
From: Dixon Monty USGR
Sent: Wednesday, March 07, 2007 3:47 AM
To: Dieterle Roland Mario CHBS
Cc: Abbott John USGR; Akins Jonathan USGR; Elliott Barry GBAP
Subject: Inteon Study Status and New Study Plans

Importance: High

Dear Roland,

Please find below a summary of the current status of the on going paraquat toxicity studies as well as background on the thoughts behind the next planned phase. As you see for studies 1 and 2, the in life portion has been completed and preparations are being made to get studies 3 and 4 underway.

Study 1: US Non-Inteon - Gramoxone Max 360g/l : in life portion completed
Study 2: Global Non-Inteon formulation 200 g/l: in life portion completed
Study 3: US Gramoxone Inteon formulation 240 g/l: start (dosing) scheduled for week of March 22
Study 4: Global Inteon formulation 200 g/l: start (dosing) scheduled for week of March 22

The **next phase** is proposed to be as follows:

Study 5: US Gramoxone Inteon formulation 240 g/l (minus the alginates)
Study 6: US Gramoxone Max (360g/l) g/l + addition of emetic up to 3x

This next phase of the study has been formulated to address the issue that the EPA has communicated to us that is their "biggest concern". Below in black text is an excerpt from the letter we received from EPA in December in response to the agencies review of the dog study protocols. Please note that as shown in point 2 that the agencies biggest concern is focused on answering the question of what is "more protective: the presence of the gel, the purgative, or the additional emetic-or any combination of these three."

- 2. Our biggest concern is that the formulations proposed for the study (Slide 9) show that, in addition to the gel and purgative that are both present in Inteon™ compared to non-Inteon™ there is 3X more emetic in the Inteon™ formulations vs. the non-Inteon™ formulations. Thus, this may not answer the question as to what may be more protective: the presence of the gel, the purgative, or the additional emetic - or any combination of these three.**

The issue boils down to the following. Without demonstrating that it is all of the components that make up Inteon (the gel, the purgative and the 3X level of emetic) that give the improved safening over the non-Inteon formulations, we face the possibility that a conclusion could be drawn that all is required is to increase the level of emetic. We have been led to believe the Makteshim-Agan has increased the level of emetic in its recently approved paraquat formulation to 2.5X. There has already been some public communications that overstate the EPAs position on this such as the excerpt included below from the January issue of Agrow Magazine. This article states the that the agency has reached a decision that all is required is increased emetic to provide the required level of safety. The footnote (1) in the article does mention the fact the Agency has issued time limited

paraquat registrations to allow the agency to review additional safety assessments. These studies are a mechanism to provide these additional assessments.

The EPA determined that an increase in the level of the emetic alone would provide a level of safety required to satisfy the FIFRA registration standard of no unreasonable harm.¹ This slight modification in formulation was determined to be sufficiently similar to the paraquat registration existing at the time the generic application was filed such that it enabled the issuance and continuation of the generic registrations.

AGROW Magazine January 2007

The planned approach specified in the **next phase** directly address the EPA's biggest concern and also the statements such as the one in the magazine article that all that is required is increased emetic. By comparing two formulations with the same level of emetic and the same level of purgative but one without alginate and one with alginate will isolate the impact of the alginate. The alginate component is vital to keep as much of the paraquat in the stomach as possible while the emetic works its way to brain vomit center. These new studies will be an important comparison of this concept as all factors but the alginate will be held constant.

Roland, I hope this is helpful. Please give me a call if I can provide additional information.

Monty