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

<table>
<thead>
<tr>
<th>Product Reference</th>
<th>Paraquat a.i. concentration</th>
<th>Inteon Technology (Y or N)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gramoxone</td>
<td>200 g/l</td>
<td>No</td>
<td>Global formulation, not registered in US</td>
</tr>
<tr>
<td>Gramoxone US</td>
<td>360 g/l</td>
<td>No</td>
<td>Registered in US as Cyclone Concentrate (alternative brand name Gramoxone Max) US Voluntary cancellation requested</td>
</tr>
<tr>
<td>Inteon</td>
<td>200 g/l</td>
<td>Yes</td>
<td>Global formulation, not registered in US, separation problems (also called A3879BU)</td>
</tr>
<tr>
<td>Inteon US</td>
<td>240 g/l</td>
<td>Yes</td>
<td>Registered in US as Gramoxone Inteon (also called A7813K)</td>
</tr>
</tbody>
</table>
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 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.
The lethal dose of non-Inteon paraquat formulations in the dog

The established toxicity of Gramoxone in the dog from studies in 1987 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 dogs

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

Gramoxone: influence of increased emetic on peak plasma paraquat levels in dog
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.
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).

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

[Graph showing plasma pentazap (microgram/mL) over time (hours), comparing historic data and current data.]
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.
Human: Dog – Comparison of GI Anatomy and Physiology

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Human</th>
<th>Dog</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chamber</td>
<td>Single/gl glandular</td>
<td>Single/gl glandular</td>
</tr>
<tr>
<td>Capacity</td>
<td>1-1.6 L</td>
<td>~2 L</td>
</tr>
<tr>
<td>pH fasted</td>
<td>1.4 – 2.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Gastric Mucosa</td>
<td>Predominantly “Proper Gastric” (see diagrams)</td>
<td></td>
</tr>
<tr>
<td>Emptying rates</td>
<td>1-2 hrs</td>
<td>1-2 hrs</td>
</tr>
<tr>
<td>Proportional GI lengths (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small</td>
<td>80</td>
<td>85</td>
</tr>
<tr>
<td>Cecum</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Colon</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Initiated by local irritation and/or similar neural reflex pathways to/from CNS</td>
<td></td>
</tr>
<tr>
<td>Total GI Transit Time</td>
<td>8 – 72 hrs</td>
<td>6 – 8 hrs</td>
</tr>
<tr>
<td>Small Intestine Transit time</td>
<td>3-4 hrs</td>
<td>&gt;4 to &lt;8 hrs</td>
</tr>
</tbody>
</table>

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 cm² 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.

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.
Species differences in acute oral toxicity

<table>
<thead>
<tr>
<th>Species</th>
<th>Median Lethal Dose (MLD) paraquat ion mg/kg</th>
<th>Inteon US mg formulation/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>~12</td>
<td>Non-lethal at 602 (128mg paraquat ion/kg)</td>
</tr>
<tr>
<td>Human</td>
<td>50 – 80 (15-25 ml Gramox.)</td>
<td></td>
</tr>
</tbody>
</table>

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

An analysis of Syngenta Poison Control Center Database (ProFar) 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 spilt, 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 13 year 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](image)

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.
Figure 12

Inteon Sri Lankan formulation: Illustration of formulation separation

Homogeneous formulation:
- 200 g/L paraquat
- 1 g/L emetic
- 9 g/L alginate
- ~100 g/L surfactants

Days to months

Tops:
- Decreased Paraquat loading
- Increased Emetic loading
- Greatly increased Surfactant loading
- Decreased alginate

Bottom:
- Increased Paraquat loading
- Decreased Emetic loading
- No Surfactant
- Slightly increased alginate

Figure 13

Inteon formulation in Sri Lanka: Plasma Paraquat Levels in Dogs

<table>
<thead>
<tr>
<th>mg formulation/kg</th>
<th>Plasma paraquat (ug/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>100</td>
<td>1</td>
</tr>
<tr>
<td>200</td>
<td>2</td>
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<td>600</td>
<td>6</td>
</tr>
<tr>
<td>700</td>
<td>7</td>
</tr>
<tr>
<td>800</td>
<td>8</td>
</tr>
</tbody>
</table>

- Separated Inteon formulation shows reduced safening but safer than Gramoxone

- Margosafe (Non-Inteon)
- Separated Formulation (A187986) 173g/L
- Homogeneous Formulation (A187986) 126g/L

- Gramoxone
- Separated Formulation (A187986) 173g/L
- Homogeneous Formulation (A187986) 126g/L

- 15 -
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

![Skin Irritation Graph](image-url)
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 1 mm)
4  Severe (raised >1 mm and extending beyond exposure area)

Figure 16

Eye Irritation Comparisons

Key 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

syngenta
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

Berry C (2006) Declaration of Professor Sir Colin Berry (previously submitted to EPA)


Swain C and Heylings JR (2006). Effects of increased emetic levels on toxicokinetics in the dog. Syngenta Report No: CTL/026698/RESEARCH/REPORT


B Elliott and M Clapp 31.5.2006