From: Cook Andy GBJH <Andy.Cook@SYNGENTA.COM>
Sent: Friday, January 13, 2017 3:51 PM
To: Minnema Daniel USGR
Subject: PP796
Attachments: Concentration of PP796 Required to Produ.pdf; Original rationale for emetic loading.pdf; emetic level GMX360 - 110902.pptx

Sensitivity: Confidential

Hi Dan,

As discussed.

The Value of the Emetic in Paraquat formulations

As part of a series of stewardship measures to address accidental ingestion of paraquat, mainly as a result of grossly negligent practices such as decanting into drinks bottles, ICI (now Syngenta) introduced a potent emetic, the phosphodiesterase inhibitor PP796, into all its paraquat formulations, along with a dye (blue green colour) and olfactory alert. This now recommended in the FAO specification (2003).

Paraquat is rapidly absorbed from the gastrointestinal tract resulting in peak plasma paraquat levels 1-2hours after ingestion. The main site of absorption is the jejunum (Heylings 1990) and if emesis occurs within 30minutes this may limit the amount of paraquat absorbed and thus improve survival.

Between 1980 and 1988 the London Centre of the National Poisons Information Service collected data on all reported cases of paraquat ingestion and compared the outcome of cases involving the 'old', formulation without emetic, with the 'new', formulation with emetic (Bramley and Hart, 1983; Denduyts-Whitehead et al 1985; Onyon and Volans, 1987). It could be conclusively demonstrated that the formulation with emetic induced earlier vomiting, and the difference between the number of patients in each group (emetic vs. non-emetic) who vomited either before or after 30 minutes (or not at all) was highly statistically significant (Meredith and Vale 1995). Furthermore, it was possible to show that following ingestion of the formulation with emetic, vomiting was more likely to occur the larger the quantity of paraquat ingested.

A detailed scientific review by Garnier et al (2003) concluded that poisoning as a result of accidental ingestion of paraquat was now rare in Europe because of improved training and the

addition of alerting agents and emetic to commercial products. A 20 year survey from the National Poisons Information Centre (London) noted in 2001 that most of the cases of poisonings from mistaken ingestion occurred at the start of the study in the early 1980s with the last one recorded in 1992, confirming the virtual disappearance of fatalities due to accidental ingestion since their peak in the early 1970's (Northall and Wilks, 2001). There are no comparative statistics available for developing countries, but it is believed that the introduction of safety and alerting agents (colour and stench) and emetic have made significant contributions to the reduction in mistaken ingestion (Sabapathy, 1995).

However, a beneficial effect of the emetic, PP796, in reducing the overall number of fatalities has not been demonstrated (Bismuth et al, 1982; Naito and Yamashita 1987). The most likely reason for this is that the vast majority of poisoning cases result from deliberate ingestion with suicidal intent, when relatively large quantities of paraquat concentrate are swallowed.

There has been considerable debate about the value of administering an emetic following oral poisoning resulting in an agreed position statement from the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists in 1997. They recommend that the only approved clinically used emetic syrup of ipecac, which acts both local and centrally to cause emesis, should not be routinely administered in the management of poisoned patients (Clinical Toxicology Position Statement, 1997). This was based on lack of evidence from clinical studies that ipecac improves the outcome of poisoned patients. However they also concluded that there was insufficient data to support or exclude ipecac administration soon after ingestion.

In contrast to ipecac, PP796, which is centrally acting and produces early emesis, has been incorporated into the formulation. This may have value in preventing serious poisoning when relatively small quantities of paraquat concentrate are swallowed which would be the case in the majority of accidents. The presence of emetic does not increase the toxicity of paraquat and consequently there is no justification for abandoning this approach to prevention since it has been shown in combination with other FAO specified components (olfactory alert and blue green colour) to have resulted in a significant reduction in accidental deaths (Garnier 2003). Further with new formulations now under development, based on acid triggered gelling, this offers an opportunity for more productive emesis prior to passage of paraquat into the small intestines.

In conclusion, Syngenta believes that the inclusion of PP796 may have a beneficial effect by causing the early expulsion of paraquat following oral ingestion. The results of the detailed scientific review of Garnier et al (2003) are consistent with the current formulations, which include emetic, resulting in very low incidences of accidental ingestions.

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Regards.

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