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.

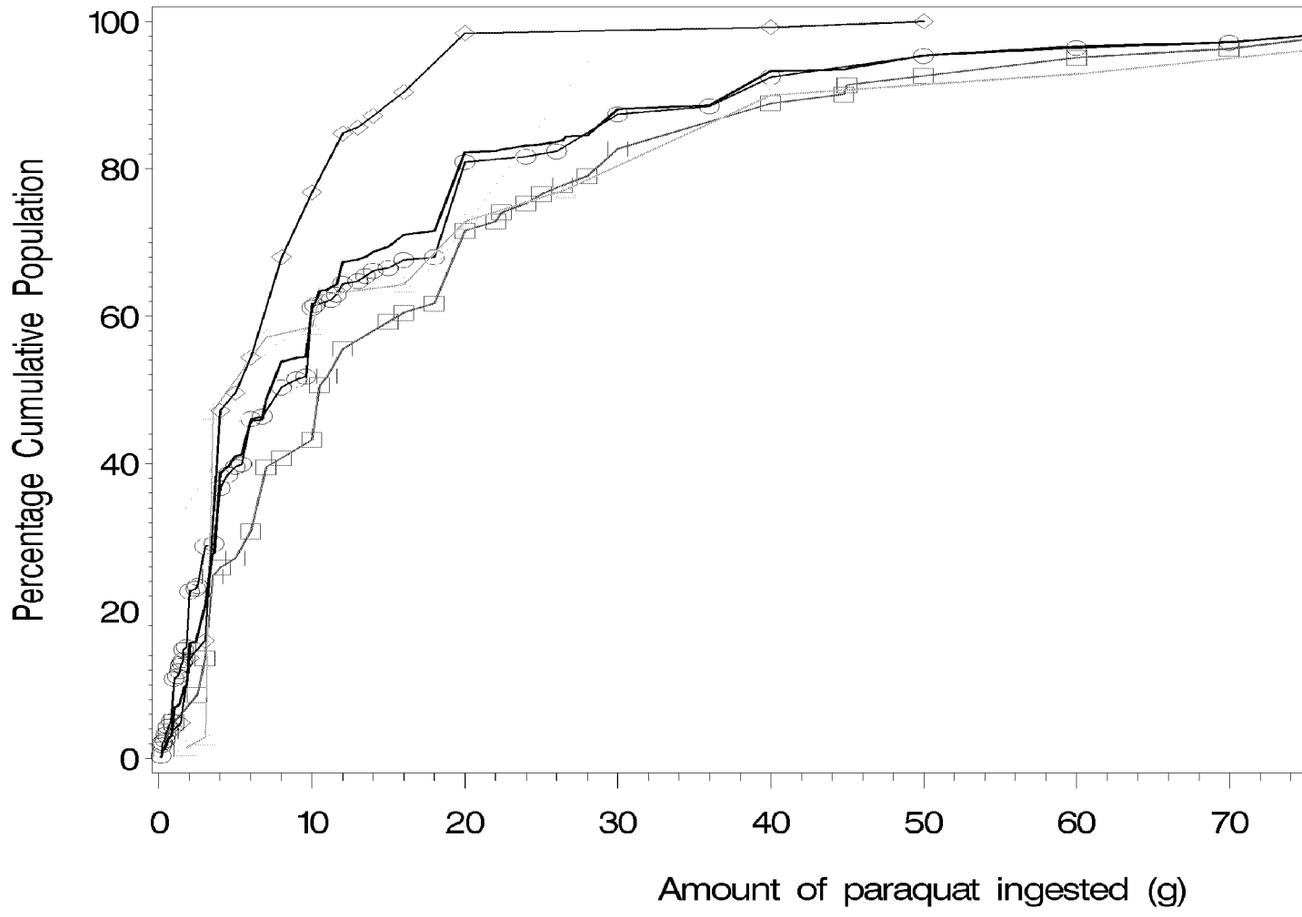
The same data as presented in Table 1 has also been plotted in Figure 1 as amount of paraquat ingested for the cumulative population. The data presented in Figure 1 demonstrates that approximately 50% of those deliberately ingesting paraquat formulations consumed less than 50mls in volume of paraquat 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.



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

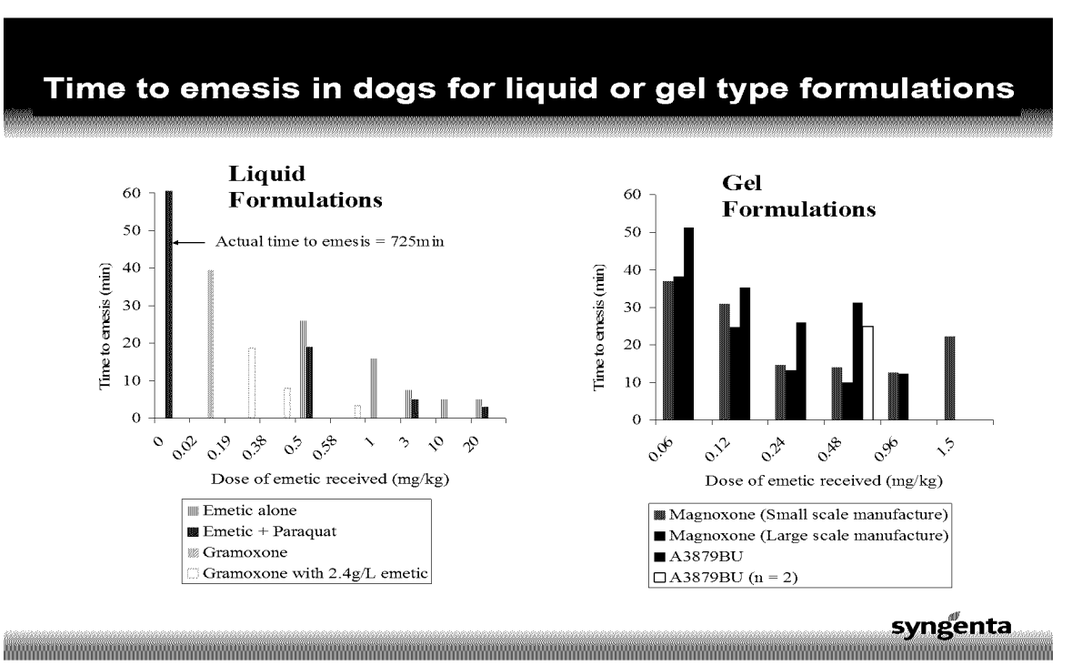


Figure 3 Incidence of spontaneous vomiting within 30minutes of ingestion of an emeticised or non emeticised formulation of the paraquat formulation, Gramoxone

References:

1. Bramley, A., and Hart, T. B. (1983) Paraquat poisoning in the United Kingdom. *Human Toxicol.* **2,** 417.

2. Denduy ... (1985) ... addition of an emetic to paraquat formulations on acute poisoning in man. *J Toxicol. Clin. Toxicol.* **23,** 4...

3. G... Professi... du Pa...

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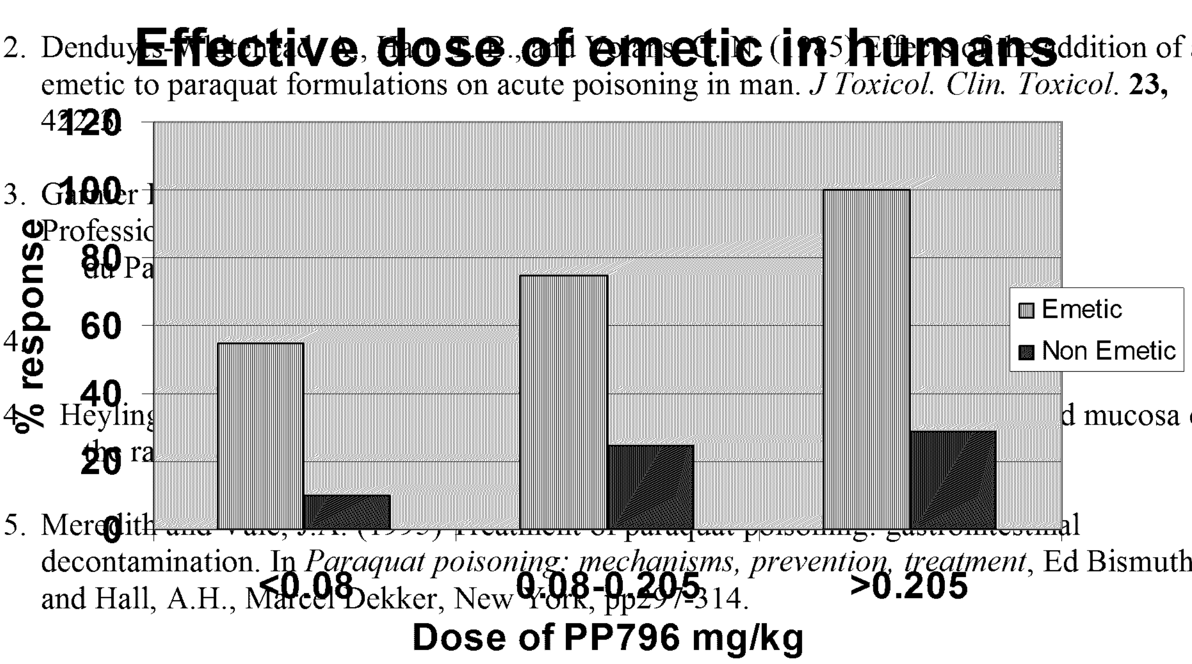
4. Heyling ... d mucosa of the ra...

5. Meredith ... Treatment of paraquat poisoning: gastrointestinal decontamination. In *Paraquat poisoning: mechanisms, prevention, treatment*, Ed Bismuth, C. and Hall, A.H., Marcel Dekker, New York, pp297-314.



6. Northall F S, Wilks M F (2001). Two Decades of Paraquat Surveillance in the UK. *J Tox Clin Tox* **39**: 283 - 284.

7. Onyon, L. J., and Volans, G. N. (1987) The epidemiology and prevention of paraquat poisoning. *Hum. Toxicol.* **6,** 19-29.

8. Sabapathy, N N (1995). Paraquat Formulation and Safety Management. In: Bismuth, C., Hall, A. H. (eds) *Paraquat Poisoning.* pp 335-47, Marcel Dekker Inc, New York.

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