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PARAQUAT: ABSORPTION AND ACUTE ORAL TOXICITY OF YF8004A IN THE DOG

by

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THE DATA IN THIS REPORT HAVE NOT BEEN QUALITY ASSURED

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PARAQUAT: ABSORPTION AND ACUTE ORAL
TOXICITY OF YF8004A IN THE DOG

I, the undersigned, declare that this report constitutes a true record of the actions undertaken and the results obtained in the above study.

J R Heylings (Study Director) ..... 19th Jan 1993

PARAQUAT: ABSORPTION AND ACUTE ORAL
TOXICITY OF YF8004A IN THE DOG

The following contributed to this report in the capacities indicated:

M J Farnworth (Biochemical Analyst) ..... 19th Jan 1993

This study was conducted under the authority of the Alleviation of Chemically-Induced Toxicity Home Office Project Licence.

J R Heylings (Project Licence Holder) ..... 19th Jan 1993

PARAQUAT: ABSORPTION AND ACUTE ORAL TOXICITY OF YF8004A IN THE DOG

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PARAQUAT: ABSORPTION AND ACUTE ORAL TOXICITY OF YF8004A IN THE DOG

SUMMARY

The objective of this study was to examine the acute oral toxicity of YF8004A, a paraquat formulation, in the adult male dog. YF8004A, a liquid concentrate containing 200g/l paraquat, was dosed orally to dogs over the range 8-128mg/kg (paraquat ion). This was equivalent to 0.04-0.64ml/kg of formulation. There was a dose related reduction in the time taken for emesis to occur between 8-32mg/kg. This feature together with the physical properties of the formulation prevented lethal concentrations of paraquat from being absorbed. At high paraquat doses (64-128mg/kg), the time to emesis did not shorten but the physical and pharmacological properties of the formulation enabled the animals to tolerate very high doses of paraquat. Emesis remained an effective de-toxification mechanism for high doses of formulation remaining in the stomach for a relatively long time period. In addition, the purgative action of the formulation cleared paraquat rapidly from its absorptive site in the small intestine. Following oral dosing of neat YF8004A concentrate, clinical signs of paraquat toxicity were only seen in one animal out of three at the highest dose level, 128mg/kg. The median lethal dose of paraquat formulated as YF8004A is therefore greater than 128mg/kg in the adult male dog. This is more than ten times the MLD value for GRAMOXONE in the adult male dog. The formulation additives in YF8004A have therefore markedly reduced the oral toxicity of paraquat almost certainly by reducing the absorption of the herbicide from the gastrointestinal tract.

1. INTRODUCTION

GRAMOXONE and other paraquat based products have been associated with human poisonings. Current research has been directed towards devising a new formulation which reduces paraquat oral toxicity. This has centred on the optimization of a paraquat formulation containing additives which have specific pharmacological properties designed to reduce the absorption of paraquat from the gastrointestinal tract (Heylings J R, 1990, 1991a). This formulation, YF8004A, is based on the 200g/l paraquat product GRAMOXONE, and is sometimes unofficially referred to as MAGNOXONE. Most of the research studies have been carried out in the dog, since this animal has been shown to be very similar to man in terms of paraquat pharmacokinetics (Hawksworth G M et al, 1981).

The present study reports on a large scale preparation of a new formulation has been examined over a wide dose range in the adult male Beagle dog. YF8004A, like GRAMOXONE contains 200g/l paraquat ion, the same wetter system and alerting agents which include pyridine stench and blue dye and emetic agent. The emetic concentration in YF8004A was based on the absorption of an effective dose which will produce emesis within 30 min when it is combined with a minimal lethal dose of paraquat.

2. MATERIALS AND METHODS

2.1 Test Substance

YF8004A was supplied by ICI Agrochemicals, Yalding, Kent, UK, as a dark blue/green opaque viscous liquid. It contained 16.9% w/w (19.8% w/v) paraquat ion and 1.85g/l PP796, and had a density of 1.17g/ml at 20°C (ICI Agrochemicals, Yalding, Certificate of Analysis). The formulation reference number was YF8004A and sample reference RS180/B. The CTL reference number was Y00061/170/001.

2.2 Sample Handling

YF8004A was handled according to the COSHH safety regulations in force. Previous batches of YF8004A were shown to be stable for at least three months. The formulation was stored in the dark in a fume cupboard at room temperature and used within three months of preparation. The formulation was thoroughly shaken prior to use. The volume of formulation was calculated for each animal and dispensed using a positive displacement wide-ended pipette into gelatin capsules. Each individual dosing volume (calculated to ± 0.1ml) was checked by both the Study Director and analyst immediately prior to dosing. In all cases the neat concentrate formulation was used. All doses were calculated as mg paraquat ion per kilogram body weight and are also shown as ml of formulation per kilogram in Table 1.

2.3 Animals, Accommodation and Husbandry

Fifteen male beagle dogs, all of which were at least six months old, were obtained from the colony maintained at ICI Pharmaceuticals, Alderley Park, Cheshire, UK. They were acclimatised to the CTL environment for at least two months prior to the study. The animals were uniquely identified by ear number and had been vaccinated. Dogs were housed individually in indoor pens consisting of sleeping quarters (which have a heated floor) and a separate exercise area. The environment had an artificial day/night cycle of approximately 12 hours each and a nominal temperature of 20°C. The ventilation system ensured approximately twelve air changes per hour.

2.4 Randomisation

Dogs were housed in replicates (numbered 1, 2 and 3). Each replicate consisted of one animal from each group. Randomisation was designed to result in an even distribution of age and bodyweight across the groups. After randomisation each was given an experimental number. Thereafter dogs were identified by this experimental number which was displayed on the pen card together with the unique ear number, study number and Project Licence code.

2.5 Diet

Each dog received 400g of expanded LABORATORY DIET A (Special Diets Service Ltd., Stepfield, Essex, UK), between 9am and 12 noon daily. Food was witheld on the morning of dosing but offered 12 hours after dosing. Water was available to each dog throughout the study.

The diet and water used are not considered to contain any additional substances in sufficient concentration to have an influence on the outcome of the study. An analysis of each batch of LABORATORY DIET A for major constituents and contaminants was supplied by Special Diets Service Limited and retained by the Animal Breeding Unit.

2.6 Dosing

The YF8004A formulation was dosed at 8, 16, 32, 64 and 128mg paraquat ion/kg. The dose levels were staggered over several weeks to allow for full appraisal of clinical observations and blood paraquat levels. A group size of 3 animals was used for each dose level. Each dog was weighed on the afternoon prior to dosing for calculation of dose volume. Animals were dosed between 9 and 10am which is prior to the normal feeding time. The dosing details are summarised in Table 1. Food was witheld until 12 hours after dosing. The formulation was dispensed into gelatin capsules in a fume cupboard to prevent the animals from detecting the volatile stenching agent, present in the formulation. Each animal was given a single capsule which was passed directly down the oesophagus to avoid any contamination of the mouth. Animals were then allowed to move freely round the whole exercise area of the pen. Water was available ad libitum throughout the study.

2.7 Clinical Investigations

A daily record of food residues was made for all dogs throughout the study. Clinical examinations including cardiac and pulmonary auscultation were made by a veterinary surgeon prior to dosing and following dosing at the discretion of the study investigator. Following dosing of the animals, each dog was monitored continuously for the first 2 hours. Records were

made of all clinical signs. Particular care was made to record the time of first emesis for each animal together with the appropriate amount, colour and consistency of both emesis and faeces produced following dosing. Close observation of each animal was continued up to 12 hours and prior to each blood sampling time point.

Animals were monitored closely at least twice daily thereafter with particular attention to food residues or prolonged GI tract symtoms, such as diarrhoea which is caused by the purgative in the formulation. Care was also taken to identify any symptoms of pulmonary failure which is a common feature of paraquat toxicity. Animals which did not fully recover from the initial symptoms on the day of dosing were humanely terminated in accordance with the conditions of the Project Licence and advice of the study investigator and veterinary surgeon.

2.8 Blood Sampling

Samples of blood (5ml) were taken from the jugular vein just prior to dosing, then at 15 and 30 minutes, and at 1, 2, 4, 7, and 24 hours after dosing. The anticoagulant in the collection tube was lithium heparin.

Samples were placed on a roller to ensure thorough mixing. After centrifugation at 4°C, plasma was collected and frozen at -20°C prior to analysis. Plasma paraquat concentrations were measured in duplicate by radioimmunoassay according to SOP CT05-085. The remainder of the plasma sample was stored at -20°C for possible further analysis.

The concentration of paraquat in plasma was calculated in μg/ml for each time point. The total Area-Under-Curve (AUC) was calculated for 0-24 hours and expressed as μg.hr/ml for each animal. Mean values $\pm$ SEM were calculated for each group of three animals at each dose level.

3. RESULTS

3.1 Clinical Observations on Day 1

All animals were successfully dosed with the formulation. There was no immediate regurgitation of the gelatin capsule. As the dose level of formulation was increased from 8mg/kg to 64mg/kg there was a dose related reduction in the time taken to cause emesis due to the concomitant increase in the emetic dose. Thus, at the lowest dose level (8mg/kg) the mean time to emesis was 38.3 ± 3.5min, which fell progressively to 10.0 ± 1.7 min at 64mg/kg.

The times to emesis for each dose of paraquat are shown in Table 2.
The emetic effect was very reproducible for each group of animals. A more detailed assessment of the number of times of emesis plus the colour, consistency and amount of emesis was recorded for each dog and is shown in Appendix 1. In all cases the first emesis contained the vast majority of the blue coloured formulation. The appearance of the formulation had altered to a thicker gel like consistency. In some cases there were small capsule fragments present but none of the animals regurgitated an intact capsule. The frequency of emesis reduced markedly about one hour after the onset of this symptom. By two hours after dosing the incidence of emesis for all dose levels was low with no visual evidence of the formulation, ie. the dye present in the formulation, from about one hour after dosing.

Throughout the episode of emesis all the animals remained alert and mobile. At the end of the acute emesis phase, one or two animals, particularly at the higher dose levels were shivering (presumably as a consequence of reduced thermoregulation which is associated with repeated episodes of emesis). One animal 472 (128mg/kg) was quiet for 2-3 hours but was fully active later in the day. Animal 470 (128mg/kg), which was later terminated, showed no additional clinical signs in the first two hours after dosing. All the other animals, with the exception of dog 430, were alert and active for the remainder of the day of dosing. Water intake appeared to be normal.

A second important clinical observation was related to the purgative action of the formulation. All of the animals passed a stool between the time of dosing and two hours after dosing. The stools passed after dosing were softer than normal and this effect was most pronounced at doses above 16mg/kg. It was envisaged that formulation not removed by emesis would stimulate the production of a watery diarrhoea. This appears to be the case from these observations.

3.2 Clinical Observations on Day 2-14

There was no evidence of continued emesis beyond Day 1 for any animal. Food had been re-presented at 12 hours after dosing. The majority of the animals had ingested this food before 24 hours. On Day 2 there were significant food residues with the three dogs receiving the 128mg/kg dose. Dog 470 was quiet and slightly dehydrated and had a significant food residue at the end of Day 2. Dog 472 was fully active and feeding normally. Dog 430 which had been subdued after dosing was now more active but still not readily accepting food: it was not dehydrated. All the remaining animals were feeding normally by Day 2.

On Day 3, following assessment of the plasma paraquat profiles for each animal (see later in Section 3.3), all but two animals were clinically normal and feeding. Dog 430 had a low plasma paraquat profile and, apart from continual food residues for several days, was clinically normal. Dog 470 had the highest plasma paraquat concentrations in the first 2 hours after dosing (but not to a level which normally causes irreversible paraquat toxicity). However, following veterinary examination this animal was identified as having altered pulmonary function. This, together with persistent inappetance and, under the conditions of the Home Office Project Licence, led to the decision to humanely terminate this animal on Day 4. Dog 470 had not been previously dosed with paraquat and at post mortem it was confirmed that there were some pulmonary changes which had been caused by the 128mg/kg dose level. These changes were characteristic of paraquat toxicity and are usually irreversible. Dog 430 became fully appetant by Day 7 and this animal, plus the other 13 animals used in the study, remained healthy. The clinical observations (apart from emesis) are summarised in Appendix 2.

3.3 Plasma Paraquat Analysis

Figures 1-2 and Tables 2-4 show the mean plasma paraquat profile and individual animal data for each dose of YF8004A used. There was a dose related increase in both peak plasma paraquat concentration and area-under-curve (AUC) from the 8 to 128mg/kg paraquat dose levels. The magnitude of change is undoubtedly reduced by the fact that the time to emesis falls as the dose level of paraquat (and hence emetic), increases. This is substantiated by the fact that the time to peak plasma level falls from 120 min to 15 min between 16 and 128mg/kg doses. The plasma profile at each dose level shows that paraquat reaches the bloodstream rapidly after oral dosing. However, it is particularly apparent at the higher dose levels (Figure 2) that paraquat blood levels are relatively low due to a combination of reduced GI tract absorption and normal renal excretion. This results in very low plasma paraquat levels by 7 hours.

3.4 Assessment of the Median Lethal Dose

Although the determination of the median lethal dose (MLD) for YF8004A was not the primary objective of the study, the MLD for paraquat formulated as YF8004A is certainly greater than 128mg/kg in the adult male dog.

4. DISCUSSION

The present study has shown that YF8004A has an MLD above 128mg/kg in the dog. The absorption of paraquat from the GI tract was very low with YF8004A. This was directly as a result of the formulation additives which accelerate the removal of paraquat from its site of absorption in the small intestine (Heylings J R, 1991b, 1991c). This results in lower blood levels of paraquat.

Past experience has shown that blood levels of paraquat which are sustained above 3μg/ml at 7 hours prove invariably lethal. Detectable paraquat levels above 1μg/ml beyond 12 hours are additional indicators of likely paraquat toxicity. In all cases in this study, the clearance of paraquat from the blood, as evidenced from the plasma profile, was very effective.

The AUC for paraquat is a particularly useful prognostic parameter. In all previous oral dosing studies in dogs with paraquat, AUC values below 25μg.h/ml have been 100% survivable. Usually AUC values around 40μg.h/ml are approximately 50% survivable. AUC values above 50μg.h/ml are invariably lethal. Dog 470 gave the highest AUC in this study at 28μg.h/ml and would normally be in the survivable category. However, the animal also had the highest peak plasma value (7.8μg/ml at 15 min) and was the last to undergo emesis in its group (albeit by only 3 minutes). Furthermore, it had the highest plasma value at 7 hours. A combination of these factors undoubtedly resulted in paraquat lung damage.

An important observation in this study centres on the dose and time to first emesis. Formulations containing emetic have not caused emesis earlier than 6-8 min after dosing since the gelatin capsule has first of all to disintigrate in the stomach. Then, following its absorption, the emetic agent has to achieve a high enough plasma concentration to trigger the vomit centre in the brain. At the low dose of 8mg/kg paraquat, emesis is delayed until almost 40 minutes. This only reduces to 25 minutes at 16mg/kg. Thus, at low paraquat doses, emesis, even though it is delayed, is sufficient to prevent paraquat toxicity. As the paraquat dose, and hence dose volume is increased at 32mg/kg, the animal receives a more effective emetic dose. At very high paraquat doses (64-128mg/kg) emesis did not occur any earlier than at the 32mg/kg dose. However, the animal is now receiving therapeutically effective dose of other formulation additives which are counteracting the increased paraquat intake. As a result the dog can tolerate much higher doses. It has therefore been possible to demonstrate only a small increase in plasma paraquat AUC between 32-128mg/kg paraquat with the YF8004A formulation.

5. CONCLUSION

The paraquat formulation YF8004A has been tested in the adult male beagle dog. Following a single oral dose of this 200g/l paraquat concentrate over the dose range 8-128mg/kg, the median lethal dose (MLD) of this formulation was above 128mg/kg. Therefore formulation YF8004A has an MLD more than ten times that the 200g/l paraquat concentrate GRAMOXONE in the adult male dog.

6. REFERENCES

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TABLE 1

DOSING OF YF8004A

Animal No.	Body Wt kg	Paraquat mg/kg	Dose Vol ml/kg
447	15.5	8	0.04
449	17.4	8	0.04
451	16.2	8	0.04
452	17.0	16	0.08
453	17.2	16	0.08
462	14.1	16	0.08
459	17.8	32	0.16
463	17.2	32	0.16
464	15.9	32	0.16
430	22.5	64	0.32
431	21.1	64	0.32
439	18.0	64	0.32
470	17.3	128	0.64
471	18.3	128	0.64
472	15.8	128	0.64

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TABLE 2

MEAN VALUES OF PARAQUAT IN PLASMA, AUC VALUES AND TIMES TO EMESIS

Paraquat dose mg/kg	Peak plasma paraquat μg/ml (±SEM)	Time to peak min	Time to emesis min (±SEM)	Plasma paraquat AUC μg.h/ml (±SEM)
8	3.3 ± 0.21	60	38.3 ± 3.5	7.9 ± 1.3
16	3.3 ± 0.09	120	24.7 ± 1.5	10.1 ± 0.6
32	4.9 ± 0.57	60	13.3 ± 3.4	21.0 ± 3.6
64	4.5 ± 0.47	30	10.0 ± 1.7	16.4 ± 3.3
128	6.1 ± 0.85	15	12.3 ± 1.5	25.7 ± 2.0

(n=3 at each dose level)

PARAQUAT: ABSORPTION AND ACUTE ORAL TOXICITY OF YF8004A IN THE DOG

TABLE 3

INDIVIDUAL PLASMA PARAQUAT CONCENTRATIONS AND TIMES TO EMESIS (8-32mg/kg)

Plasma Paraquat (ug/ml)

Magnoxone YF8004A large batch	time (Hrs) Dog	0	0.25	0.5	1	2	4	7	12	24	Time to emesis
	447	0	0.000	2.674	3.680	2.964	0.380	0.000	0.000	0.000	33.000
8mg/Kg	449	0	0.000	0.000	3.212	3.380	0.705	0.000	0.000	0.000	45.000
	451	0	0.000	0.361	2.942	2.048	0.000	0.000	0.000	0.000	37.000
MEAN		0	0.000	1.012	3.278	2.797	0.362	0.000	0.000	0.000	38.333
SD			0.000	1.451	0.374	0.681	0.353	0.000	0.000	0.000	6.110
SE			0.000	0.839	0.216	0.394	0.204	0.000	0.000	0.000	3.532
Magnoxone YF8004A large batch											
	452		0.682	1.841	3.599	3.457	0.883	0.000	0.000	0.000	27.000
16mg/Kg	453		4.174	3.263	2.660	3.272	0.122	0.000	0.000	0.000	25.000
	462		0.000	0.000	0.000	3.180	2.282	0.000	0.000	0.000	22.000
MEAN		0	1.619	1.701	2.086	3.303	1.096	0.000	0.000	0.000	24.667
SD			2.239	1.636	1.867	0.141	1.095	0.000	0.000	0.000	2.517
SE			1.294	0.946	1.079	0.081	0.633	0.000	0.000	0.000	1.455
Magnoxone YF8004A large batch											
	459		4.471	5.638	5.973	3.135	0.142	0.409	0.034	0.000	9.000
32mg/Kg	463		2.306	3.359	4.044	3.351	1.316	1.404	0.032	0.601	20.000
	464		3.540	4.095	4.711	4.735	1.475	1.039	0.721	0.000	11.000
MEAN		0	3.439	4.364	4.910	3.740	0.978	0.951	0.263	0.200	13.333
SD			1.086	1.163	0.980	0.868	0.728	0.504	0.397	0.347	5.859
SE			0.628	0.672	0.566	0.502	0.421	0.291	0.230	0.201	3.387

PARAQUAT: ABSORPTION AND ACUTE ORAL TOXICITY OF YF8004A IN THE DOG

TABLE 4

INDIVIDUAL PLASMA PARAQUAT CONCENTRATIONS AND TIMES TO EMESIS (64-128mg/kg)

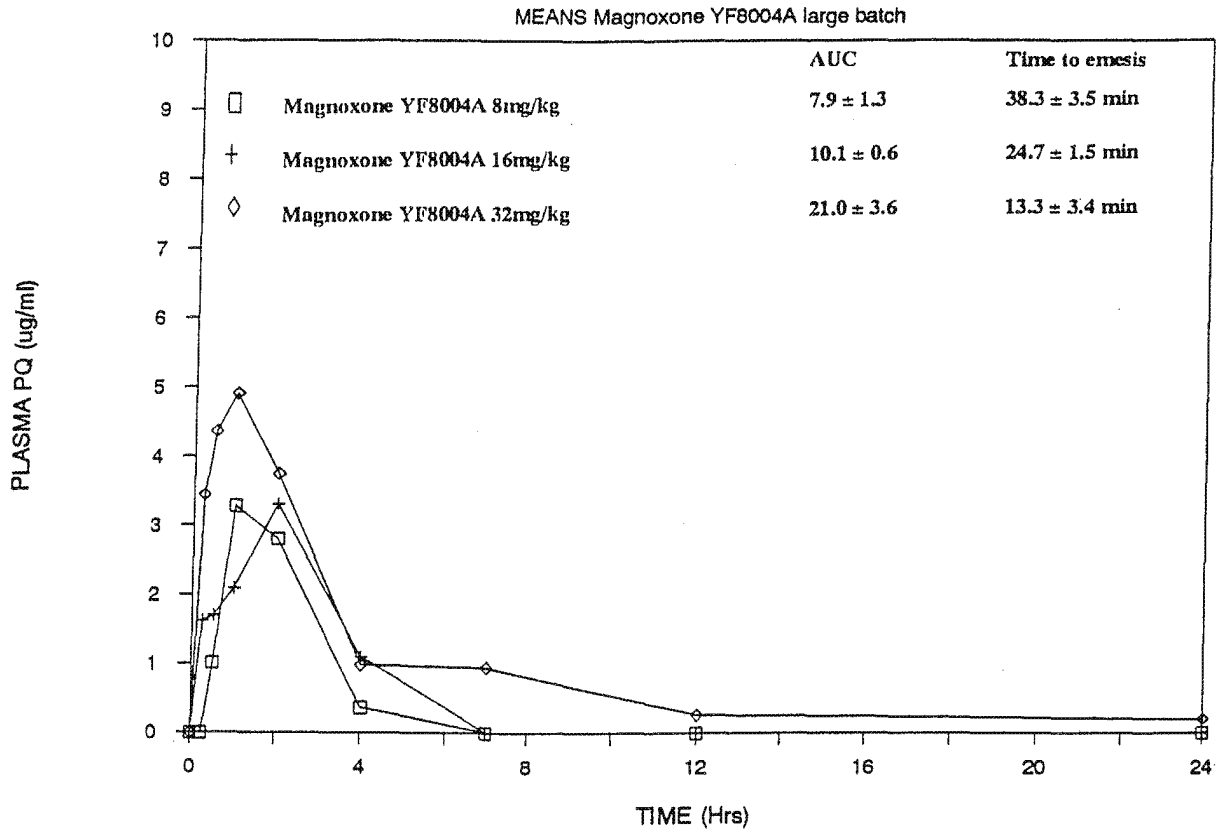
Plasma Paraquat (ug/ml)

Magnoxone YF8004A large batch	time (Hrs) Dog	0	0.25	0.5	1	2	4	7	12	24	Time to emesis
	430	0	5.981	5.197	4.694	5.034	1.639	0.000	0.000	0.000	7.000
64mg/Kg	431	0	3.473	3.607	2.965	3.180	0.551	0.000	0.000	0.000	13.000
	439	0	5.035	4.638	4.713	2.969	0.561	2.385	0.000	0.000	10.000
MEAN		0	4.830	4.481	4.124	3.728	0.917	0.795	0.000	0.000	10.000
SD			1.266	0.807	1.004	1.136	0.626	1.377	0.000	0.000	3.000
SE			0.732	0.466	0.580	0.657	0.362	0.796	0.000	0.000	1.734
Magnoxone YF8004A large batch											
	470		7.814	6.894	6.258	4.476	3.149	1.428	0.000	0.000	15.000
128mg/Kg	471		5.524	5.051	5.979	5.340	2.817	1.194	0.000	0.000	10.000
	472		5.058	5.091	5.119	4.521	1.292	1.353	0.000	0.000	12.000
MEAN		0	6.132	5.678	5.785	4.779	2.419	1.325	0.000	0.000	12.333
SD			1.475	1.053	0.594	0.486	0.990	0.119	0.000	0.000	2.517
SE			0.853	0.608	0.343	0.281	0.573	0.069	0.000	0.000	1.455

PARAQUAT: ABSORPTION AND ACUTE ORAL TOXICITY OF YF8004A IN THE DOG

FIGURE 1

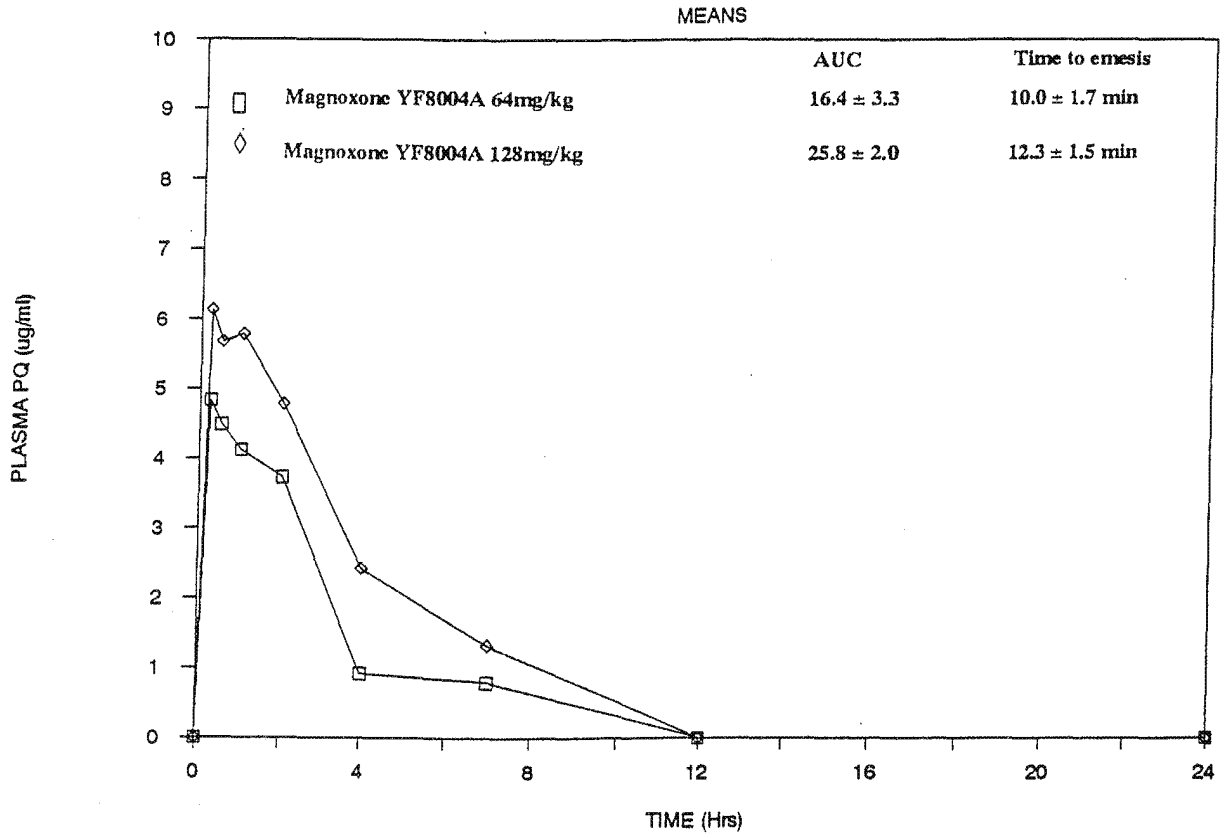
MEAN PLASMA PROFILES (8-32mg/ml/kg)



PARAQUAT: ABSORPTION AND ACUTE ORAL TOXICITY OF YF8004A IN THE DOG

FIGURE 2

MEAN PLASMA PROFILES (64-128mg/kg)



PARAQUAT: ABSORPTION AND ACUTE ORAL TOXICITY OF YF8004A IN THE DOG

APPENDIX 1

INDIVIDUAL CLINICAL OBSERVATIONS: EMESIS

Dog	Paraquat Dose mg/kg	Emesis times min	Emesis volume	Emesis colour	Emesis consistency
447	8	33	Medium	Green/Blue	Frothy
449	8	45	Small	Pale green	Frothy
451	8	37	Medium	Pale green	Frothy
		65	Medium	Clear	Watery
452	16	27	Large	Green	Gel
		29	Large	Green	Gel
453	16	25	Large	Green	Gel
		53	Large	Green/Yellow	Gel
462	16	22	Medium	Green	Gel
459	32	9	Large	Green	Gel
		25	Medium	Green	Gel
		39	Small	Green	Gel
		45	Small	White	Frothy
		62	Small	White	Frothy
463	32	20	Large	Green	Gel
		33	Medium	White	Frothy
464	32	11	Large	Green	Gel

PARAQUAT: ABSORPTION AND ACUTE ORAL TOXICITY OF YF8004A IN THE DOG

APPENDIX 1 - continued

INDIVIDUAL CLINICAL OBSERVATIONS: EMESIS

Dog	Paraquat Dose mg/kg	Emesis times min	Emesis volume	Emesis colour	Emesis consistency
430	64	7	Medium	Green/blue	Gel
		9	Medium	Green/blue	Gel
		18	Medium	White	Frothy
		33	Small	White	Frothy
		41	Small	White	Frothy
		42	Small	White	Frothy
		58	Small	White	Frothy
		62	Small	White	Frothy
431	64	13	Medium	Green/blue	Gel
		40	Medium	White	Frothy
439	64	10	Medium	Green/blue	Gel
		15	Large	Green	Gel
		19	Medium	White	Frothy
		39	Medium	White	Frothy
		66	Small	White	Frothy

PARAQUAT: ABSORPTION AND ACUTE ORAL TOXICITY OF YF8004A IN THE DOG

APPENDIX 1 - continued

INDIVIDUAL CLINICAL OBSERVATIONS: EMESIS

Dog	Paraquat Dose mg/kg	Emesis times min	Emesis volume	Emesis colour	Emesis consistency
470	128	15	Large	Blue	Gel
		17	Small	Blue/green	Gel
		20	Medium	Blue	Frothy
		27	Medium	White	Frothy
		35	Small	White	Frothy
		44	Medium	Blue	Frothy/Gel
		60	Small	White	Frothy
		67	Small	White	Frothy
471	128	10	Large	Blue	Gel
		12	Medium	Blue/Green	Gel
		21	Medium	Yellow	Frothy
		36	Medium	Yellow	Frothy
		48	Medium	Yellow	Frothy
		53	Small	Clear	Clear
472	128	12	Large	Blue/Green	Gel
		25	Medium	Blue	Frothy
		46	Small	White	Frothy
		53	Small	White	Frothy
		61	Small	White	Frothy

PARAQUAT: ABSORPTION AND ACUTE ORAL TOXICITY OF YF8004A IN THE DOG

APPENDIX 2

INDIVIDUAL CLINICAL OBSERVATIONS: GENERAL

Dog	Paraquat Dose mg/kg	Observations (apart from emesis)
447	8	No Abnormalities Detected
449	8	No Abnormalities Detected
451	8	No Abnormalities Detected
452	16	No Abnormalities Detected
453	16	No Abnormalities Detected
462	16	No abnormalities Detected
459	32	Loose stool with greenish tinge at 60 minutes
463	32	Soft stool at 13 min
464	32	Soft stool at 11 min
430	64	Fluid faeces at 12 min Subdued, shivering 30 min - 2 hours Quiet 2 hours - 12 hours Food residues but normal, Day 2 - Day 4
431	64	No Abnormalities Detected
439	64	No Abnormalities Detected
470	128	Diarrhoea at 58 min Subdued 4hr - 24hr Slightly dehydrated Day 2 Food residues Day 2 - Day 4 Lung sounds Day 4 Terminated Day 4
471	128	No Abnormalities Detected
472	128	Subdued 2-4hrs