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June 19, 2006

Mr. Jim Tompkins, PM 25
Document Processing Desk
Office of Pesticide Programs (7504P)
U.S. Environmental Protection Agency
Room S-4900, One Potomac Yard
2777 South Crystal Drive
Arlington, VA 22202-4501

SUBJECT: SUBMISSION OF ADDITIONAL INFORMATION RELATED TO SAFETY IMPROVEMENT OF GRAMOXONE INTEON, EPA REG. NO. 100-1217

Dear Mr. Tompkins:

Syngenta Crop Protection is herein submitting additional information related to the safety improvement of Gramoxone Inteon. This information was presented at a meeting with USEPA on April 24, 2006. Included are:

1) Attachment A: *Gramoxone Inteon and Improved Safety,* a document reviewing the information presented at the meeting by Dr. Mike Clapp,
2) Attachment B: A review of global paraquat incidence data,
3) Attachment C: *Declaration of Sir Colin Berry*
4) A study, not previously submitted; *"Gramoxone Effects of Increased Emetic Levels on Toxicokinetics in the Dog"* which is listed on the attached Transmittal Document.

This information is submitted for informational purposes. The submission is outside the scope of PRIA. If you have any questions regarding this submission please contact me at 336-632-6324.

Kind Regards,

Jerry Wells
Senior Regulatory Product Manager

VOLUME 1 OF 2 OF SUBMISSION
(TRANSMITTAL DOCUMENT)

1. Name and Address of Submitter

Syngenta Crop Protection, Inc.
P.O. Box 18300
Greensboro, NC 27419

2. Regulatory Action in Support of which this Package is Submitted

SUBMISSION OF ADDITIONAL INFORMATION RELATED TO SAFETY IMPROVEMENT OF GRAMOXONE INTEON, EPA REG. NO. 100-1217

3. Transmittal Date

6/19/2006

4. List of Submitted Studies

MRID NUMBER	VOLUME NUMBER	STUDY TITLE	EPA GUIDELINE NUMBER
	1 OF 2	Transmittal document	NA
	2 OF 2	Effects of Increased Emetic Levels on Toxicokinetics in the Dog;(XD1328, 026698-RES,T003396-06), (09003aeb801feed9),(445557)	NA

COMPANY OFFICIAL: JERRY WELLS _____ _____
(NAME) **(SIGNATURE)**

COMPANY NAME: SYNGENTA CROP PROTECTION, INC.

COMPANY CONTACT: JERRY WELLS _____ 336-632-6324 _____
(NAME) **(PHONE)**

ATTACHMENT A:

GRAMOXONE INTEON AND IMPROVED SAFETY, A DOCUMENT REVIEWING THE INFORMATION PRESENTED AT THE MEETING BY DR. MIKE CLAPP

GRAMOXONE INTEON AND IMPROVED SAFETY

May 31, 2006

A listing of the formulations discussed in this document is given below.

Product Reference	*Paraquat a.i. concentration*	*Inteon Technology (Y or N)*	*Comments*
Gramoxone	*200 g/l*	*No*	*Global formulation, not registered in US*
Gramoxone US	*360 g/l*	*No*	*Registered in US as Cyclone Concentrate (alternative brand name Gramoxone Max) US Voluntary cancellation requested*
Inteon	*200 g/l*	*Yes*	*Global formulation, not registered in US, separation problems (also called A3879BU)*
Inteon US	*240 g/l*	*Yes*	*Registered in US as Gramoxone Inteon (also called A7813K)*

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GRAMOXONE INTEON AND IMPROVED SAFETY

1. Introduction

Gramoxone Inteon (referred to as Inteon or Inteon US hereafter in this document) is a novel formulation of paraquat developed by Syngenta. The formulation was specifically developed to improve the acute oral toxicity in the event of ingestion by humans. To test the new formulation, the dog was selected as the most appropriate surrogate for humans. Tests in the dog indicate a significant improvement in acute oral toxicity indicated by reduced paraquat absorption and survival. All dogs survived a dose containing greater than ten times the amount of paraquat shown to be lethal to dogs with non-Inteon formulations (referred to as Gramoxone or Gramoxone US hereafter in this document) in previous studies. The principle components of the formulation responsible for this improvement are a natural alginate (that causes the liquid formulation to gel under the acidic conditions of the stomach), emetic and purgative. This technology is expected to result in fewer deaths following accidental or intentional paraquat ingestions in humans.

2. Rationale for reduced oral toxicity in the Inteon formulation

Inteon formulations have been designed to offer improved oral safening compared to previously registered Gramoxone formulations through a reduction in the amount of paraquat absorbed following ingestion. A natural alginate that immediately gels when entering the low pH environment of the stomach has been included in Inteon formulations. The amount of emetic has also been increased three-fold in Inteon formulations compared to the currently sold Gramoxone formulation. The increase in emetic was made to ensure efficacy of the emetic after gelling of the formulation in the stomach. The purpose of these changes is to cause the formulation to gel in the stomach and for the gel mass in turn to cause the pyloric valve at the base of the stomach to constrict, holding paraquat in the stomach and allowing the critical time needed for the emetic to reach the brain and cause vomiting. Paraquat expelled in this manner does not reach the intestine where most absorption would occur, thereby minimizing exposure (Heylings et al 1991). A purgative, magnesium sulphate is also added to the Inteon formulation to help purge any product that does pass into the intestines, further minimizing exposure time.

3. Method of assessing improvement in oral toxicity of Inteon

In order to investigate the benefit of the combination of alginate gelling and emetic effect, as well as evaluate consequent oral safening, a vomiting species is required and the dog was selected (see No. 8 for additional considerations for selecting the dog as a surrogate for humans). Oral safening (degree of toxicity) has been evaluated for the Inteon formulations by measuring plasma paraquat levels in the dog after administration. Due to animal welfare concerns, lethality studies with paraquat in the dog are not

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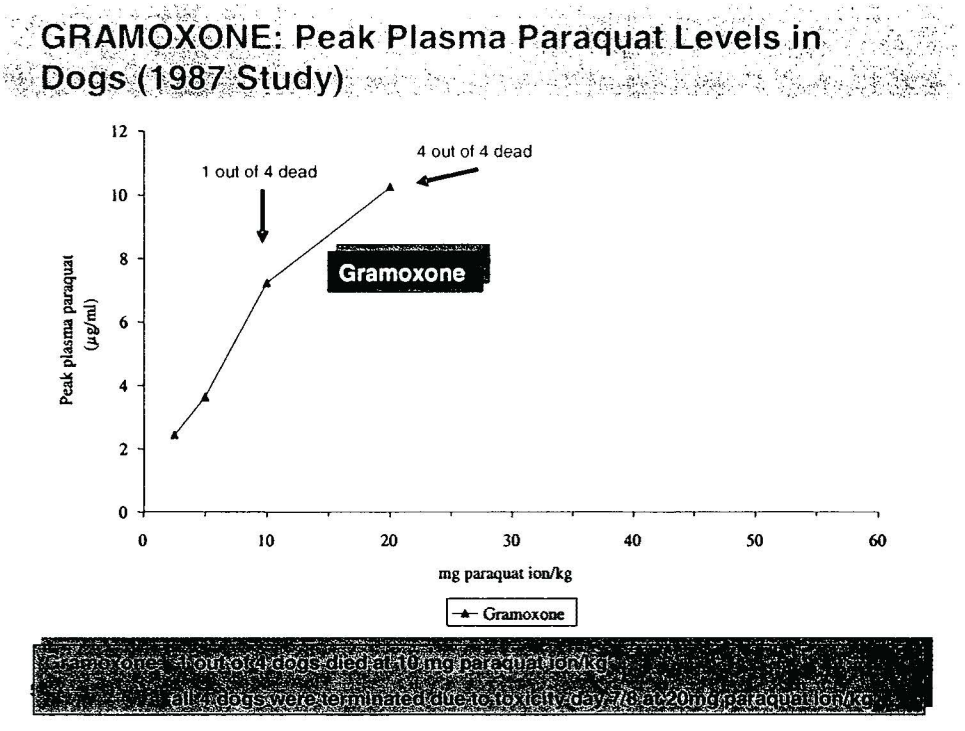
permitted under the animal experimentation Project Licence administered through the UK Home Office. The main parameters evaluated to reflect the paraquat absorbed following oral dosing have been the peak plasma level and the 24 hour area under the curve (AUC) value. For the same animal welfare reasons, no concurrent Gramoxone dose response was included in the study design as all doses except the lowest have been shown to be lethal to the dog or are above such a lethal dose. Two formulations are reported, Inteon (a 200g/l paraquat formulation with built in wetters for use outside the US and Inteon US (a 240g/l paraquat formulation without built in wetters for use in the US). The basic study design was to dose three dogs with a dose (8 mg paraquat/kg bw) just below the lethal threshold for Gramoxone (approximately 10 mg paraquat/kg bw) and monitor paraquat plasma levels. The same dogs would be dosed 30 days later at a higher dose if they met certain health criteria. The doses used in the assessment of Inteon were 8, 16, 32, 64, and 128mg/kg bw. The Inteon US assessment was done after that of Inteon and based on the Inteon results, the Inteon US doses selected were 32, 64, and 128mg/kg bw.

4. The lethal dose of non- Inteon paraquat formulations in the dog

The established toxicity of Gramoxone in the dog from studies in1987 is shown in Figure 1, where the peak plasma level is correlated with deaths observed. This provides a rationale for not testing Gramoxone at doses higher than 8mg/kg since these would be expected to result in mortality (Swain 2005; Cockrill and Goburdhum 1988). The calculated LD50 was 12 mg/kg, which is consistent with Widdop et al (1977) who reported deaths at 10mg/kg bw.

Figure 1



5. The effect of increasing emetic levels in non- Inteon formulations on reducing oral toxicity in dog

The effect of increasing the emetic level in a Gramoxone (non- Inteon) formulation was established in a research study in 1990. The peak plasma levels are shown in Figure 2 and the 24h area under the curve (AUC) are shown in Figure 3. Increasing the amount of emetic in Gramoxone reduced absorption of paraquat (peak plasma) at dose levels up to 48mg/kg bw, but at this dose the overall systemic exposure resulted in mortality (2 out of 3 dogs were humanely killed following a dose of 48 mg paraquat/kg bw with the high emetic formulation). The peak plasma level of paraquat is fairly constant (between 4 to 5ug/ml) 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 with mortality observed at the higher dose level. Increasing the emetic level alone therefore, confers some, but limited oral safening (Swain and Heylings 2006). Increasing the emetic level in the Gramoxone formulation produced earlier emesis than that observed with Inteon US (at approx 3 vs. 15 minutes). Therefore, increasing emetic level alone reduced time to emesis and reduced peak plasma and AUC levels but only offered minimal improvement in preventing lethality compared with Inteon US which showed a greater than 10X improvement.

Figure 2

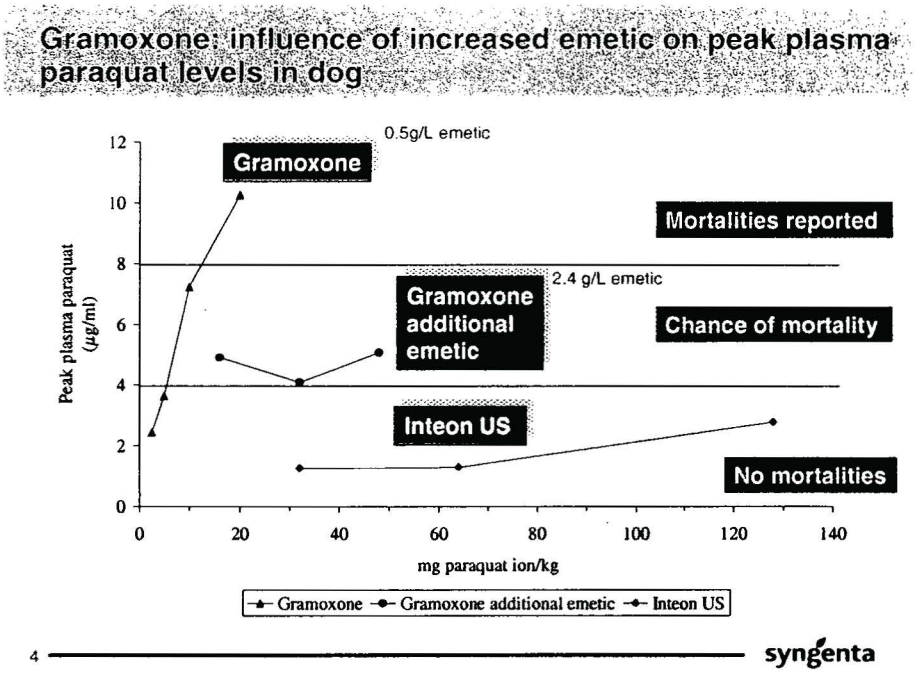


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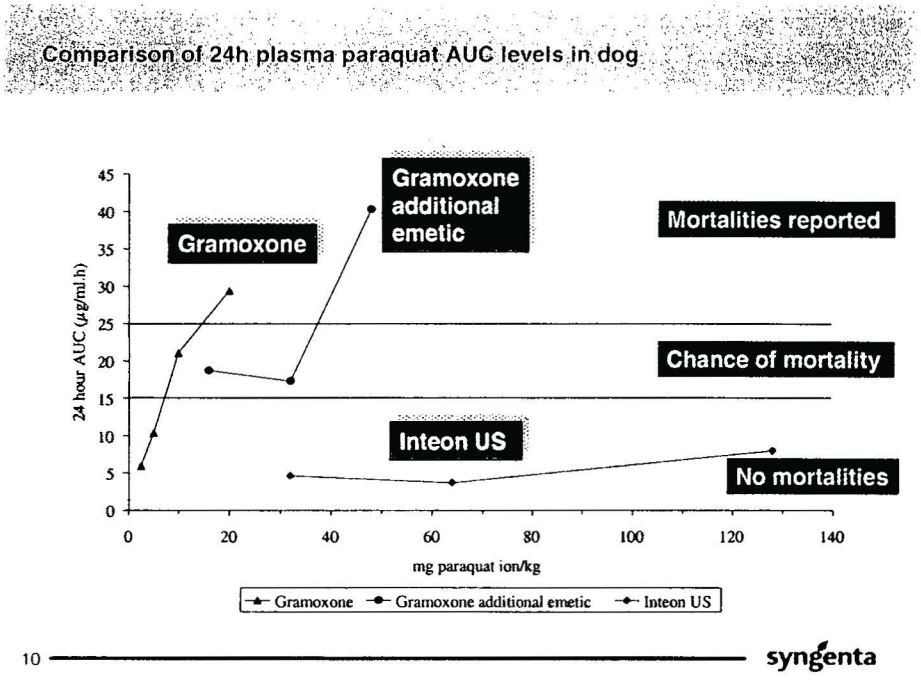
Figure 3

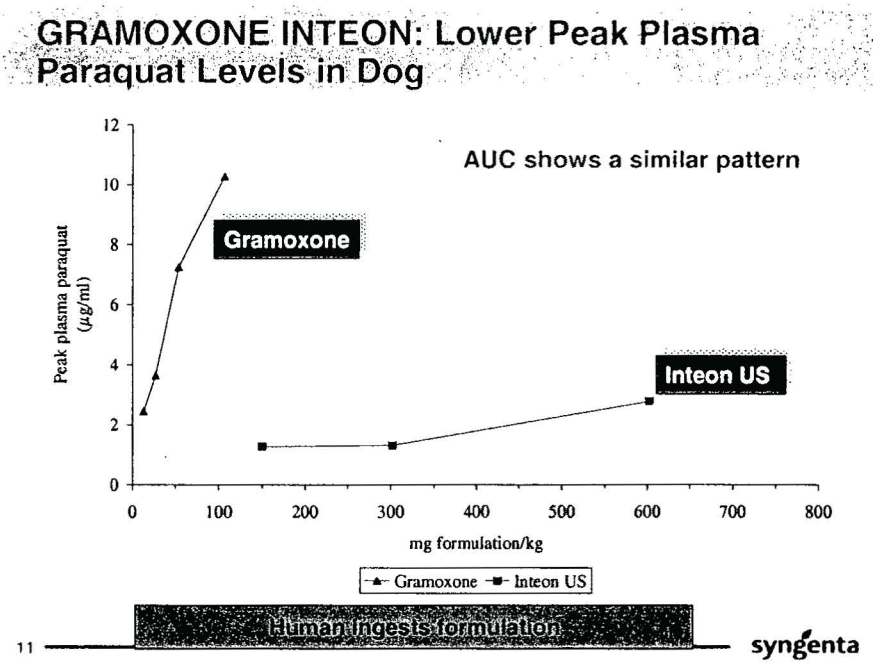


6. Comparison of oral toxicity in the dog between Inteon and Gramoxone

Inteon US has a much greater impact on reducing paraquat exposure (based on plasma peak or AUC) in dog than increasing emetic. Figure 3 shows the 24h AUC values for Gramoxone, Gramoxone with increased emetic, and Inteon US. The Inteon US formulation resulted in lower levels of systemic absorption of paraquat in the dog, as measured by both peak plasma level and 24h AUC over a dose range of more than 10 fold greater than that for Gramoxone. The acid-triggered gelling with Inteon holds the formulation in the stomach resulting in productive emesis and a consequent reduced systemic exposure. Examining this in terms of the amount of formulation ingested (rather than a normalised mg/kg of paraquat ion) results in a similar picture as shown in Figure 4.

The pharmacokinetic and oral toxicity data indicate that Inteon US affords a greater than 10-fold improvement in oral safety over non-Inteon formulations in dogs and as dogs are an excellent surrogate for humans a significant improvement in human survival following paraquat ingestion is expected.

Figure 4



7. Comparison of oral toxicity in dog between Inteon and Gramoxone at a sublethal dose

Dogs given a sublethal dose (8 mg paraquat/kg) of Inteon had lower paraquat peak plasma levels when the levels are compared with those seen in historical studies (1988-1991) with Gramoxone where dogs were dosed with the same level of paraquat (Heylings *et al* 2004). However, due to the results of one outlier dog, there does not appear to be an improvement when the paraquat peak plasma levels from the average of 3 dogs dosed with Inteon are compared to levels seen in a contemporaneous study with Gramoxone (Brammer *et al* 2004) (Figure 5).

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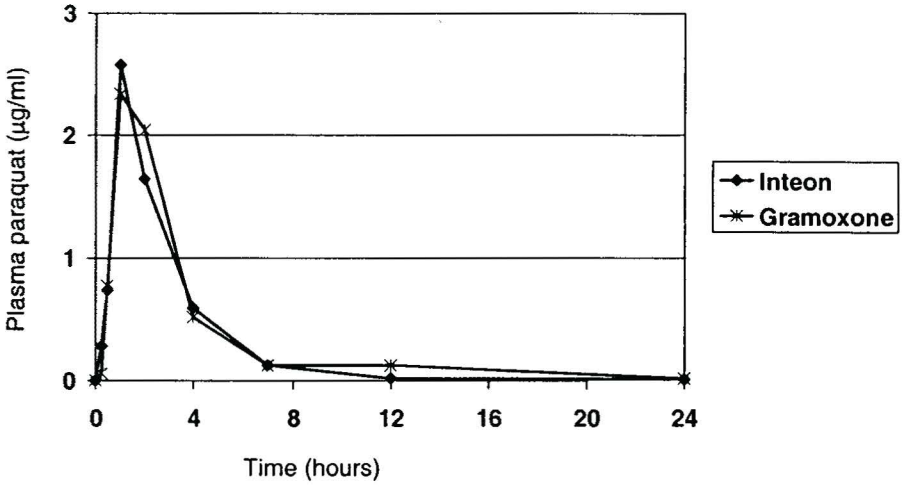
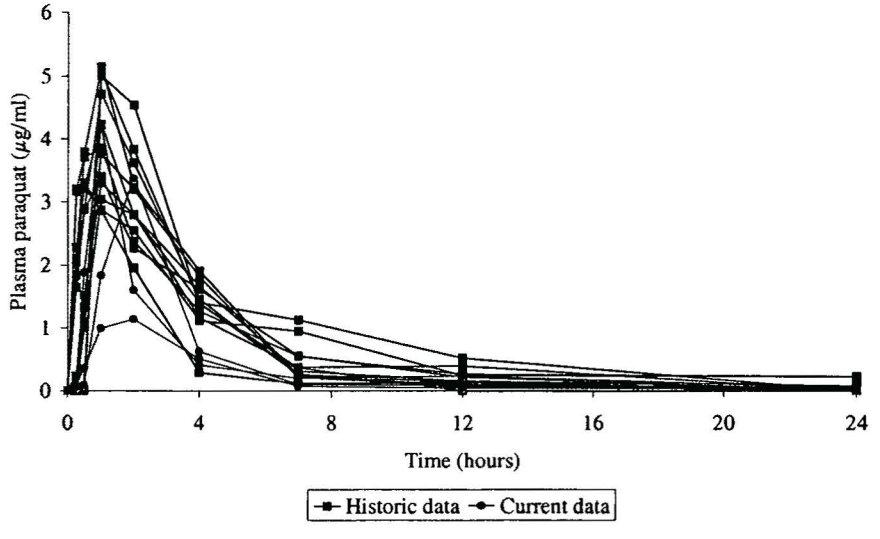
Figure 5



In the Brammer *et al* (2004) study, plasma levels of dogs dosed with Gramoxone were higher when compared to dogs dosed at the same level with Inteon for two of the three dogs tested. One dog dosed with Gramoxone, however, showed an atypical and unusually low value. This is clearly shown in Figure 6, where one of the three dogs in red (the contemporaneous control dogs referred to above) is an outlier with regard to the other two dogs and also all the other historical dogs.

Figure 6



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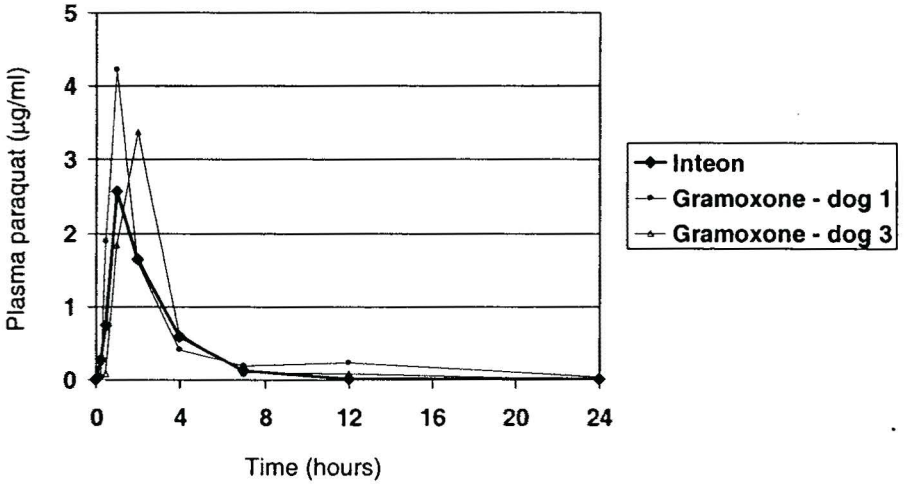
If the results from the one dog are removed as an outlier, the peak plasma levels (approximately 3.5 ug/ml) of the remaining two dogs dosed with Gramoxone at 8 mg/kg are consistent with the historical control (Figure 7). The mean peak plasma level (approximately 2.5 ug/ml) in dogs dosed with the same level of Inteon indicate the Inteon formulation does reduce exposure at the sublethal dose.

Figure 7



In view of the results of the dog studies with Inteon (no lethal effects up to 128mg/kg), the 8 mg/kg dose level was not repeated in the Inteon US study (the doses used in the Inteon US study were 32, 64 and 128 mg/kg). Therefore, there is a "weight of evidence" to support a significant improvement in oral toxicity at the low dose of Inteon US.

8. The selection of the dog as an acceptable surrogate for human safety

The main requirements for an animal model for assessing the toxicity of Inteon/Inteon US are for similarity in the gastro-intestinal (GI) tract, stomach pH, an ability to vomit, and ability to respond to the centrally acting emetic PP796. The relevant characteristics of the dog and human have been compared (Figures 8 & 9; Berry, 2005). They fully support the dog being an appropriate surrogate for use in toxicokinetic studies to reach a determination of human responses to ingestion of Inteon formulations.

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Figure 8

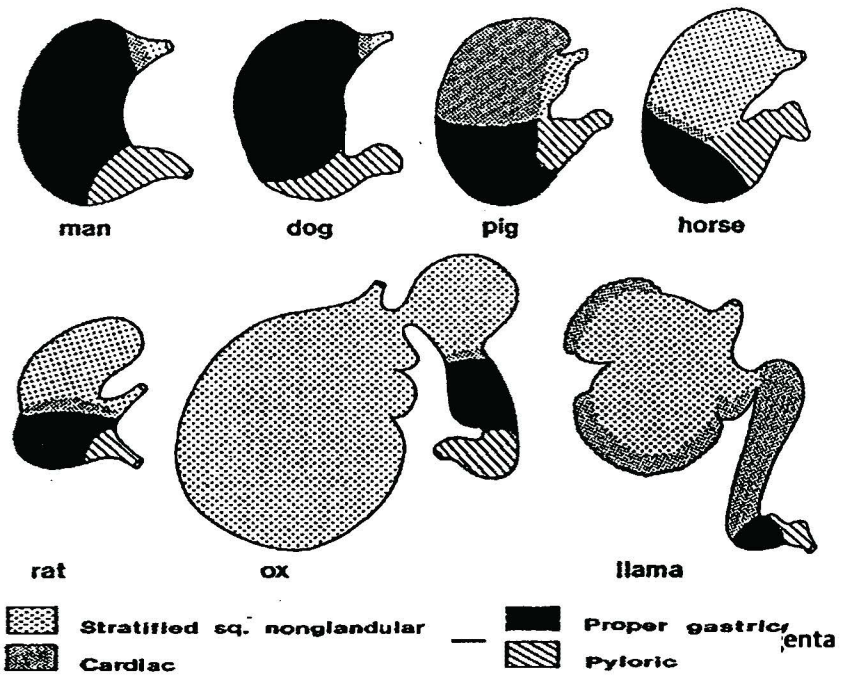

Figure 9

Human: Dog – Comparison of GI Anatomy and Physiology

	Characteristic	Human	Dog
Relevant Similarities	Chamber	Single/glandular	Single/glandular
	Capacity	1-1.6 L	~2 L
	pH fasted	1.4 – 2.1	1.5
	Gastric Mucosa	Predominantly "Proper Gastric" (see diagrams)	
	Emptying rates	1-2 hrs	1-2 hrs
	Proportional GI lengths (%): Small	80	85
	Cecum	3	2
	Colon	17	13
	Vomiting	Initiated by local irritation and/or similar neural reflex pathways to/from CNS	
Potentially Relevant Differences	Total GI Transit Time	8 – 72 hrs	6 – 8 hrs
	Small Intestine Transit time	3-4 hrs	>4 to <8 hrs

20 From: Kararli, TT (1995). Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals. Biopharm & Drug Disp. 16: 351-380. syngenta

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9. The relevant endpoint for evaluating oral safety improvement in humans

Accidental or intentional ingestions in humans may result in fatalities due to an initial organ failure (including renal and hepatic failure) or a subsequent progressive pulmonary fibrosis. The different scenarios are determined by the amount ingested. In the event of a lower intake of paraquat such that these two phases are not encountered, a recovery is normally made and the individual survives. The intention of the Inteon technology is to provide a reduction in the amount of paraquat being absorbed relative to existing Gramoxone formulations for any given amount ingested, and consequently reduce the number of fatalities from what would otherwise have been a fatal dose. Therefore, the relevant parameter for assessing improved oral safety in humans is lethality arising from rapid organ failure or subsequent progressive lung fibrosis.

In the toxicity studies conducted with the dog, physical condition and lethality were directly assessed through observation. Clinical chemistry was also undertaken, and at the end of the study, animals were subject to post mortem examination and histopathological examination. All the dogs tolerated well the highest dose of Inteon US (128mg paraquat/kg, equivalent to 602 mg formulation/kg bodyweight) and there was no clinical evidence of toxicity from pulmonary auscultation or clinical chemistry. There was minimal bodyweight loss, which was quickly recovered. Small discoloured areas of less than 1 cm^2 were present in the lungs of a single animal at post mortem, and these were areas of minimal interstitial fibrosis and associated change. These changes are considered to be treatment related but not progressive, and not life-threatening. This fully supports a dose of 602 mg formulation/kg bodyweight of Inteon US formulated product as the appropriate dose for risk assessment and the one of relevance to assessing oral safening in humans. This dose level provides an improvement over existing Gramoxone formulations of approximately 10 fold.

10. Progression of lung lesions in humans surviving paraquat ingestion

One of three dogs receiving the highest dose of Inteon US (greater than 10X the known lethal dose of Gramoxone) showed a small non-progressive lung lesion when lungs were examined after being sacrificed at the conclusion of the study (10 days after the last dose). The lesion was not considered life threatening or progressive. In human cases where an individual survives an accidental or intentional ingestion of paraquat, the reports from the literature indicate that the lung lesion does not subsequently progress with time, and that some recovery is seen. The recovery of respiratory function in survivors of acute paraquat poisoning has been studied (Lin et al 1995; Bismuth et al 1996). The results demonstrate that paraquat induced respiratory function impairments progressively recover, at least partially with time. In addition, pulmonary structure damage improved as shown in the follow-up chest radiographs. A third paper (Yamashita et al 2000) which is based on a group of only 12 patients is more difficult to interpret and concluded that patients surviving paraquat poisoning should be followed up with detailed lung function studies.

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11. Species differences in paraquat lethality between human and dog

The median lethal dose (MLD) for Gramoxone in the dog is approximately 12 mg paraquat ion/kg. An estimate of the MLD in humans is 50-80 mg/kg paraquat ion, derived from Pond (1990) assuming a bodyweight of 60kg (Figure 10). Therefore, the dog is more sensitive to paraquat lethality compared to humans.

Figure 10

Species differences in acute oral toxicity

Species	Median Lethal Dose (MLD) paraquat ion mg/kg	Inteon US mg formulation/kg
Dog	~12	Non-lethal at 602 (128mg paraquat ion/kg)
Human	50 – 80 (15-25 ml Gramox.) (Pond,1990)	

12. The ratio of intentional and accidental paraquat ingestions in the US

An analysis of Syngenta Poison Control Center Database (Prosar) for the 6 year period 2000 – 2005 revealed 29 cases of paraquat poisoning in the US. Eleven (38%) of these were classified as deliberate (intentional) and 18 (62%) as accidental. The accidental cases included people ingesting material decanted into drinks bottles, a man denying a suicide attempt, someone ingesting what he thought was tobacco spit, a doctor suspecting paraquat poisoning without confirming paraquat exposure and a 15 month old child drinking from a container in the back of a car. In 2 accidental cases there was predominantly topical exposure. Very often the information was from a third party and not the patient themselves and therefore, factual information is limited and in many cases detailed hospital records were not available. Ten of eleven people who intentionally ingested paraquat (91%) died and 8 of the 16 people who accidentally ingested paraquat (50%) died as a result.

13. Ingested volumes in the rest of the world and survival

Data collected from 563 cases of deliberate ingestion from several countries mainly in the Asia Pacific region shows that approximately 50% of those deliberately ingesting paraquat formulations consumed less than 50mls in volume of paraquat formulation (10g paraquat ion) (Submitted to EPA August 2005). Although the median amount of paraquat ion ingested varies from country to country and may differ from region to region within these countries. The overall survival rate of this population was approximately 25%.

14. Typical ingested volumes for accidental and deliberate ingestions in the US and survival

In 7 out of 11 of the intentional ingestions reported by PROSAR for the years 2000-2005 the amount ingested is unknown, in 3 cases it was approximately 3-8 ounces (90-240mls) and in one case a sip. The latter individual, a 16 year old girl was the only one out of the 11 to survive.

Of the accidental ingestions, the amount ingested was unknown in 55% (10/18) of the cases. Two were topical exposures, and the amount ingested for the other six ranged from a sip to 2 swallows, although there was an estimation of 100ml ingested by a 13year old child who survived. Considering the Syngenta product contains an olfactory alert it is possible, but difficult, to envisage someone consuming more than one mouthful (~15ml) accidentally. The overall survival from accidental ingestions, excluding the topical exposures who survived, was just under 50%.

From the records available in the cases considered it is very difficult to establish the amount ingested with any accuracy, although the greater survival in the case of accidental ingestions suggests less volume is ingested.

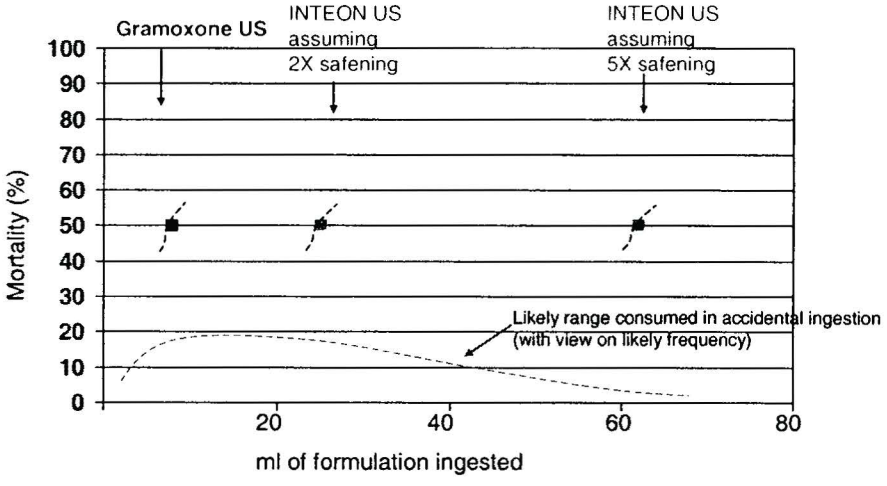
15. Significance of the improvement in oral toxicity on reducing human fatalities

Inteon US has been shown to be non-lethal in the dog at doses up to 128 mg/kg paraquat ion, a dose greater than ten times the MLD for Gramoxone in the dog (approximately 12 mg/kg paraquat ion). This level of safening in the dog, a more sensitive species than humans, indicates a real and significant safening and reduction in lethality. From these results, and the similarities between dog and man in the mechanism of toxicity and relevant anatomy and physiology, a significant improvement in oral toxicity is to be expected in humans. The oral toxicity improvement from Inteon is expected to be particularly relevant to ingestions that are accidental or to intentional ingestions of lower volumes of formulation. Effectively, a shift to the right is expected in the toxicity curve for survival against paraquat ingestion, as illustrated schematically in Figure 11. In this figure, the shift in the 50% mortality point is illustrated starting from a value of 50mg/kg for Gramoxone (source taken from Pond in Section 11 above), and scaling from this to

Gramoxone US and then to Inteon US with 2x or 5x assumed safening factors (well below the 10X suggested by the dog data). The likely (anticipated) range of volumes consumed in accidental ingestions is also shown, although the available data for this category are limited and of varying quality as discussed in Section 13 above. This Figure is shown for illustrative purposes only.

Figure 11

Possible improvement in human survival following accidental ingestion of INTEON US compared with Gramoxone US (*illustrative schematic only*)



16. Relationship between paraquat plasma levels and human survival

The measurement of paraquat plasma concentration has proved to be a reliable indicator of the prognosis of the intoxication. Based on results from 79 patients with a reasonably well established time of ingestion, Proudfoot *et al* (1979) found that those patients whose plasma paraquat concentration did not exceed 2.0, 0.6, 0.3, 0.16, and 0.1 mg/l at 4, 6, 10, 16, and 24 hours after ingestion, survived. This semi-logarithmic plot has become known as the predictive line, or 'Proudfoot's curve'. Subsequently, using a sample size of 219 patients, Hart *et al* (1984) were able to calculate the probability of survival of the patient from the initial paraquat plasma concentration. It was noted that the line denoting a 50% probability of survival correlated well with Proudfoot's curve.

17. Status of Sri Lanka observational monitoring survey

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

ingestion. Nine hospitals are involved in this survey and data have included the estimated dose of paraquat ingested and outcome. The data collected before the introduction of Inteon comprised some 350 cases, and there were 224 cases confirmed with Inteon when the survey was closed at Jan. 26, 2006. The data are now under evaluation and a summary of findings is expected in June 2006 following review by the independent scientific advisory panel that is overseeing the survey. The formulation in Sri Lanka is a 200g/l Inteon formulation containing built-in wetters and is different to that developed for the US. During the period of the survey it became apparent that the formulation was not optimal and suffered a degree of separation as illustrated in Figure 12. This formulation separation resulted in a reduction in the degree of safening in studies in dogs. Despite this, there was still an improved safening over Gramoxone (Figure 13). The Inteon formulation in Sri Lanka is therefore considered to be 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 improvement in safety than the data that will be generated from the Sri Lanka survey.

Inteon US is a formulation without built-in wetters and does not (cannot) suffer the same separation issue as the Sri Lanka formulation. Inteon US has a greater improvement in oral safety in the dog than the Inteon formulation undergoing evaluation in Sri Lanka.

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Figure 12

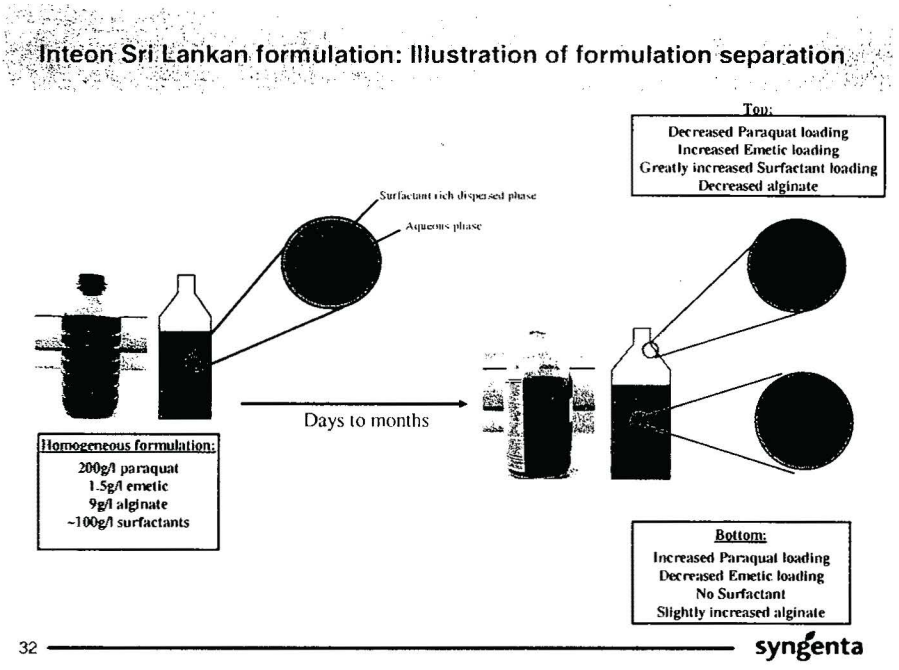
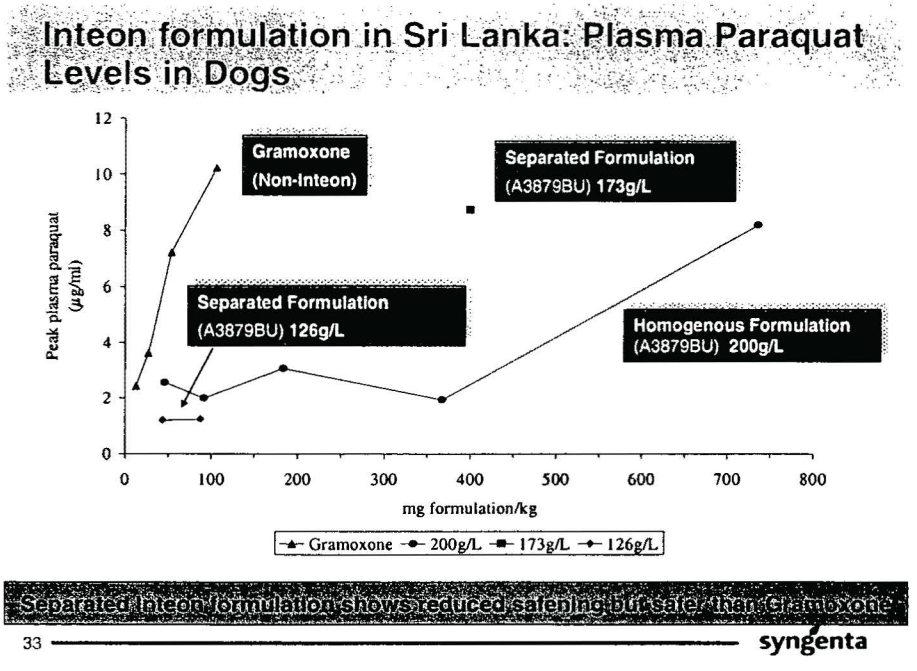


Figure 13



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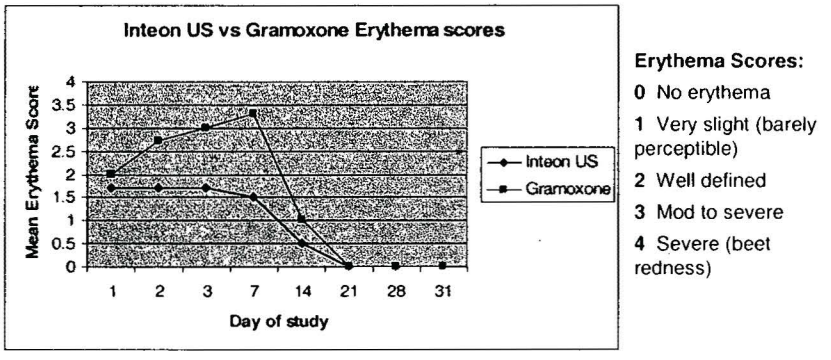
18. Impact of Inteon formulations on lesions on the lips and mouth as reported in the literature with Gramoxone

Swallowing Gramoxone has been reported to produce a caustic lesion including the lips and mouth, but recovery is also reported (Bismuth *et al* 1995). In animal tests, Inteon formulations have been found to show reduced irritancy to skin and eye compared with Gramoxone, but the extent to which this may offer a benefit in poisoning cases is not established. A comparison of Inteon US with Gramoxone in rabbit irritation tests is shown in Figures 14 -16, showing a reduced irritancy for the Inteon formulation.

Figure 14

Skin Irritation Comparisons



Erythema Scores:

0 No erythema

1 Very slight (barely perceptible)

2 Well defined

3 Mod to severe

4 Severe (beet redness)

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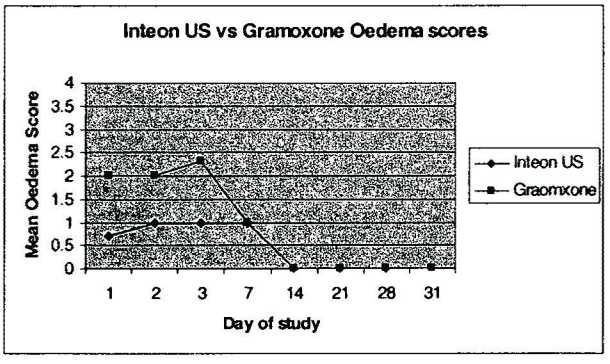
Figure 15

Skin Irritation Comparisons



Oedema Scores:

0 No oedema

1 Very slight (barely perceptible)

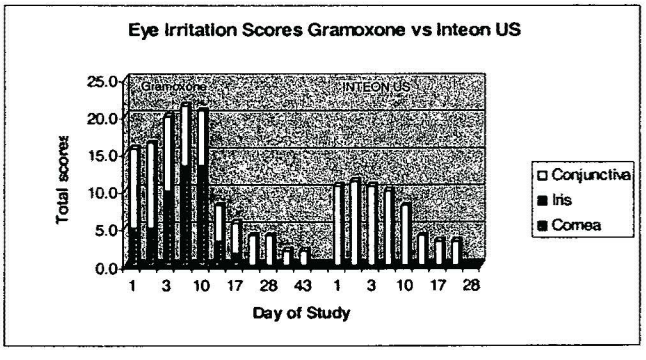
2 Slight (edges of area defined by definite raising)

3 Moderate (raised approx 1mm)

4 Severe (raised >1mm and extending beyond exposure area

Figure 16

Eye Irritation Comparisons



Kay and Callandra ratings (based on mean total score days 1-4):

0 to 0.5: None to practically non-irritating

0.5 to 2.5: Practically non-irritating

2.5 to 15: Slight to mild irritant

15 to 25: Mild to moderate irritant

25 to 100: Moderate to severe

SYNG-PQ-01228726

19. Summary

Intentional or accidental ingestions occur with paraquat as with many other materials. Over the years, Syngenta has introduced formulation improvements to deter ingestion, including colour and stench, and has introduced an emetic to reduce paraquat absorption. Syngenta has now introduced alginate technology into a new formulation (Inteon) that clearly shows reduced paraquat absorption and 10-fold safening (reduction in volume to cause lethality) in the dog. The data indicate that changing to Inteon formulations will save lives in the USA and internationally.

20. References

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B Elliott and M Clapp 31.5.2006

SYNG-PQ-01228728

Paraquat Human poisonings:

Estimates of the amount of paraquat ingested are not routinely recorded by hospitals and poison centres since the main objective for the medic is treatment with the aim of saving life. However, we have been able to compile data collected from some cases of deliberate ingestion from several countries mainly in the Asia Pacific region (Table 1). This data shows that the median amount of paraquat ion ingested varies from country to country and may differ from region to region within these countries. The estimates provided are for total paraquat ingested and, since bodyweights of the patients were not recorded, these are estimated values derived using amounts of the Gramoxone 200g/l formulation (with built in wetting agents). Hence, a dose of 10g paraquat ion would equate to approximately 50mls of end-use product formulation.

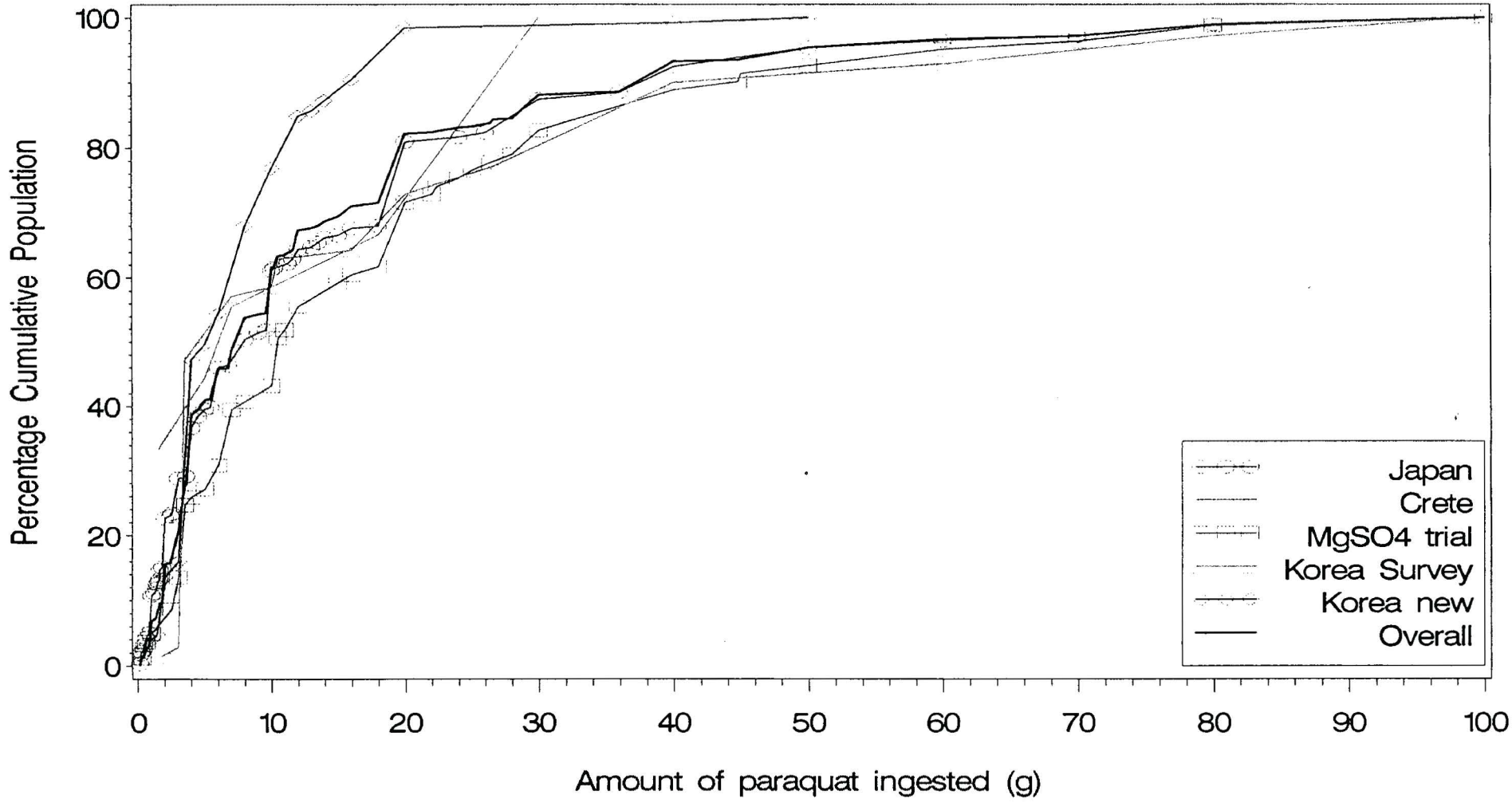
The same data as presented in Table 1 has also been plotted in Figure 1 as amount of paraquat ingested for the cumulative population. The data presented in Figure 1 demonstrates that approximately 50% of those deliberately ingesting paraquat formulations consumed less than 50mls in volume of paraquat formulation (10g paraquat ion). For some subpopulations this figure is as low as 25mls of paraquat formulation (5g paraquat ion). Based upon this data, the greater than 10 fold reduction in toxicity in the dog and the perceived benefits that the INTEON formulation can bring to the marketplace, Syngenta believes that the INTEON formulations will have a significant improvement on survival in humans (deliberately or accidentally) ingesting paraquat formulations at the volumes of ingestion documented and presented.

Table 1
Estimates of median amount of paraquat ion ingested and resulting survival rates for different sub-populations

Source	Years	No of cases	Survival rate	Median amount (g) paraquat ion ingested (mls of Gramoxone formulation)
ICI Japan	1979-1985	209	25%	9.6 (~48.0)
Ohno (Japan)	1985	175	- a	20 (~100)
Ohno (Japan)	1986-1987	69	25%	6 (~30)
Crete	?	9	50%	7 (~35)
MgSO4 trial (Sri Lanka/Korea)	2000	81	25%	10.5 (~52.5)
Epidemiology study (Korea)	2000-2001	70	26%	7 (~35)
Hong (Korea)	2002 – 2003	125	50%	5 (~25)

a **data only reported fatalities, not used in subsequent analysis**

Figure 1. Cumulative population data for human poisonings from paraquat ingestion.



SYNG-PQ-01228730

Ingestion Incidents in the United States

Over the last five years, Syngenta has received approximately one to five reports of intentional or accidental ingestions of paraquat-containing formulations per year in the United States. On average, approximately two to four people per year are involved in lethal or life-threatening incidents in the United States as a result of accidental or intentional ingestion of paraquat-containing herbicides. The majority of the intentional ingestion incidents were self-harm attempts, and the majority of accidental ingestion incidents involved illegal removal and storage in soda or sport's drink containers that were subsequently and accidentally consumed.

Similar to the rest of the world, poison control centers or hospitals in the United States rarely obtain a detailed or accurate description of the quantity of paraquat or end-use formulation consumed. However, based on Syngenta's experience in the United States over the last five years, there appears to be a general trend:

- **Accidental Ingestions:** Individuals who accidentally drink paraquat-containing formulations tend to consume only one swallow of the liquid formulation (e.g., Gramoxone), which is often rapidly vomited out. The amount of one swallow can be debated, however it is likely to be in the range of < 0.5 to 2 ounces (< 15 - 60 ml) of liquid. Due to the liquid nature of the formulation, complete emesis is unlikely to be achieved (due to incompleteness of regurgitation from the small intestines), and the ingestion of this volume of Gramoxone Max formulation can be lethal, even though rapid emesis occurred.

- **Intentional Ingestions:** There is large variability and uncertainty regarding the volumes consumed during intentional ingestions incidents. Furthermore, the reliability of the reported volumes is questionable due to the poor quality of investigation or minimal fact-gathering activities. Nevertheless, based on our experience, most intentional ingestion cases involve the ingestion of relatively small volumes of Gramoxone (e.g., < 2 to 4 ounces). In some rarer instances, however, large amounts (e.g., < 8 to 24 ounces) appear to have been consumed.

The Value of the Emetic in Paraquat formulations

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

Paraquat is rapidly absorbed from the gastrointestinal tract resulting in peak plasma paraquat levels 1-2 hours after ingestion. The main site of absorption is the jejunum (Heylings 1990) and if emesis occurs within 30 minutes, it was originally proposed that this may limit the amount of paraquat absorbed, and thus improve survival. Since the incorporation of the emetic, dye and alerting agent, survival data collected confirms this theory.

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 as the quantity of paraquat ingested increased demonstrating the positive effect of the emetic.

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 farmer 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 of paraquat occurred in the early 1980s, at the start of the study, 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 instances of mistaken ingestion (Sabapathy, 1995).

With new formulations based upon INTEON technology and acid triggered gelling there is an opportunity for more productive emesis prior to passage of paraquat into the small intestines. Limiting the passage of paraquat into the small intestines, the primary site of absorption, is expected to significantly reduce paraquat absorption and consequentially improve the survival rate of humans who ingest paraquat (accidental or intentional). Previous research studies in the dog showed that early emesis was achieved with liquid formulation and dosing the emetic in combination with paraquat dichloride or paraquat formulations shortened the time to emesis (Figure 2). However despite shortening the time to emesis it resulted in higher paraquat exposure with increasing paraquat doses due to passage of the formulation into the small intestines. The threshold for emesis within 30mins with liquid formulations was between 0.02 and 0.19mg PP796/kg. With the INTEON triggered gel formulations emesis does not occur as quickly but is more productive as demonstrated by the reduced paraquat absorption across a large dose range (16 fold). The threshold dose for emesis within 30 mins with INTEON formulations is approximately 0.2mg PPR796/kg (Figure 2).

From data reported by Meredith and Vale 1987, showed that an increased incidence of emesis within 30mins occurred following the inclusion of the emetic in the formulation and this was dependent on dose. All those ingesting 25mls (5g paraquat ion) or greater vomited within 30mins, this equates to a dose of 0.205mg PP796/kg (Figure 3).

In conclusion, Syngenta believes that the inclusion of increased emetic (PP796) and acid triggered gels will have a beneficial effect by causing a more productive expulsion of paraquat following oral ingestion, thus reducing the amount of paraquat absorbed systemically. 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 fatalities following accidental ingestions.

MJLC 15th August 2005

Figure 2 Time to emesis vs. dose of emetic in the dog for liquid and acid triggered gel INTEON formulations

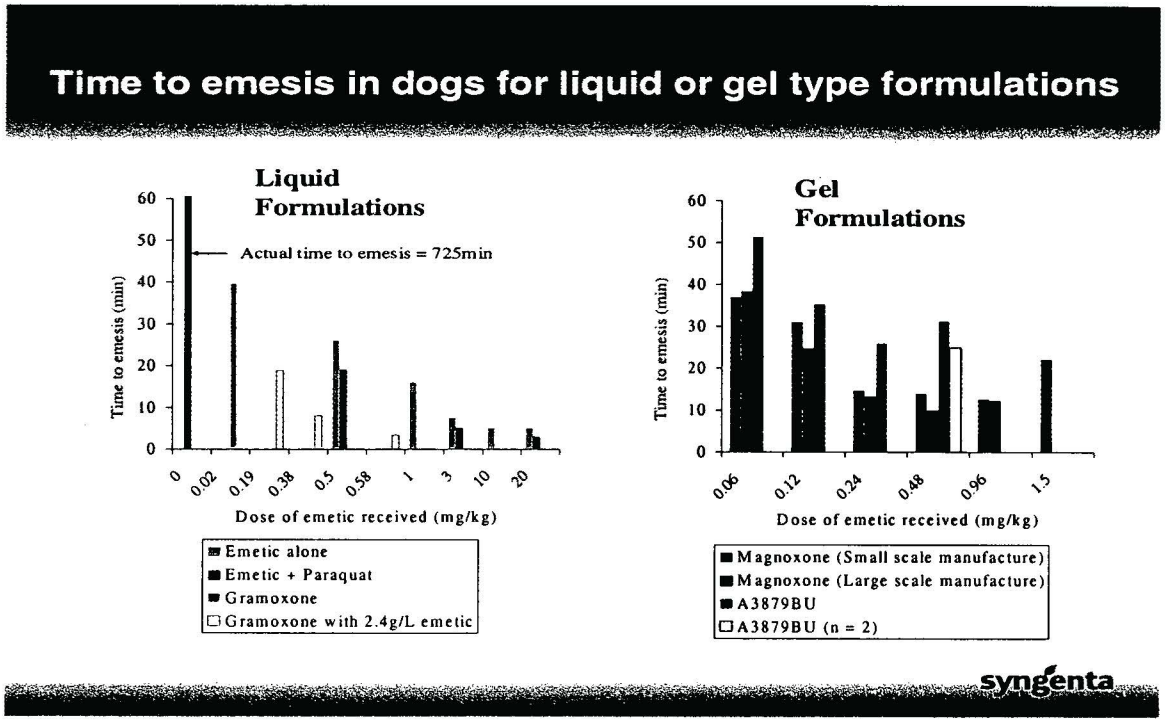
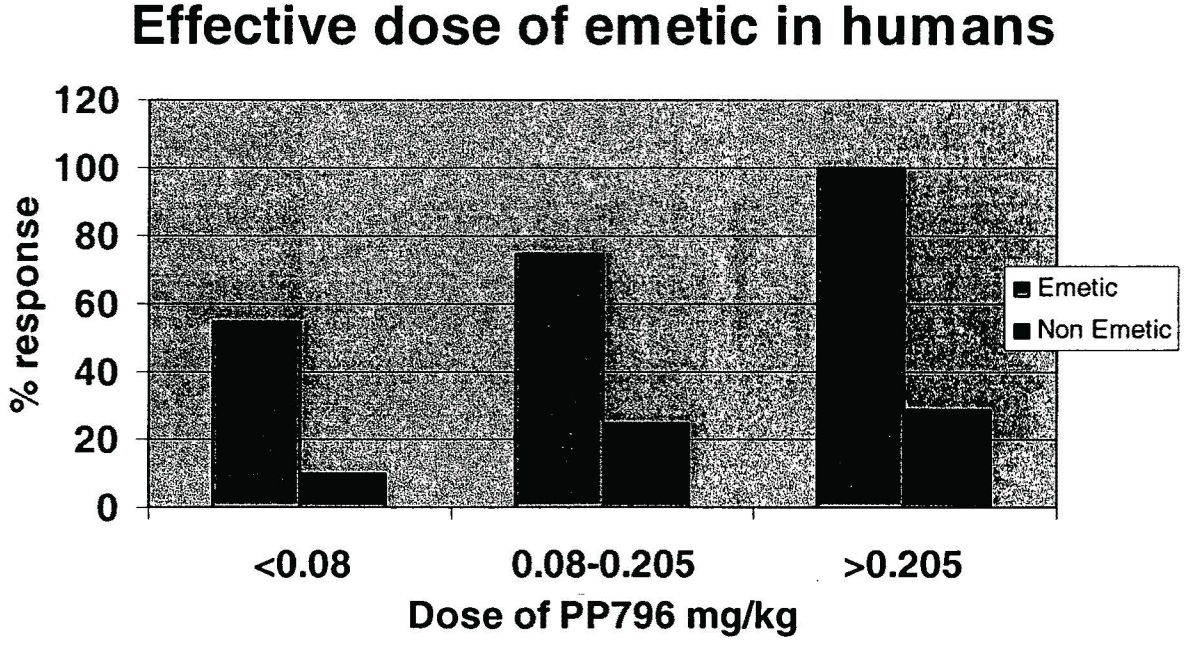


Figure 3 Incidence of spontaneous vomiting within 30minutes of ingestion of an emeticised or non emeticised formulation of the paraquat formulation, Gramoxone



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ATTACHMENT B:

A REVIEW OF GLOBAL PARAQUAT INCIDENCE DATA

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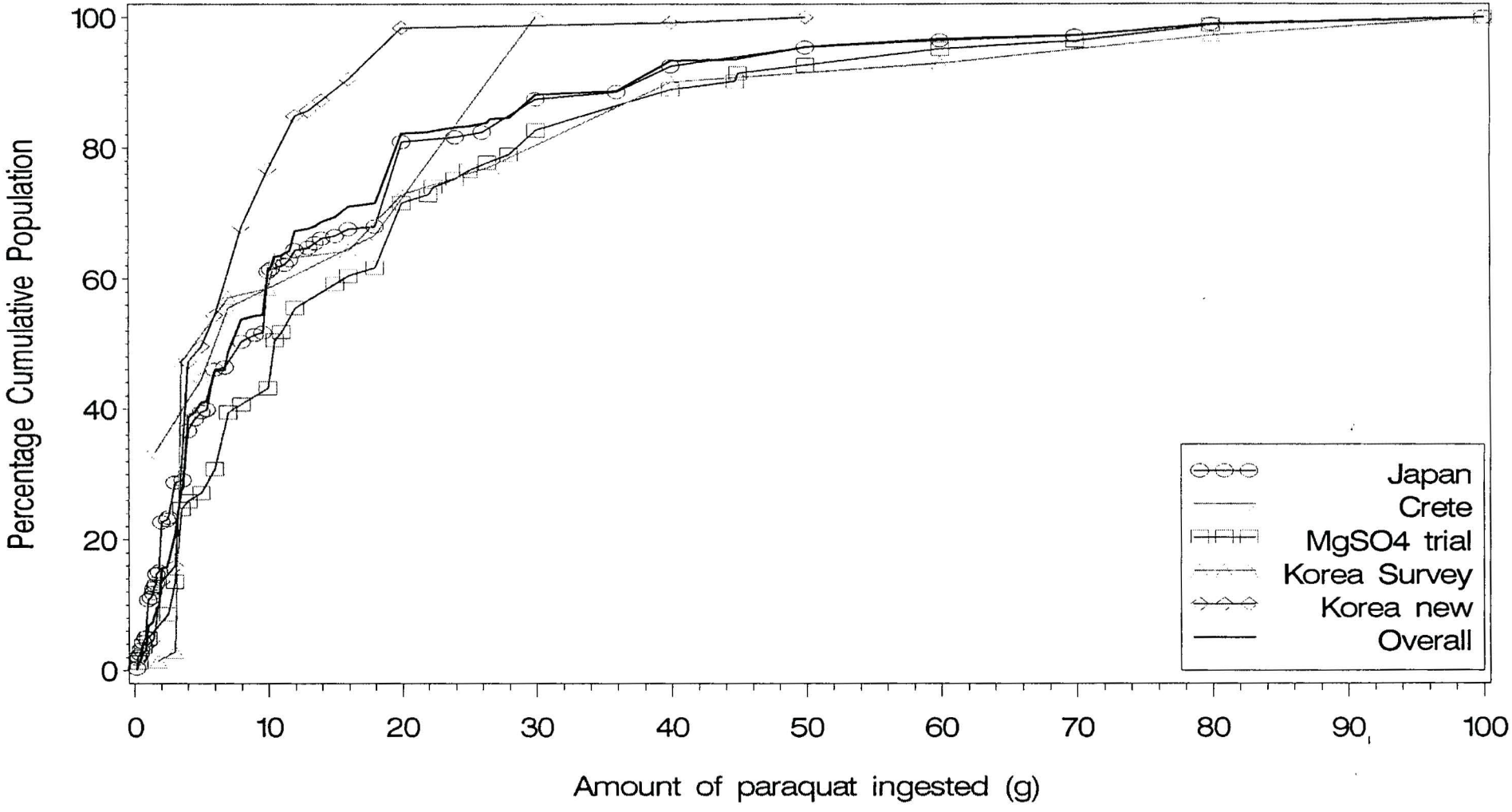

SYNG-PQ-01228737

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MJLC 15th August 2005

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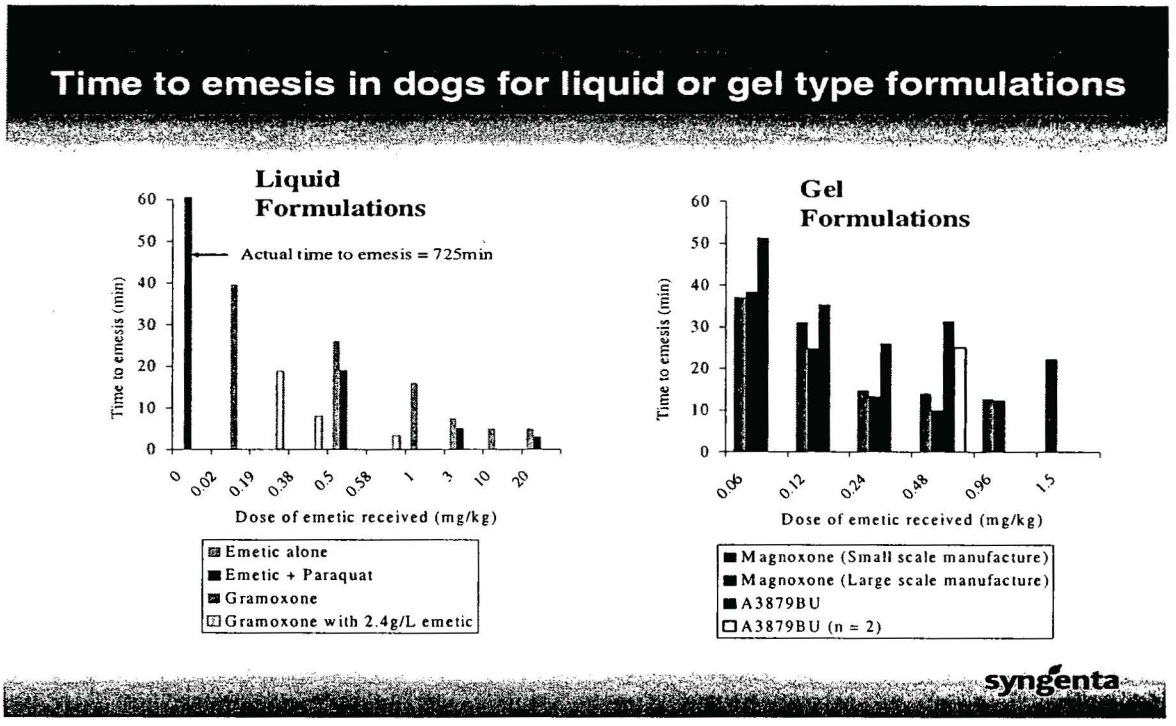

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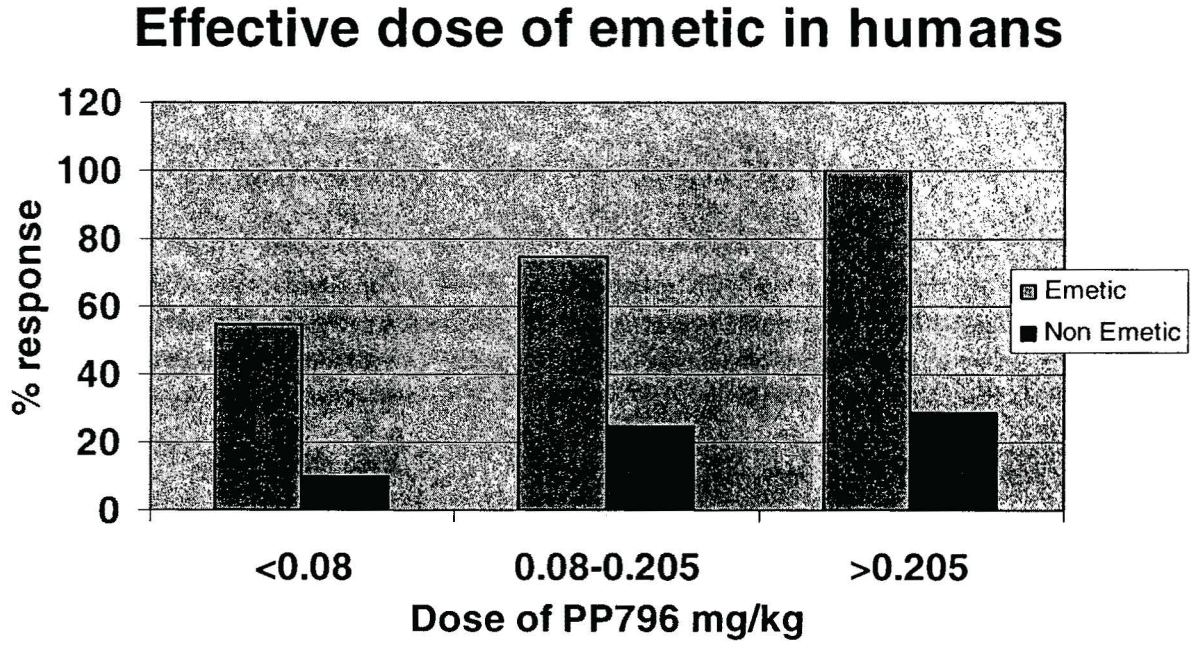

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ATTACHMENT C:

DECLARATION OF SIR COLIN BERRY

Privileged & Confidential
Attorney Work Product

1/16/06

Declaration of Sir Colin Berry

I, Sir Colin Berry, declare under penalty of perjury that the following is true and correct.

1. I am Professor Emeritus of Pathology at Queen Mary, London. . I am presently in active pathology practice and act as consultant in toxicology for regulatory agencies, pharmaceutical and agrochemical companies and for groups with environmental concerns. I serve on the advisory boards of "Sense about Science", the Scientific Alliance and am a consultant at the Science Media Center of the Royal Institution.
2. I was a member of the UK regulatory body for Pesticides for more than 20 years in various capacities; serving as Chairman of the Advisory Committee on Pesticides for 10 years – reporting to six government departments. I have also been Chairman of the Committee of Dental and Surgical Materials and served on the Committee of Safety of Medicines. In these capacities I have taken part in a number of reviews of many compounds, including UK, EU and WHO related reviews of Paraquat. My present publications relate mainly to risk evaluation and assessment and I have recently addressed the Parliamentary and Scientific Committee on related issues.
3. CV attached
4. I have been asked to provide my opinion as an expert in toxicology and pesticide testing on the reliability of Syngenta data for predicting human responses to ingestion of Syngenta's Inteon formulation.
5. This Declaration explains the biochemical mechanism of the Inteon formulation in the digestive tracks of mammals, the results of tests of Inteon when ingested by dogs, and the science supporting the application of these data to assessing the consequences of Inteon ingestion by humans.

Biochemical Mechanism of Inteon

6. The main site of absorption of paraquat is the small intestine, particularly the jejunum (the central section of the small intestine), with limited absorption from either the oesophagus or stomach (Heylings, 1991). The oral toxicity of paraquat may therefore be reduced by limiting the exposure of the small intestine to ingested paraquat material.
7. The key to Inteon's safety mechanism is the formation of an alginate gel in the stomach that helps prevent the release of any paraquat into the small intestine. Alginates are non-toxic carbohydrates of polymannuronic and polyguluronic acid and are commonly used in the food industry as gelling agents. They are also used therapeutically, for example in treating dyspepsia (Mandel *et al,* 2000) and wound healing (Agren, 1996). An alginate that gels under low pH conditions (pH 1-3) was selected for Inteon, as the material remains liquid and flowable as a formulation, but if it is swallowed and reaches the acidic conditions of the stomach, it forms a semi-solid gel. This change holds the material in the stomach, and allows emesis (vomiting) to be more effective in removing the semi-solid material than it would be in removing a liquid. Inteon also contains an emetic agent that induces vomiting following ingestion.

8. The gelling process reduces the amount of paraquat that might be released to the small intestine.

Results of Toxicity Study on Inteon Formulation in Dogs

9. Inteon formulations have been shown to reduce the systemic absorption of paraquat in the dog, resulting in a greater than ten-fold reduction in oral toxicity when compared with non-Inteon paraquat formulations (Brammer et al. 2004).

Extrapolation from dogs to humans

10. The choice of the dog in Syngenta's experiments depends on this species having the necessary digestive attributes, including a vomit reflex. The vomit reflex is controlled centrally by the vomit centre in the brain, responding to changes in cAMP (a molecule that regulates several biological processes) – which is the same in dog and man. This is significant because phosphodiesterase inhibitors, like Syngenta's emetic agent (PP796), work through a cAMP-regulated process. It is worth noting that other species such as the rat were deemed inappropriate since rats do not vomit.
11. The toxicokinetics processes for paraquat (and many drugs and other chemicals) are similar in dog and humans. Dogs, like humans are omnivores and intermittent feeders. The physiology of digestion in both species is also very similar.

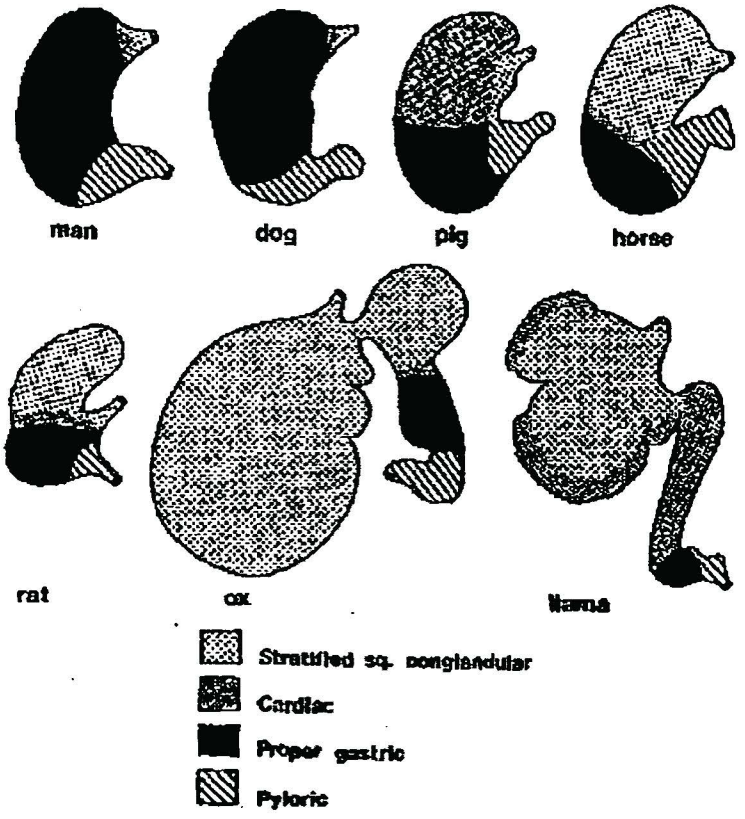
Reactions to paraquat in dog and human

12. Data in man indicates that the plasma paraquat kinetic profile and area under the curve (AUC) at a minimally toxic dose is similar between dog and man. Across species there are differences in the acute oral lethal dose which is thought to be due to differences in the amount of paraquat absorbed from the gastrointestinal tract. Analysis of the 0-24h AUC across these species shows similar paraquat systemic exposure at a peri-lethal oral dose (Heylings, 1994).

Comparable gastrointestinal tract characteristics

13. It was concluded by Kararli (1995) that current data indicated that no single animal can mimic the gastrointestinal tract characteristics in humans. However, in considering stomach morphology and emptying characteristics, the dog and human were found to be very similar. The Inteon technology is predominantly focused on the interactions within the stomach in order to prevent the ingested dose from reaching the intestine. The stomach size, volume and pH are similar between dog and man.

Figure 1. Variations in the type and distribution of gastric lining tissue in different mammals. The dog and human are closest in structure of stomach tissue. (Stomachs are not drawn to scale).



Humans have a highly regulated gastrointestinal physiology. The human digestive system is sensitive to a variety of potentially ingested toxins and is particularly sensitive to topical irritants of the gastric mucosa (lining tissue), some bacterial and viral toxins, and foods and drinks that have a high salinity. Vomiting can be initiated centrally or locally.

14. Local irritation by compounds (such as alcohol or paraquat) is a slow and inefficient emetic stimulus, while centrally acting emesis (mediated via the hypothalamus) is very efficient in all higher mammals. The vomit centre, once triggered, causes a complete closure of the pyloric sphincter, followed by gastric muscle contraction from the pylorus upwards through the fundus. Following relaxation of the oesophageal sphincter, the pressure effect expels the gastric contents very effectively. There is no anatomical or physiological reason why human vomiting should be less effective than that seen in dogs.

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Emesis in dogs and humans

15. The efficiency of emesis (vomiting) generally depends on the dose of the emetic and the physical constitution of the stomach contents. When ingested, the Inteon product gels and stays in the stomach while the human receives a dose of the emetic (PP796) that causes prompt emesis, coupled with closure of the pylorus. Human vomiting will be as productive as vomiting by the dog. From analysis of poisoning data reported by Meredith and Vale (1987), the threshold dose of the PP796 emetic required to produce emesis in 100 percent of human patients within 30 minutes was greater than or equal to 0.2mg/kg. It is important to note that this is also the threshold dose in the administration of Inteon formulations in the dog (Brammer et al 2004).

Conclusion

16. The similarities between the human and dog gastrointestinal systems, including similar stomach emptying and emesis processes, allow for valid extrapolation from dog toxicokinetics studies to reach a determination of human responses to ingestion of Inteon formulation.

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NOTE Missing reference to be added

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