the amount of paraquat ingested is usually small even when this product is swallowed deliberately. (4 sachets of Weedol, a large quantity to take, even for someone attempting suicide, are equivalent to 30ml of Gramoxone.)

During the past year or more we have followed the effect of the emetic fairly closely in the UK and Japan. These observations have confirmed that PP796 is a highly effective emetic in man. However, no statistical evidence has emerged that the emetic has reduced the number of deaths with the product in either country. Particularly disappointing, perhaps, is that this conclusion also applies to cases of suicides with Weedol and Pathclear in the UK. In addition to these overall observations, close scrutiny has been applied to many individual poisoning incidents especially in the UK. Although it remains difficult to discover all the facts surrounding such incidents, the conclusion that emerges from this scrutiny is that, at best, only a few people have survived paraquat poisoning because of the inclusion of the emetic. Even in these cases we cannot be certain that the emetic has contributed to saving life.

The position that must now be taken on the effectiveness of the emetic formulation thus comes down to a belief that it may contribute to saving a small number of lives, all of them of people who have swallowed small amounts of paraquat. Whatever ICI's views on the subject, however, the outside world may independently reach a harsher conclusion. There are already some in the toxicological field outside ICI who consider that the emetic is ineffective in saving life. Such a view may

Cont./...

.../Cont.

spread and be publicised, and although we shall continue to monitor the situation, it may be difficult, perhaps impossible, for us to produce evidence to the contrary.

In view of the changing perceptions about the toxicological benefits from the emetic formulation over the period since 1976, when it was first devised, it is likely that there are different levels of understanding within PPD and the Overseas Companies about what can now be expected of PP796-containing formulations. Sooner or later those who need to know must be made aware of our current belief in the effectiveness or otherwise of the emetic. It is important that undue hopes should not be raised for what PP796 can achieve toxicologically, and equally, that registration authorities should not be actively misled into thinking that the emetic formulation will "solve" the paraquat toxicity problem.

## 2 Policy on emetic introductions

### a) General

The original policy decision to include PP796 in all paraquat products was subsequently modified : the current policy is that the inclusion should be decided on a case by case basis. In the light of the current view of the probably small toxicological benefit which arises from inclusion of the emetic in paraquat, it is difficult to see how a case can now be made to registration authorities that an emetic should be included in all paraquat products, which is the means by which a commercial benefit is obtained from the emetic.

The current cost of PP796 to PPD is about £80/Kg. Inclusion of the emetic in paraquat therefore costs 4p/litre of Gramoxone or £200/tonne of paraquat ion at PPD cost level. Future reductions in emetic cost to PPD to about £60/Kg can be expected.

### b) Markets where ICI already has an exclusive position

The requirement that paraquat products should contain an emetic has resulted in Gramoxone plus PP796 having a effectively exclusive position in the UK, France, Australia, New Zealand, Japan (except in the non-agricultural outlets) and Venezuela. Indeed in some countries (notably France and Venezuela) it is probable that the emetic has prevented paraquat from being banned. Our exclusive position is threatened by the possibility that alternative emetic agents will be approved : several attempts have been made to register such compounds. It can be expected that some of these attempts will eventually be successful.

However, an additional serious threat to our position could arise soon in some or all of these countries. The registration authorities may wish to see evidence that the emetic formulation is helping to save life from paraquat poisoning. It is obviously questionable, at least, whether the evidence discussed above will be sufficient to convince all the authorities that our effectively exclusive position should be retained. In some cases, it is even conceivable that an inability to demonstrate that the emetic is reducing the number of deaths from paraquat poisoning may lead to a ban on the product.

### c) USA

After a long delay it seems likely that the EPA will approve PP796 as an "inert ingredient" for paraquat formulations by the end of 1981. This follows considerable prompting of Chevron by ICI to press EPA to approve the emetic,

Cont./...

.../Cont.

and a good deal of apparent hesitation on EPA's part as to how the emetic should be treated (which involved discussions with the F&DA).

The background to the registration of PP796 thus includes active encouragement from ICI and Chevron. The reasons for this pressure were the hopes that the emetic would contribute to reducing the already relatively small number of deaths from paraquat poisoning in the USA, and, linked to this, that the EPA would make an effective emetic a requirement for all paraquat products : this coupled with our patent on the emetic would have put us in a strong competitive position.

These hopes are now much diminished. Firstly, there is our current view that the emetic may have at best a marginal effect on reducing the chances of death from paraquat poisoning. Secondly, following from this, the chances of the EPA being persuaded to make the emetic a mandatory inclusion in all paraquat must now be negligible, if it was ever a likelihood. (If, as now seems almost certain, no RPAR is issued on paraquat by EPA, it will be a further indication that EPA are not seriously concerned about acute toxicity. As far as is known, the possibility that an emetic might be included in paraquat, did not influence EPA's thinking on RPAR.)

What is certain, however, is that inclusion of PP796 in US paraquat will add at least 27¢ per gallon of product, or about \$300 per tonne of paraquat ion (using current cost to PPD of PP796 and £1 = \$1.80). How this cost would be handled if the emetic is introduced requires discussion : it may be that Chevron, or the US farmer will pay the total cost. If Chevron are very keen to introduce PP796, they may be prepared to pay a high price for it, leading to additional profit for ICI. However, whichever method is used, the cost represents a loss of profit from the paraquat business. If the annual US paraquat sales are 1500t, the total lost profit is \$0.45m; at 2000t the lost profit is \$0.6m. (based on current cost of PP796 to PPD).

There are two possible penalties to face if we do not introduce PP796 in the USA. The first is that we could be attacked for not doing everything possible to try to reduce paraquat poisoning deaths. (However, in this context it should be noted that Chevron have still not introduced the valeric acid stenching agent, even though it was registered over two years ago.) The second relates to markets outside the USA in which the emetic is maintaining ICI paraquat in an exclusive position. It is possible that a decision by ICI/Chevron against introduction of the emetic in the USA would become known to the regulatory authorities in these markets. Our exclusive position could obviously then be seriously undermined.


The most prudent course of action therefore seems to be to delay introduction of PP796 in the USA until our views on its efficacy and the possibility of the EPA giving us an exclusive position are further clarified; by this time PP796 may no longer be giving us an exclusive position in several markets, in which case we need not fear difficulties in those markets because of non-introduction of emetic in the USA. A year's delay is suggested : such a delay can be explained to the outside world by referent to "production difficulties".

The alternative course of action, ie to introduce the emetic in the USA as soon as possible, whilst probably achieving little in the USA itself, may have the merit of bolstering the confidence of the registration authorities in our "exclusive" markets in the effectiveness of the emetic. However, there is a high price to pay for what might turn out to be an illusory benefit.

Cont./...

.../Cont.

The next step is to ensure that policy for the USA on the emetic is agreed within PPD and ICI Americas. The policy then requires debate with Chevron. Our reasons for not introducing the emetic immediately, if that is the agreed policy, would obviously have to be understood and agreed by them. Doubtless the cost argument will appeal to them (unless ICI volunteers to bear the full cost!) However, it is important that Chevron should fully understand our current view on the effectiveness of PP796, and this issue must be thoroughly discussed with Chevron as soon as possible.

  
PS/SB  
21.8.81