N.B. PQ. Safer formulat ions.

From
Dr J R Heylings
Biochemical Toxicolog

To
Dr L L Smith
Section Head

| Your ref | Our ref | Direct line | Tel ext | Date |
|---|---|---|---|---|
| | JRH064/AMD | Redacted -PII | | 21 Sep 90 |

RE : UPDATE ON RESEARCH INTO SAFER FORMULATIONS OF PARAQUAT

Our latest dog studies in August and September have further clarified the safety components in 'Magnoxone'. There is a clear dose response relationship between 0, 10 and 100g/l Magnesium Trisilicate and reduction in paraquat plasma AUC values. This occurs at 8, 16, 32 and 100 mg/kg paraquat ion and is independent of the emetic (PP796) concentration in the formulation.

A trade-off situation between emetic and magnesium trisilicate is emerging from data with 8 and 16 mg/kg paraquat. This position will be confirmed at 32 mg/kg paraquat in October.

The intrinsic safening of Magnoxone (i.e. with no extra emetic) is better than first anticipated, even with relatively low levels of magnesium in our latest dog studies. Our research studies in rats have shown that Gramoxone-induced gastric lesions and plasma paraquat is dose dependently reduced with increasing luminal [$Mg^{2+}$]. However, we have recently found that at very high [$Mg^{2+}$], there is damage to the surface epithelial cells of the gastric mucosa. This raises plasma $Mg^{2+}$ (and paraquat) which can cause renal toxicity. Consequently, paraquat renal excretion may be impaired.

Another possible reason why such a magnesium/paraquat formulation with no extra emetic has proved less toxic than we thought is that the emetic is a weak base. According to its lipophilicity and pka it should be better absorbed (in its unionized form) at neutral pH compared to normal gastric acid pH of 2-3. Magnesium trisilicate raises intragastric pH to 7 and may therefore increase gastric absorption of PP796. This pH effect should not affect paraquat absorption. We are examining this hypothesis in rats following the successful development of a fluorescence assay in our lab for PP796 in blood which can detect down to 10-100 nanogram/ml levels of this emetic in plasma.

Cont...

From
Dr J R Heylings
Biochemical Toxicology

ICI Central Toxicology Laboratory

Alderley Park
Macclesfield Cheshire SK10 4TJ

Tel: 0625 582711
Telex: 669095/669388
Fax: 0625 582897

To
Dr L L Smith
Section Head

Copies to
Dr T Green
Dr R S Morrod
Dr S E Jaggers

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We therefore currently have four options to follow as possible candidates for the development of a safer paraquat formulation:-

Option 1 We have conducted more than 15 dog studies with various emetic levels combined with different paraquat doses over the last year in order to determine the minimum level of PP796 required to effectively prevent paraquat toxicity. There is a very steep relationship between onset of emesis and PP796 dose. It is clear that the current level of emetic marketed worldwide of 0.5g/l does not cause vomiting in dogs in the first hour after a minimally lethal dose of Gramoxone. This is equivalent to 0.02mg/kg for an 8mg/kg dose of Gramoxone. However, increasing the PP796 concentration to 2.4g/l effectively produces emesis within 30 minutes and allows up to 5 lethal doses of Gramoxone to be given orally to dogs without toxicological consequence. Having reviewed the human data within PP796, I suggest that such a maneouvre alone would probably reduce toxicity in man by a similar factor.

Option 2 The consequences of discovering a new safer formulation of paraquat which does not require an increase in the level of emetic may prove more acceptable to the Agrochemicals business for a number of reasons. I therefore predict that we can provide a magnesium trisilicate formulation which will be 10x safer orally than Gramoxone in dogs using the current 0.5g/l level of PP796. This involves increasing the concentration of magnesium trisilicate in the formulation to 100g/l.

Option 3 A third option is to trade off trisilicate for increased emetic. Extensive dose response studies demonstrate the requirement to produce emesis within 30 minutes of oral dosing to reduce paraquat toxicity. Increasing the emetic concentration by just 3 fold to 1.5g/l allows us to reduce the trisilicate from 100 to 10g/l without losing safening. Such a formulation is also likely to achieve a 10x safety factor over Gramoxone.

Option 4 Finally, the best option "toxicologically" speaking is to develop a formulation which contains both high trisilicate (100g/l) and higher emetic (1.5g/l). In our current dog studies this formulation (M19) is certainly the 'safest' formulation we have ever tested since this programme began in 1987. I would predict by extrapolation of available data at 128mg/kg paraquat that the LD50 for this version of Magnoxone will be above 150mg/kg compared to 12mg/kg for Gramoxone.

The Magnesium Trisilicate (10-100g/l)/high emetic (0.5-2.4g/l) formulations all contain the purgative $MgSO_4$ (100g/l) and the thickener kelzan (3g/l). They are all sprayable and herbicidally equal to Gramoxone. However, in the absence of Formulation support at Agrochemicals, there is no official storage stability data on these CTL derived paraquat formulations.

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I hope this is a useful update for the impending Board Paper discussion with ICI Agrochemicals.

Jon R. Heylings

DR J R HEYLINGS
Biochemical Toxicology

| Formulation | Composition | g/l | Estimated Safety Factor |
|---|---|---|---|
| Gramoxone | Paraquat ion | 200 | x1 |
| | PP796 | 0.5 | |
| High Emetic Gramoxone (Option 1) | Paraquat ion | 200 | x5 |
| | PP796 | 2.4 | |
| Magnoxone (M20) (Option 2) | Paraquat ion | 200 | |
| | PP796 | 0.5 | |
| | Mg Trisilicate | 100 | (x10) |
| | MgSO4 | 100 | |
| | Kelzan | 3 | |
| Magnoxone (M17) (Option 3) | Paraquat ion | 200 | |
| | PP796 | 1.5 | |
| | Mg Trisilicate | 10 | (x10) |
| | MgSO4 | 100 | |
| | Kelzan | 3 | |
| Magnoxone (M19) (Option 4) | Paraquat ion | 200 | |
| | PP796 | 1.5 | |
| | Mg Trisilicate | 100 | (x15) |
| | MgSO4 | 100 | |
| | Kelzan | 3 | |

The above options are included in ICI Patent Application UK 9015134.1 filed on July 10th 1990.