SYNGENTA RESPONSE TO SPECIFIC USEPA QUESTIONS REGARDING GRAMOXONE INTEON SAFETY IMPROVEMENT
(August 04, 2006)

EXECUTIVE SUMMARY

USEPA requested Syngenta's response to specific questions regarding the data submitted to support the improved acute oral toxicity of US Gramoxone Inteon. During the process of providing additional data and information it was discovered that that a dog study conducted in 1988 (Cockrill and Godburhun) utilized a Gramoxone formulation that does not contain emetic. The lack of emetic in this study is incorporated in this response. However, there are other submitted studies that further support and confirm that US Gramoxone Inteon reduces oral toxicity and will save human lives. An overview of which is included in this response. This conclusion is based on dog studies with emeticized non-Inteon formulations and the initial data from the Sri Lankan human observational monitoring survey.

The non-Inteon Gramoxone with emetic studies indicate the US Gramoxone Inteon formulation provides a meaningful level of improvement of oral toxicity to dogs compared to emeticized non-Inteon Gramoxone. Also, the initial view of the Sri Lankan human observational monitoring survey data provide further data on the potential of the Inteon technology to improve the oral toxicity in humans compared to non-Inteon formulations and save lives. Syngenta will request a meeting with USEPA and a member of the research panel will present the details of the Sri Lanka human observational monitoring survey.

INTRODUCTION

In recent telephone discussions with the USEPA, USEPA toxicologists asked a number of questions to clarify the data submitted in support of the Gramoxone Inteon formulation and to request studies that were cited by Syngenta yet not previously submitted to the Agency. One of the questions was whether or not the Cockrill and Goburdhun (1988) study contained emetic. Syngenta's understanding was that the study did contain emetic as was previously stated and presented by Syngenta. However, we now realize we were incorrect. On review of the report and archived formulation data, Syngenta's conclusion is that the Cockrill study used a non-emeticized Gramoxone formulation.

Our original understanding was based on the incorrect assumption that the Gramoxone formulation used in the study titled "Gramoxone Single Dose Oral Toxicity Study in Dogs" (Cockrill and Goburdhun, 1988) referred to the standard UK Gramoxone formulation available at that time, which included 0.5g/l emetic. However there are other submitted data available to estimate the magnitude of oral toxicity improvement by Gramoxone Inteon.

In assessing toxicity of US Gramoxone Inteon formulations relative to existing non-Inteon Gramoxone formulations, kinetic studies have been conducted rather than lethality studies for animal welfare reasons. One study involved the use of a single dose level (8 mg/kg) for the non-Inteon emeticized Gramoxone. When the paraquat peak plasma and AUC were compared

between non-Inteon paraquat formulations containing emetic (Brammer, 2004a) and US Gramoxone Inteon (Brammer, 2004b), the differential was between 14 to 16 fold. The 16-fold improvement statement is based on the similar AUC results in the studies; the average AUC was 15.59 in the 8mg/kg (43 mg/kg formulation) dose group with non-Inteon formulations containing emetic (Brammer, 2004a), and the average AUC was 7.96 in the 128 mg/kg (602 mg/kg formulation) dose group with US Gramoxone Inteon. When the mg of formulation tested is compared, which may be more relevant to human ingestion incidents, the degree of safening by Inteon formulation was approximately 14 fold (602/43 = 14). The DER (DP Barcode 309472; PCcode 061601) for the study stated, "Study results also demonstrated that the A7813K [US Gramoxone Inteon] formulation was less toxic to dogs while providing levels and a systemic dose similar to that achieved with an existing formulation (Gramoxone) [non-Inteon formulation with emetic]. Further, "the protection afforded by the new formulation [US Gramoxone Inteon], however, was not absolute since one of the three dogs [at the highest dose, 128 mg/kg] showed some lung lesions consistent with paraquat toxicity."

The 8 mg/kg non-Inteon Gramoxone with emetic study described above has some limitations because it tested only one, non-lethal dose level. However, another study (MRID No. 46865501) also supports the safening properties of Inteon formulation over paraquat formulations containing elevated levels of emetic (formulation contained approximately 5x emetic over levels used in non-Inteon formulations). At the 32 mg/kg dose groups, the level of safening for the US Gramoxone Inteon appears to be 3 to 4 fold better than the non-Inteon paraquat formulation containing 5x amount of emetic, based on the peak and AUC data (3.81/1.26 and 17.34/4.65). When comparing higher (yet not the same dose) levels of the US Gramoxone Inteon (64 mg/kg) and non-Inteon paraquat formulation containing elevated emetic (48 mg/kg), the level of safening for US Gramoxone Inteon appears to be > 4 to 11 fold based on the peak (4.95/1.29) and AUC data (40.25/3.69) compared to the elevated emetic non-Inteon formulation, even with the higher dose level in the US Gramoxone Inteon (64 mg/kg compare to 48 mg/kg). When lethality is considered as the endpoint of comparison between the studies, the level of safening for US Gramoxone Inteon was estimated to be > 2.66 to > 4 fold (e.g., 128/32 and 128/48) compared to elevated emetic non-Inteon formulation. However, the US Gramoxone Inteon study only tested up to 128 mg/kg, and the minimum lethal dose was not achieved at this level with non-lethal, minor lung lesions observed in only one dog. The initial data from the Sri Lanka observational monitoring survey appears to verify that the dog model is appropriate for human extrapolation. Overall, the weight of evidence indicates that the Inteon technology provides a meaningful reduction in oral toxicity as compared to non-Inteon formulations of paraquat.

Specific questions from the USEPA Toxicologists and Syngenta response:

1) Do the historical or concurrent paraquat, Gramoxone, and Inteon studies in dogs contain emetic?

Based on the realization that the Cockrill and Goburdhun (1988) study did not contain emetic, Syngenta has re-reviewed the studies summarized below to confirm their utility for comparing non-Inteon formulations containing emetic and Inteon formulations.

Prior to discussing the toxicity and toxicokinetics studies with dogs, it should be first stated that Syngenta Crop Protection, Inc. and predecessor companies make every attempt to avoid conducting lethality studies with dogs. When dog studies are required, the conduct of these

studies are made under the supervision of a veterinarian, and several parameters, including body weight changes, clinical observations and plasma paraquat levels, are considered in reaching a decision to allow an animal to remain on study or require termination. In the case of dogs, persistent inappetance (refusal to eat food) and resulting body weight decrement is an important indicator of adverse condition. Knowledge from a number of studies over a number of years, has allowed an integration of these factors by the veterinarians to prevent suffering of treated dogs. This consideration is mandatory for conducting studies on paraquat under the UK Home Office legislation. Therefore, dog studies are specifically designed to answer a scientific question pertaining to kinetics, absorption, and emesis. The following studies have been conducted with paraquat formulations without emetic, with emetic, with different levels of emetic, and with Inteon technology.

PARAQUAT DOG STUDIES WITHOUT EMETIC:

In a non-Syngenta published study (Widdop et al, 1977), hemoperfusion was investigated as a potential method of treatment in the event of paraquat ingestion. In this study, a group of six dogs as a control group received 10 mg/kg paraquat via gastric intubation. It is assumed that no emetic was provided. All six dogs died between 9 and 12 days after dosing with symptoms of renal impairment and progressive respiratory distress. Peak plasma levels ranged from 4.7 to 24.0 ug/ml, with a mean value of 9.6 ug/ml; plasma area under the curve (AUC) was not reported in the study. Based on this published study, it was determined that peak plasma paraquat levels ranging from 4.7 to 24 ug/ml are lethal to dogs.

In a non-published study (Cockrill and Goburdhun, 1988), four dogs were dosed with 2.5, 5, 10, or 20 mg/kg paraquat and observed for 14 days. The formulation (a non-Inteon Gramoxone) did not contain emetic, however emesis occurred in 1 out of 4 animals in the 10 mg/kg dose group and in 3 out of 4 animals in the 20 mg/kg dose group, even though the report indicated an anti-emetic (metoclopramide HCL) was administered. There were no mortalities in the 2.5 and 5.0 mg/kg dose groups, one out of four animals in the 10 mg/kg dose group was found dead seven days after dosing, preceded by body weight loss in the previous two days. Following the dose of 20 mg/kg, all animals were terminated by 8 days after dosing due to inappetence and resulting weight loss. Premature decedents exhibited severe anorexia and lost between 1.2 and 2.0 kg before death, while the remaining animals showed only minor body weight losses or moderate weight gains. The LD50 of the study was calculated to be 11.9 mg/kg. Kinetic analysis data from the study is reported in Swain, 2005. Animals receiving doses of 2.5, 5.0, 10.0, or 20.0 mg/kg had resulting average peak plasma paraquat values of 2.13, 3.51, 6.39, and 6.78 ug/ml and average 24 hour plasma paraquat AUC of 5.97, 10.40, 21.07, 29.38 ug/ml.h, respectively. This study will be submitted to the USEPA.

DOG STUDIES WITH EMETIC:

Non-Inteon Gramoxone (with 0.5g/l emetic): In the 2004 study (Brammer et al., 2004a; MRID No. 46364511), a non-Inteon Gramoxone formulation was tested. This formulation contained paraquat, colorant, stenching agent and emetic, but no alginate nor purgative. Three dogs received an oral dose of 8 mg/kg paraquat. All animals survived the study, and there were no effects on body weight or food consumption. Emesis occurred in 1 out of 3 dogs tested. Animals receiving doses of 8 mg/kg had resulting average peak plasma paraquat value of 2.3 ug/ml (range from 1.14 to 4.22 ug/ml) and average 24 hour plasma paraquat AUC value of 7.98 ug/ml.h (range from 4.56 to 10.26 ug/ml.h).

Non-Inteon Gramoxone (Increased emetic study, ca 5x standard emetic equivalents): A study was conducted to determine the magnitude and extent of safening that could be achieved by simply increasing the level of the emetic in non-Inteon formulations (Swain and Heylings, 2006; MRID No. 46865501). In this study, a non-Inteon formulation (100 g/l paraquat) was used with additional emetic to a level of 1.2g/l, resulting in the equivalent of 2.4g/l emetic for a 200g/l paraquat concentration. The test solution therefore contained paraquat and additional emetic, but no alginate or purgative. Three dogs received oral doses of 16, 32, and 48 mg/kg paraquat. All dogs survived following 16 and 32 mg/kg, however due to signs of adverse effects at the 32 mg/kg dose group (one animal had peak paraquat levels indicating potential toxicity), it was decided to reduce the highest dose level from the planned next dose level of 64 mg/kg to 48 mg/kg. Two of the top dose animals (48 mg/kg) were humanely sacrificed due to clinical signs (persistent vomiting for 6 hours and 58 minutes) or inappetence/weight loss (> 15% body weight decrease due to inappetence). Animals receiving doses of 16, 32, or 48 mg/kg paraquat formulation with the 5x emetic had resulting average peak plasma paraquat values of 4.91, 3.81, and 4.95 ug/ml and average 24 hour plasma paraquat AUC of 18.74, 17.34, and 40.25 ug/ml.h, respectively. The peak plasma level of paraquat is fairly constant across administered doses of 16 to 48 mg paraquat ion/kg for the formulation with high emetic, but the 24 hour paraquat plasma AUC increases significantly between 32 and 48 mg paraquat ion /kg. The effect of adding higher levels of emetic (ca 5x emetic) did not reduce levels of paraquat peak and AUC or dog toxicity as compared to that achieved by higher doses of US Gramoxone Inteon.

US Gramoxone Inteon: In this study (Brammer et al., 2004b; MRID No. 46364510), three dogs were dosed with increasing levels of Inteon formulation with approximately 30 day intervals for recovery. Dogs were dosed with US Gramoxone Inteon formulation equivalent to 32, 64, and 128 mg/kg paraquat ion. All animals survived the study. Some food was left uneaten on the day of dosing, but, otherwise there was no effect on food consumption. One dog (Male #2) lost a small amount of weight (0.3kg) on week 11, following the highest dose, but otherwise there was no effect on body weight. Animals receiving doses of 32, 64, or 128 mg/kg had resulting average peak plasma paraquat values of 1.26, 1.29 and 2.77 ug/ml and average 24 hour plasma paraquat AUC values ranging from 4.65, 3.69, and 7.96 ug/ml.h, respectively. One dog (Male #2) in the top dose group showed lung effects in the pathology report and had a peak plasma paraquat level of 5.16 ug/ml.

In the case of Inteon US (A7813K), the dogs treated throughout the study, including the top dose level of 128mg/kg paraquat ion did not show clinical signs indicative of entering the area of significant paraquat toxicity. Less food was eaten following the highest dose given, but the reduction in food consumption was transient, and was not accompanied by other indications of significant toxicity. Only one animal showed a small reduction in bodyweight, but this was then recovered in the following days. This was considered a limited expression of toxicity. The animals were killed for pathological examination two weeks after the final dose, and so were allowed sufficient time to show any signs of paraquat toxicity (MRID No. 46364510).

Global Gramoxone Inteon: In this study (Brammer et al., 2004c; MRID No. 46364517), three dogs were dosed with 8, 16, 32, 64, and 128 mg/kg paraquat ion in a formulation know as Global Gramoxone Inteon, which also contains wetters. All animals survived in the study. There were no body weight effects, except for one dog in the top dose that lost 0.9 kg due to inappetance. Animals receiving doses of 8, 16, 32, 64, or 128 mg/kg had resulting average peak plasma paraquat values of 2.57, 2.00, 3.07, 1.94, and 8.21 ug/ml and average 24 hour plasma paraquat AUC ranging from 6.94, 6.38, 8.51, 6.62, 14.60 ug/ml.h, respectively.

Table 1. Resulting peak plasma, AUC, and inappetence and body weight loss from paraquat studies in dog

Formulation	Dose (mg/kg Paraquat)	Average Peak Plasma Paraquat Conc. (ug/ml)	Plasma Paraquat AUC at 24 (ug/ml.h)	Inappetence	Body weight loss	Mortality/ humane sacrifice	Reference
Paraquat, without emetic	10	9.6	Not reported	Not reported	Not reported	6/6	Widdop, 1977
Paraquat, without emetic	2.5 5 10 20	2.13 3.51 6.39 6.78	5.97 10.40 21.07 29.38	Yes	Yes	0/4 0/4 1/4 4/4	Cockrill and Goburdhun, 1988
Paraquat + 0.5 g/L emetic	8	2.3	15.59	No	No	0/3	Brammer 2004a
Paraquat, 2.5 g/L emetic	16 32 48	4.91 3.81 4.95	18.74 17.34 40.25	Yes	Yes	0/3 0/3 2/3	Swain and Heylings, 2006
Inteon US	32 64 128	1.26 1.29 2.77	4.65 3.69 7.96	No	No	0/3 0/3 0/3	Brammer 2004b
Inteon Global	8 16 32 64 128	2.57 2.00 3.07 1.90 8.21	6.94 6.38 8.51 6.62 14.60	Yes	Yes	0/3 0/3 0/3 0/3 0/3	Brammer 2004c

Based on the existing database, toxicity and plasma paraquat peak and AUC data from studies with paraquat formulations containing no emetic, emetic, increased levels of emetic and Gramoxone Inteon formulation were compared. For comparison purposes, the data in the table above were combined into dose level groups (e.g., 8-10, 16-32, 48-64 mg/kg) and plotted (Fig 1 and 2), since some formulations were not tested at the same but similar dose levels.

In each of the dose groupings (e.g., 8-10, 16-32, 48-64 mg/kg), the US Gramoxone Inteon provides additional level of safening as compared to paraquat formulations containing paraquat or paraquat plus emetic, most dramatically as the dose levels increase. The magnitude of safening is more obvious in the plasma AUC data (Figure 1).

Figure 1. Comparison of plasma paraquat AUC level in paraquat, paraquat + emetic and Inteon formulations

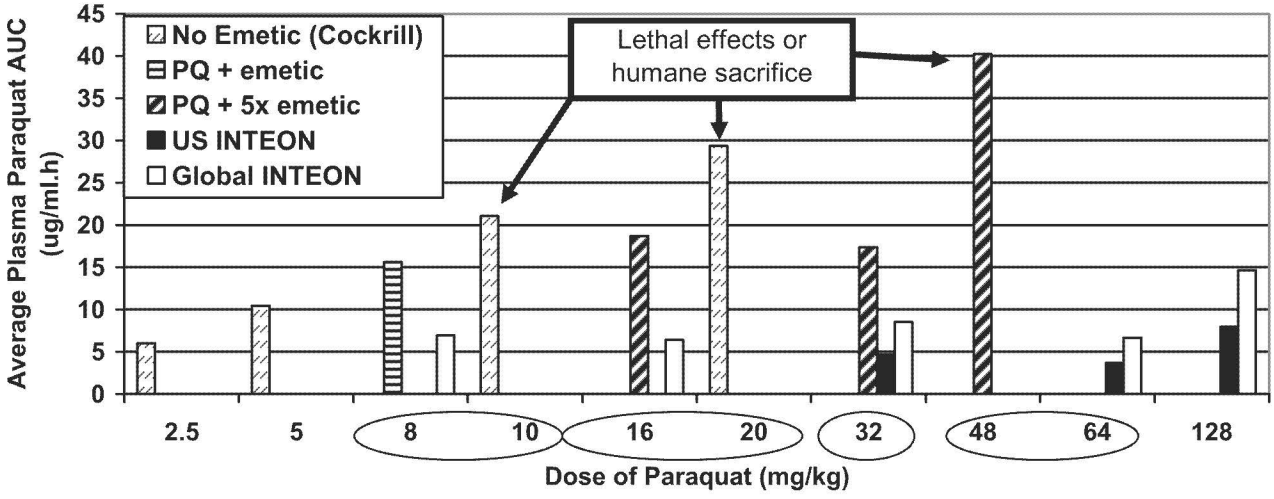
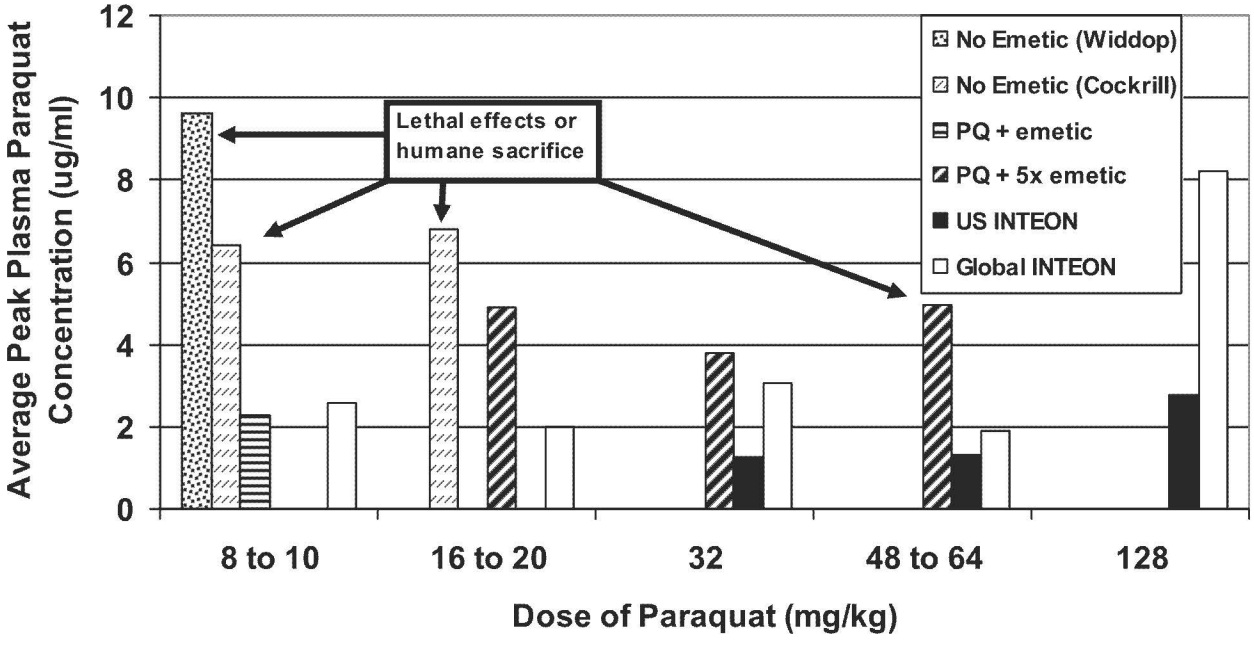


Figure 2. Comparison of peak plasma level in paraquat, paraquat + emetic and Inteon formulations



In assessing toxicity of US Gramoxone Inteon formulations relative to existing non-Inteon Gramoxone formulations, kinetic studies have been conducted rather than lethality studies for animal welfare reasons. One study involved the use of a single dose level (8 mg/kg) for the non-Inteon emeticized Gramoxone. When the paraquat peak plasma and AUC were compared between non-Inteon paraquat formulations containing emetic (Brammer, 2004a) and US Gramoxone Inteon (Brammer, 2004b), the magnitude of safening appeared to be between 14 to 16 fold. The 16-fold improvement statement is based on the similar AUC results in the studies; the average AUC was 15.59 in the 8mg/kg (43 mg/kg formulation) dose group with paraquat formulations containing emetic (Brammer, 2004a), and the average AUC was 7.96 in the 128 mg/kg (602 mg/kg formulation) dose group with US Gramoxone Inteon. When the mg of formulation tested is compared, which may be more relevant to human ingestion incidents, the dose of paraquat was increased by approximately 14 fold (602/43 = 14). The DER (DP Barcode 309472; PCcode 061601) for the study stated, "Study results also demonstrated that the A7813K [US Gramoxone Inteon] formulation was less toxic to dogs while providing levels and a systemic dose similar to that achieved with an existing formulation (Gramoxone) [non-Inteon formulation with emetic]. Further, "the protection afforded by the new formulation [US Gramoxone Inteon], however, was not absolute since one of the three dogs [at the highest dose, 128 mg/kg] showed some lung lesions consistent with paraquat toxicity." However, the 8 mg/kg non-Inteon Gramoxone study was later determined to be limited for comparison because it tested only one, non-lethal dose level. A dose response study would be more useful for comparison to the US Gramoxone Inteon dog data.

Another study (MRID No. 46865501) also supports the safening properties of Inteon formulation over paraquat formulations containing elevated levels of emetic (formulation contained approximately 5x emetic over levels used in non-Inteon formulations). At the 32 mg/kg dose groups, the level of safening for the US Gramoxone Inteon appears to be 3 to 4 fold better than the non-Inteon paraquat formulation containing 5x amount of emetic, based on the peak and AUC data (3.81/1.26 and 17.34/4.65). When comparing higher (yet not the same dose) levels of the US Gramoxone Inteon (64 mg/kg) and non-Inteon paraquat formulation containing elevated emetic (48 mg/kg), the level of safening appears to be > 4 to 11 fold based on the peak (4.95/1.29) and AUC data (40.25/3.69), even with the higher dose level in the US Gramoxone Inteon (64 mg/kg compare to 48 mg/kg). When lethality is considered as the endpoint of comparison between the studies, the level of safening was estimated to be > 2.66 to > 4 fold (e.g., 128/32 and 128/48) safening. However, the US Gramoxone Inteon study only tested up to 128 mg/kg, and the minimum lethal dose was not achieved at this level with non-lethal, minor lung lesions observed in only one dog. The initial data from the Sri Lanka observational monitoring survey appears to verify that the dog model is appropriate for human extrapolation. Overall, the weight of evidence indicates that the Inteon technology provides a meaningful reduction in oral toxicity as compared to non-Inteon formulations of paraquat.

However, benefits of the Inteon technology, even with a suboptimal formulation, are evident with the recent release of the Sri Lankan human observational monitoring survey, which will be presented at a toxicology conference in August 2006 and in a follow-up meeting with the USEPA.

SRI LANKA OBSERVATIONAL MONITORING SURVEY

The dog studies with Inteon were conducted to provide a surrogate model to predict the level of improved oral toxicity provided by Inteon formulation following ingestion. The completion of an observational monitoring survey in Sri Lanka now allows an assessment of the Inteon technology directly in humans.

Syngenta has undertaken a survey of paraquat poisonings in Sri Lanka to monitor the effect of introducing an Inteon formulation on the survival of humans following accidental or intentional ingestion. Nine hospitals were involved in this survey and data includes the estimated dose of paraquat ingested and the outcome. The data will be presented at a scientific meeting in August 2006, however the authors allowed Syngenta to view and share the data in Table 1 with USEPA, but they requested that it be considered confidential until the formal publication of the results. While all of the details of the data have not yet been provided, the Sri Lanka data do provide some insight into the volumes ingested and the impact on survival. Overall, Inteon increases the chance of survival compared to non-Inteon formulations following ingestion. In the Sri Lankan observational monitoring survey abstract, conclusions were made that "The survey has shown that Inteon® technology significantly improves the survival of patients following paraquat ingestion. Formulation developments have now overcome the phase separation problems and it is expected that this may lead to a further reduction in toxicity."

Table 1. Gramoxone Inteon formulation increases survival compared to non-Inteon formulations following human ingestion

Amount ingested	Non-Inteon (n=297)			Confirmed or Probable Inteon (n=289)		
	Alive	Unknown	Total	Alive	Unknown	Total
< 5 mls	26 (70.3%)	2	37	22 (68.8%)	1	32
5-10 mls	6 (33.3%)	0	18	17 (68.0%)	0	25
10-15 mls	7 (29.2%)	0	24	19 (44.2%)	0	43
15-30 mls	4 (12.9%)	1	31	18 (40.9%)	2	44
30-50 mls	2 (9.1%)	0	22	6 (20.0%)	1	30
50-100 mls	1 (3.8%)	0	26	5 (16.1%)	0	31
100-150 mls	1 (4.0%)	1	25	1 (7.1%)	0	14
> 150 mls	0	0	38	1 (3.6%)	0	28
Unknown	29 (38.2%)	2	76	13 (31.0%)	0	42
Total	76 (25.6%)	6	297	102 (35.3%)	4	289

The Inteon formulation in Sri Lanka was a 200g/l Inteon formulation and contains built-in wetters and is different from the US Gramoxone Inteon that does not contain built-in wetters. During the period of the survey it became apparent that the formulation was not optimal and suffered a degree of phase-separation. This formulation separation resulted in a non-homogeneous distribution of the key Inteon components; paraquat, emetic and alginate. There was an inconsistent degree of safening in dog studies that were conducted with this sub-optimal

formulation. Despite this, there was still an improved safening in humans over non-Inteon paraquat formulations (Table 1 and Wilks et al., 2006). However, for the reasons described, the Inteon formulation in Sri Lanka is sub-optimal for demonstrating the full potential of a homogeneous Inteon formulation, like that developed for and registered in the US. A fully homogeneous Inteon formulation would be expected to show greater overall improvement in safety.

Furthermore, for ingestion incidents involving US Gramoxone Inteon in the US, survival will likely be further improved due to the high level of emergency and medical treatment available in the US and the Inteon formulation may provide a wider window of opportunity for treatment. In a recent US intentional poisoning incident with US Gramoxone Inteon, the reported quantity ingested was 4 ounces (ca 118 ml). It would be predicted from the Sri Lanka data that the patient ingested a likely lethal dose. However, the patient survived, likely due to a combination of Gramoxone Inteon technology, the rapid medical response and high quality of medical treatment received in the United States.

Syngenta will be requesting a meeting with the USEPA to have a member of the research panel present the details of the Sri Lanka human observational monitoring survey.

2) Provide additional information to compare US Gramoxone Inteon and paraquat formulations containing elevated emetic (ca 5x) with regards to humane sacrifice criteria and any resulting clinical symptoms.

Syngenta Crop Protection, Inc. and predecessor companies make every attempt to avoid conducting lethality studies with dogs. When dog studies are required, the conduct of these studies are made under the supervision of a veterinarian, and parameters that are important for considering in reaching a decision to allow an animal to remain on study or require termination include bodyweight changes (approaching 20% body weight loss), clinical observations and plasma paraquat levels. In the case of dogs, persistent inappetance (refusal to eat food) and resulting body weight decrement is an important indicator of adverse condition. This consideration is mandatory for conducting studies on paraquat under the UK Home Office legislation.

In the case of US Gramoxone Inteon study, dogs did not show clinical signs indicative of entering the area of significant paraquat toxicity, including the high dose level of 128mg/kg paraquat (Brammer et al., 2004b; MRID No. 46364510). In one of three dogs less food was eaten following the highest dose given but was transient, and was not accompanied by other indications of significant clinical signs of toxicity. Only one animal showed a small reduction in bodyweight (ca 300g), but this was then recovered in the following days. All animals were killed for pathological examination two weeks after the final dose, allowing sufficient time to show any clinical signs of paraquat toxicity. None of the dogs in the US Gramoxone Inteon study met the criteria for humane sacrifice.

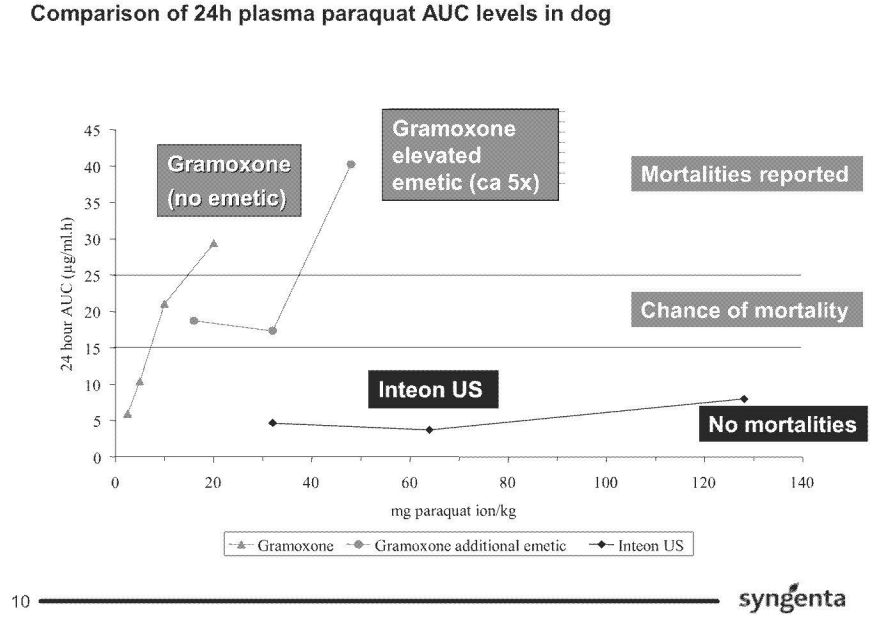
Dogs dosed with non-Inteon Gramoxone with elevated emetic (ca 5x) level exhibited greater symptoms than in the US Gramoxone Inteon study. One animal in the non-Inteon Gramoxone with elevated emetic (ca 5x) level study had reduced food intake and decreased body weight following the highest dose of 48mg/kg. This animal lost significant weight (ca 2800g) and was terminated. The weight loss was approximately 17% bodyweight and approaching the Project Licence of 20% bodyweight loss, which required termination. Another animal displayed clinical symptoms (vomiting for up to 6 hours and 58 minutes) following the 48mg/kg dose level, which was considered severe enough to result in ordering of termination by the veterinarian.

3) Why did a higher emetic concentration in non-Inteon formulation induce rapid emesis but did not result in greater safening as compared to the US Gramoxone Inteon formulation where emesis occurred later.

In this study (MRID No. 46865501), a non-Inteon formulation was used with additional emetic, resulting in the equivalent of approximately 2.5g/l emetic (ca 5x the level of emetic compared to non-Inteon Gramoxone). The non-Inteon formulation with elevated emetic (ca 5x) contained paraquat and additional emetic, but no alginate or purgative. Three dogs received an oral dose of 16, 32, and 48 mg/kg paraquat. Two of the top dose animals were humanely sacrificed due to clinical signs (persistent vomiting for 6 hours and 58 minutes) or inappetence/weight loss (> 15% body weight decrease due to inappetence). Dogs receiving doses of 16, 32, or 48 mg/kg had resulting average peak plasma paraquat values of 4.91, 3.81, and 4.95 ug/ml and average 24 hour plasma paraquat AUC of 18.74, 17.34, and 40.25 ug/ml.h, respectively. The peak plasma level of paraquat is fairly constant across administered doses of 16 to 48 mg paraquat ion/kg for the formulation with high emetic, but the 24 hour paraquat plasma AUC increases significantly between 32 and 48 mg paraquat ion /kg primarily due to the response of one animal in the 48mg/kg dose group that was humanely sacrificed.

Increasing the emetic level in the Gramoxone formulation produced earlier emesis than that observed with Inteon US. However, earlier emesis only offered minimal improvement in preventing lethality compared with the US Gramoxone Inteon formulation, where lethality and large body weight effects were not seen even at 128 mg/kg dose group (Fig. 3).

Figure 3



A major difference between Inteon and non-Inteon formulations is that Inteon contains alginates, which gel in the stomach's acid environment. Upon gelling in the stomach, the bulking mass is likely to be held longer in the stomach, slowing passage into the small intestine, and allowing for a more productive and effective emesis. Non-Inteon formulations remain liquid

and freely flowable, may more rapidly pass from the stomach into the small intestine, and may therefore prevent effective emesis. The small intestine has much greater surface area for absorption than the stomach, and the emetic (and paraquat) will be absorbed more rapidly than if they had been held in a semi-solid mass in the stomach. The emetic may therefore enter the bloodstream faster and promote a rapid onset of emesis. However, paraquat would also be rapidly entering the intestine, where absorption into the bloodstream will also take place. The rapid vomiting induced by the emetic will therefore have a reduced effect on paraquat that has passed through the stomach and entered the small intestine. It has effectively gone too far to be efficiently vomited up. This provides one theory of why the higher emetic concentration induced rapid emesis but did not result in more substantial safening as compared to the Inteon formulation where emesis occurred much later.

4) In the recent US Inteon ingestion case, can we verify (e.g., back-calculate) the amount ingested based on the measured paraquat plasma level?

Additional information was requested regarding the recent intentional ingestion of Gramoxone Inteon formulation in the United States. Plasma samples were obtained from the patient and analyzed four days after the ingestion incident occurred, and 0.08ug/ml paraquat was detected in the plasma. It was reported that the patient consumed approximately four ounces of Gramoxone Inteon; however the Agency inquired whether this estimated ingestion volume could be verified through the back-calculation of the measured plasma paraquat value. We feel additional data will be needed before back-calculation to ingested amount is meaningful due to a number of reasons.

First, the plasma sample in this incident was taken four days after the incident. The initial half-life of paraquat in human plasma is approximately 12 hours, followed by a very slow secondary elimination phase. The detection of paraquat in the plasma at 0.08 ug/ml four days after ingestion can currently only be interpreted as definitive confirmation of an elevated exposure to paraquat.

Second, there are many other complicating factors, including the extent and magnitude of renal function impairment, which can prolong the retention of paraquat in plasma.

Third, the Inteon technology is specifically designed to minimize the initial absorption of paraquat. Additional data will be needed before back-calculation to ingested amount is meaningful. Based on the current uncertainties, we feel the reported amount of Inteon ingested in this case (four ounces) provides the best estimate of the amount ingested.

For additional information on the intentional US Gramoxone Inteon ingestion case, please refer to the attached email from the treating physician.

REFERENCES

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