**From:**

**Dr Jon R Heylings**
Investigative Toxicology
CTL

**Zeneca Central Toxicology Laboratory**

Alderley Park Macclesfield
Cheshire SK10 4TJ England

Tel: 01625 514550
Fax: 01625 582897

Z-Mail:

**To:**
Dave Berry
Richa Shaunak

**Copies to:**
Mike Farnworth

| Your Ref | Our Ref | Ext | Date |
|---|---|---|---|
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**SAFER PARAQUAT PROJECT**

Following our meeting at CTL on March 1st, I would like to follow up on one of the options we discussed which is described in the Safer Paraquat Project report as a "potential winner" and is outlined as proposal H5 under the heading "emesis booster". I have a proposal to undertake a joint CTL/Yalding project on this.

**Project Proposal - Emetic Boosters**

Background

An effective method to **markedly** reduce the oral toxicity of paraquat once a lethal dose has been ingested is to rapidly remove the material from the gastrointestinal tract. Once paraquat has moved from the stomach into the small intestine it rapidly enters the bloodstream via a facilitated uptake process. Gels, emulsions, binders and chelators can delay absorption for a short time but have little overall effect on reducing the toxicity. The digestive system has a very effective way of breaking up particles by acid hydrolysis and dispersing insolubles with bile salts and enzymes until any trapped material is eventually available for absorption. By understanding the process of digestion you can delay and reduce the exposure of paraquat to the absorptive small intestine by switching off the acid hydrolysis (antacids), slowing gastric emptying (in situ gelling) and increasing water secretion (purgation). This buys more time until the bulk removal of the formulation by emesis occurs when the emetic blood levels are high enough .

The Magnoxone concept was based on this synergism and clearly demonstrated with the lead formulation, YF8004. Magnoxone also contained a 3 fold increase in the emetic agent, PP796 which maximised the effectiveness of this approach giving a 20X (or greater) safening with the very high magnesium trisilicate Magnoxone M19 variant.

The new challenge is to achieve a significant safening e.g. 10X, **without** increasing the PP796 level and **without** trisilicate. The latter approach of finding non-trisilicate gel-forming systems that removes gastric acid is the subject of a separate approach (H1 in the project report). However, we may be able to improve the effectiveness of the emetic agent by **reducing** the time it takes to reach an effective blood concentration following oral ingestion. This so-called "emetic booster" effect is based on the fact that the lipophilic phosphodiesterase inhibitor, PP796 may not be fully dispersed in the aqueous formulation concentrate at 0.5g/l and hence may not be optimally delivering an effective emetic dose. The time-to-emesis is the critical component of safening and this applies to both Gramoxone and Magnoxone. The facts that have lead us to think along these lines include the loss of some safening when we reduced the pyridine bases, since they help to disperse the PP796. Furthermore, the use of new adjuvants in the pharmaceutical industry which are designed to aid drug delivery e.g. cyclodextrins are becoming more widely used e.g. fast acting pain killers.

**Work plan**

1. Select candidate chemicals that will aid the dispersion of PP796 in an aqueous concentrate. Yalding (Richa Shaunak) has already suggested N-methyl pyrollidone and even castor oil. CTL (Jon Heylings/Mike Farnworth/Pharms) will also compile a list of drug adjuvants used with the PP796 type of chemistry in aqueous and suspension medicinal systems. Compatibility with Gramoxone's components and practicalities/cost will help to keep this a manageable number. I suggest we include the pyridine bases as one data point. **Yalding/CTL**

2. Determine the effect of these chemicals in blank non-paraquat aqueous solutions on the gastrointestinal absorption of PP796 using the in vitro isolated small intestine. This model is used routinely by my group at CTL as a pre-screen for pesticide and drug absorption. Essentially it is a membrane system that allows compounds or mixtures to be applied to the absorptive surface of the GI tract. The appearance of the chemical on the blood side is measured over a time course. Several PP796 mixtures could be tested per week by one person. We have a validated fluorometric method for PP786 and plenty of neat chemical in our stocks. **CTL**

3. Select the most promising "emetic boosters" and determine optimum concentration which enhances PP796 absorption in the in vitro model. Success criteria would be a reproducible and significant increase in the percentage, rate and extent of PP796 absorption as well as no adverse effects on the tissue. **CTL**

4. Determine the feasibility of incorporating these agents into Gramoxone. This would be an important step due to the potential interaction of co-formulants e.g. the surfactants already present and the practicalities of PP796 dispersion in a 200g/l product. **Yalding**

5. We would then examine the PP796 bioavailability from a paraquat formulation in vivo in a pharmacokinetic study using a non-vomiting species e.g. the rabbit. Success criteria here would be enhanced absorption of PP796 into blood and tolerance (safety) of the new component. This could be done over a short time course (several hours) using Gramoxone i.e. ahead of any adverse effects and would therefore be an ethically acceptable experiment. **CTL**

6. Ultimate proof of effect would be in man and human volunteer studies with PP796 have been done, so it is not out of the question to examine PP796 bioavailability in man with and without the new "dispersant" (without the paraquat, of course!). However, we would probably recourse to the dog, a vomiting species, to determine the effectiveness of a new emetic "booster", if the previous stages and decision points above warranted this. **CTL**

In terms of chances of success? If we can increase bioavailability of PP796 by a significant margin then this has got to be high. If we cannot improve the bioavailability of PP796 then this would be a minimal investment **(circa 1-2 man months)** and the project would stop at stage 2.

I would welcome your initial comments on this draft proposal which I will also share with my colleagues in the Non-Selective Herbicides project team.

**Jon R Heylings Ph.D.**