

Paraquat Emetic
Paraquat Toxic

file

23/1/95

Internal Memorandum from
B G Johnen
Manager
Stewardship & Safety Department

ZENECA Agrochemicals
Fernhurst
Haslemere Surrey GU27 3JE

To
Miss Hazel A Sutcliffe, BSD
Dr R C Scott, CTL
Mr G A Willis, RAD
Dr M F Wilks, SASD
Mr A R Cook, RAD
Mr M J Whitaker, SASD

Tel [Redacted - EU PII]
Telex [Redacted - EU PII]
Dir Fax [Redacted - EU PII]

Copies to
Davor Pisk, BSD
Peter Sutton, BSD
John Barnes, BSD

RECEIVED
24 JAN 1995

Our ref BGJ/NMW/M16D6.Z95 Direct line [Redacted - EU PII] Tel Ext [Redacted - EU PII] Date 23 Jan 1995

PARAQUAT - EMETIC CONCENTRATION IN LIQUID FORMULATIONS; SPRAY-STRENGTH DILUTION OF PARAQUAT FORMULATIONS FOR HAND-HELD APPLICATION

Please find enclosed one file note on each of the above subjects of 21.7.94, which state the Product Safety position on both subjects. The positions are not different from those previously communicated to the Business. The re-assessment and re-statement was precipitated by some confusion that appeared to have arisen in the Business as a result of ongoing paraquat safety research.

Would Andy Cook please ensure communication within RAD and Martin Wilks arrange for verbal briefing of Product Usage within SASD.

B.G. Johnen

B G JOHNEN (Dr)

Encs: Emetic concentration file note of 21.7.94
Spray strength dilution file note of 21.7.94

(2)

66080007



7-10

FILE NOTE

CONCERNING THE CONCENTRATION OF THE EMETIC PP796 IN LIQUID PARAQUAT FORMULATIONS

A meeting was held on 14.2.94 with:

Dr R C Scott, CTL
Mr G A Willis, RAD
Dr N N Sabapathy, RAD
Mr A R Cook, RAD
Dr M F Wilks, SASD
Dr B G Johnen, SASD

present, in order to agree an authoritative view on the concentration of emetic (PP796) in liquid paraquat formulations. Such a statement appeared to be necessary, since there was a perception in some parts of the Agrochemicals Business, that current research (re "Magnoxone" project) had cast doubts on the present concentration (0.5 g/l).

Rationale for the present concentration:

In 1976, PP796 was proposed to be added as an emetic agent to liquid paraquat formulations as one of a number of measures to combat the consequences of accidental oral intake of liquid paraquat formulations. The concentration of 0.5 g/l was set on the recommendation from CTL (Dr Mike Rose), who had based this recommendation on clinical data generated by ICI Pharmaceuticals (now ZENECA Pharmaceuticals), the original inventors of the compound (*Rose, 1976*). A comparison of human and experimental animal data suggested that emesis in humans was achieved at far lower doses than in animal experiments.

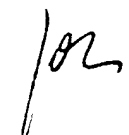
A literature review (*Meredith and Vale, 1987*) of available case studies with paraquat indicates that emesis (at a concentration of 0.5 g/l) is happening: 65% of all cases vomited in less than 30 minutes; a further 22% vomited in less than 2 hours. Thus, PP796 effectively induces emesis at a concentration of 0.5 g/l in liquid paraquat formulations. (This should not be confused with a similar success rate in ultimate survival/recovery of patients, who have ingested paraquat. In addition to emesis, the maximum effect of which in cleaning out food, agents etc from the human gut is about 65%, the success is dependent on the dose ingested and the speed with which the treatment for paraquat poisoning is administered. The Company position remains that the inclusion of PP796 in liquid paraquat formulations retains the potential of benefit for the successful treatment of paraquat poisoning cases at near lethal levels.)

Higher concentrations (than 0.5 g/l) of PP796 in the experimental "Magnoxone" formulation contribute to emesis and detoxification effectiveness, because in this formulation the ingested dose remains in the gut. The case of the commercial 'Gramoxone' liquid paraquat formulation is different. The normal 'Gramoxone' formulation passes into the intestine, from where emesis cannot remove it. Thus, increasing the concentration of the emetic would not help in getting a larger amount of paraquat eliminated from the body by emesis.

66080008

It was therefore concluded that the Product Safety position on the concentration of PP796 in liquid paraquat formulations is as follows:

1. The evidence supports the view that PP796 effectively induces emesis when ingested as part of liquid paraquat formulations. There is, therefore no case to take the emetic out of those formulations.
2. There is no evidence that a higher concentration than the present 0.5 g/l will lead to more effective emesis. There is, therefore, no case for increasing the concentration.
3. Therefore, in 'normal' (ie current commercial) liquid formulations the PP796 concentration is to remain at the present level of 0.5 g/l.


B G JOHNNEN
Manager Stewardship & Safety Department

21.7.94

FN3D6.95

REFERENCES

Meredith, T J, and Vale, J A (1987) : Treatment of paraquat poisoning in man : Methods to prevent absorption. Human Toxicology 6 : 49-55.

Rose, M S (1976) : The concentration of PP796 required to produce emesis in experimental animals and an estimation of the emetic dose in man. Report CTL/R/390(R).

66080009

FILE NOTE

CONCERNING THE DILUTION TO SPRAY STRENGTH OF PARAQUAT FORMULATIONS (FOR HAND-HELD APPLICATIONS)

At a meeting on 14.2.94 the question of the dilution to spray strength of paraquat was addressed. The meeting was attended by:

Dr R C Scott, CTL
Mr G A Willis, RAD
Dr N N Sabapathy, RAD
Mr A R Cook, RAD
Dr M F Wilks, SASD
Dr B G Johnen, SASD

CTL have recently carried out a straightforward Rabbit Skin Irritation Study with 'Gramoxone' liquid paraquat formulation. The study failed to find a dilution level with no irritation. A dilution rate of 1:40 produced 'moderate to strong' irritation; at a rate of 1:200 the irritation was 'mild'.

Based on this study and the longterm experience in use, it is the Product Safety point of view that a 1:100 should be the normal recommended dilution rate for spraying paraquat (based on a formulation strength of 200 g paraquat/l). On merit, a less diluted rate of 1:40 can be agreed in consultation with Product Safety for particular defined circumstances. It has, however, to be borne in mind that at a spray strength of 1:40 the irritation potential of the spray solution can be unpredictable. A general claim of 'safety' cannot (and must not) be made in these circumstances.



B G JOHNEN
Manager Stewardship & Safety Department

21.7.94

FN406.95

66080010