

Fernhurst
Haslemere Surrey
England GU27 3JE

Telephone Haslemere (0428) 4061
Telex 858270 and 858512 Icippp Fernhurst
Cables and Telegrams Plantector Fernhurst Telex



Imperial
Chemical
Industries
PLC

Plant
Protection
Division

Dr H A F M Custers
Medical Officer
B V Luxan
Industrieweg 2
PO Box 9
6660 AA
Elst
The Netherlands

Your ref

Our ref

Telex

Date

TBH/NMW

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Dear Dr Custers

Thank you for your letter and enclosed report 'Paraquat and the Addition of an Emetic'. I found the report very interesting and it was obvious you have spent a lot of trouble and effort in preparing it. Naturally I do have some comments related to the content of the document and perhaps it would be a useful idea to discuss these with you personally.

In general, I did not get the impression that you had adequately considered a risk versus benefit analysis. For example you talk at length about possible adverse effects with PP796, most of which are theoretical, and conclude that serious adverse effects must be expected either in adults or children. The point surely is that serious effects will occur if sufficient paraquat is swallowed. The lowest acute oral LD50 in mammals is 150 mg/kg body weight (rats). If man is as sensitive as the rat then the potentially lethal dose of PP796 will be 9 g or 90 mg (allowing for a 100-fold difference in sensitivity between man and rat). To swallow 90 mg of PP796 in emeticised 'Gramoxone' the person would have to swallow 180 ml of 'Gramoxone' (5 mg in 10 ml 'Gramoxone') or 36 g paraquat ion. As the potentially lethal dose of paraquat in man is between 2 and 5 g, I am sure you will agree that the major risk to that person must be from the paraquat.

Specifically I have other comments, some of which unfortunately may have resulted from your misunderstanding of the data. These are as follows:

1. Page 3 - paragraph 3

I presume 5 pm means 5 μ m. It is not only the pressure used, but the type of nozzle used which will determine droplet size. In any case production of fine droplet sprays is usually contra-indicated on biological grounds for herbicide use to reduce drift hazard.

2. Page 5 - paragraph 2

Howard, in his article, showed that just over 50% of patients vomited following ingestion of non-emeticised paraquat. The time to vomiting is critical and it is well recognised that the time lapse from ingestion to spontaneous vomiting with irritants, such as 'Gramoxone'



is very variable and may occur several hours after ingestion. Not only does the addition of PP796 increase the incidence of vomiting to 95% following ingestion of paraquat formulation, but the time to vomiting is early, within 30 minutes of swallowing.

3. Page 6 - paragraph 2

This idea illustrates well my first point that an adequate risk/benefit has not been conducted.

4. Page 6 - final paragraph

I agree that the effects of ipecacuanha are unpredictable and that deaths, particularly in children, have occurred following overdosage. I am not sure it is totally fair to say that ipecacuanha is only a useful vomitive at doses causing unwanted side-effects. It has been used over a long period of time with few incidences of serious adverse reactions.

5. Page 7

It is not correct that the development of PP796 was continued as an emetic. It was stopped in development as a bronchodilator, and was never intended to be used as an emetic per se. ICI Plant Protection Division then took it up as an emetic to be added to paraquat formulations.

6. Page 7 - paragraph 3

PP796 for use as an emetic per se does have a number of advantages over other emetics - including a good therapeutic ratio speed of action and potential as an injectable preparation. It was for these reasons that several government authorities throughout the world have requested ICI to develop it as an emetic. We have not done so for the reasons you have mentioned.

7. Page 9 - paragraph 2

I agree angina pectoris did occur in 2 out of 4 subjects in one of the clinical trials. Both subjects had never experienced this symptom before and neither suffered the same on cessation of the trial.

The significance of this finding must be doubtful in the context of paraquat poisoning as both patients received a dose of 2 mg, three times daily, for a period of 4 to 6 weeks. I am sure you will agree subacute dosing at those levels with emeticised 'Gramoxone' is likely to be an extremely rare occurrence.

8. Page 12 - paragraph 1

Although you quote correctly from Kawai's paper, the idea you present is taken somewhat out of context. The author himself concludes, "We were able to verify that adulteration of paraquat with an emetic to induce vomiting of the paraquat and suppress its absorption into the body is an effective means of prophylaxis in the accidental and deliberate drinking of paraquat. The life prolonging effect was more clearly manifested in the group given paraquat after fasting than in

the group given paraquat after ad libitum feeding".

It is also pertinent to this question that experiments involving dogs and monkeys to evaluate the reduction in paraquat toxicity with added emetic, involved the administration of a gruel-mixture prior to dose. These animals were therefore not fasting and yet a 3-5-fold reduction in toxicity of the paraquat formulation could be achieved.

9. Page 12 - paragraph 2

I do not understand the logic in this argument. PP796 is a bronchodilator, but this will not affect O₂ transport in normal, healthy subjects. In patients with obstructive airways disease, it will improve O₂ transport, but only to the same extent as a normal healthy subject. In no way will it simulate the administration of high concentration O₂.

Incidentally the use of hypobaric O₂, although advocated in some hospitals, as a treatment for paraquat poisoning, is the exception rather than rule. It has never been shown that it is a method which will improve the mortality or prognosis in paraquat poisoning.

10. Page 12 - paragraph 4

Again the logic of this argument escapes me. If you are suggesting that children, because of their smaller size are more susceptible to PP796, then surely the same is true for their sensitivity to paraquat. Hence the toxic hazard remains the same irrespective of the size of individual.

Also you mention serious complications which must be expected. I would be grateful if you would let me know what these might be and how they compare with serious complications resulting from ingestion of paraquat.

11. Page 13 - paragraph 2

To state that the use of PP796 and a large number of drugs is either contra-indicated or useless on the basis of the data referenced is, I feel exaggerating the case somewhat. I agree the data does suggest there may be a problem, but it is definitely not one we have encountered in practice.

12. Page 14 - paragraph 1

It is not true to say that in West Germany and the Netherlands that a negative opinion predominates over the addition of PP796 to paraquat formulations. If this were true then this addition would not be permitted. Belgium is the only country in Europe or indeed the world, which has given a negative opinion, and it has taken them 4 years to reach this conclusion.

It is also untrue that PP796 addition is banned in the USA; registration for this addition has been granted.

13. Page 14 - paragraph 2

In Denmark, the addition of an emetic to paraquat formulations is a mandatory registration requirement. The type of emetic is not specified.

14. Page 14 - paragraph 2

Again a risk versus benefit analysis appears to be lacking when considering only the strong physiological action of PP796.

15. Conclusions

I do not believe dependability is lacking at all with the addition of PP796 to paraquat formulations. A 95% success rate with spontaneous vomiting after ingestion of emeticised 'Gramoxone' does not support your conclusion.

The comment about children and the estimated dose remains the same as above.

Interaction with other drugs may be expected on theoretical consideration. It certainly does not appear to the case in practice.

Potential of oxygen metabolism in the lungs does not appear to make any sense with respect to PP796 addition.

To say that PP796 will give an initial decrease in renal clearance presumes that you have positive evidence to show this. I have certainly not seen any evidence to support this in practice.

PP796 is not a legally allowed pharmaceutical although there is a very good chance it would be, if ICI Pharmaceuticals Division wished to develop it.

Page 16 - 3rd paragraph - this statement tends to contradict the previous conclusion concerning dependability.

I am not sure that improved information supply to individuals will reduce the paraquat poisoning problem. It depends largely on which individuals are informed and how they are informed. In the UK, press information about paraquat toxicity has helped to reduce accidents, but has certainly contributed to an increase in suicides.

I would be very interested to see your ideas on a safety campaign.

I apologise if many of these comments appear harsh, but I am afraid I do feel there are a number of serious errors in your document. I would welcome a personal discussion with you.

Best wishes.

Yours sincerely

Bernard Hart

T B HART (Dr)
Product Safety Auditor

uc.c. Dr L L Smith, CTL
Mr A Potter, WER
Ir B P Anema, ICI Holland