PARAQUAT MONITORING SURVEY AND INTRODUCTION OF GRAMOXONE AWT (Inteon ®) IN SRI LANKA

CTL Review Meeting 15 April 2005

Agenda

1.	Introduction and aims of meeting	MFW	15 mins
2.	Formulation - manufacturing issues - impact of formulation issues on safety - way forward - messages for SAP	MJLC	30 min
3.	Progress of Survey - descriptive study results - Gramoxone v Inteon cases - projection for completion of data for descriptive study - issues for discussion with SAP	JT/DJB/ BHW	90 min
4.	Confirmation of messages and issues for SAP	All	15 min

Aims of CTL Meeting

Consider impact of formulation issues on the survey

- On the basis of current knowledge, should we continue and/or extend the survey

Review and discuss results from descriptive study

- Does the analysed data from the comparative study indicate we have the right parameters to analyse and interpret the descriptive study?
- Should we change/modify any parameters?
- Has the prolonged phase in of Inteon had any impact on the survey?

Messages for the SAP

- Consider publication strategy implications

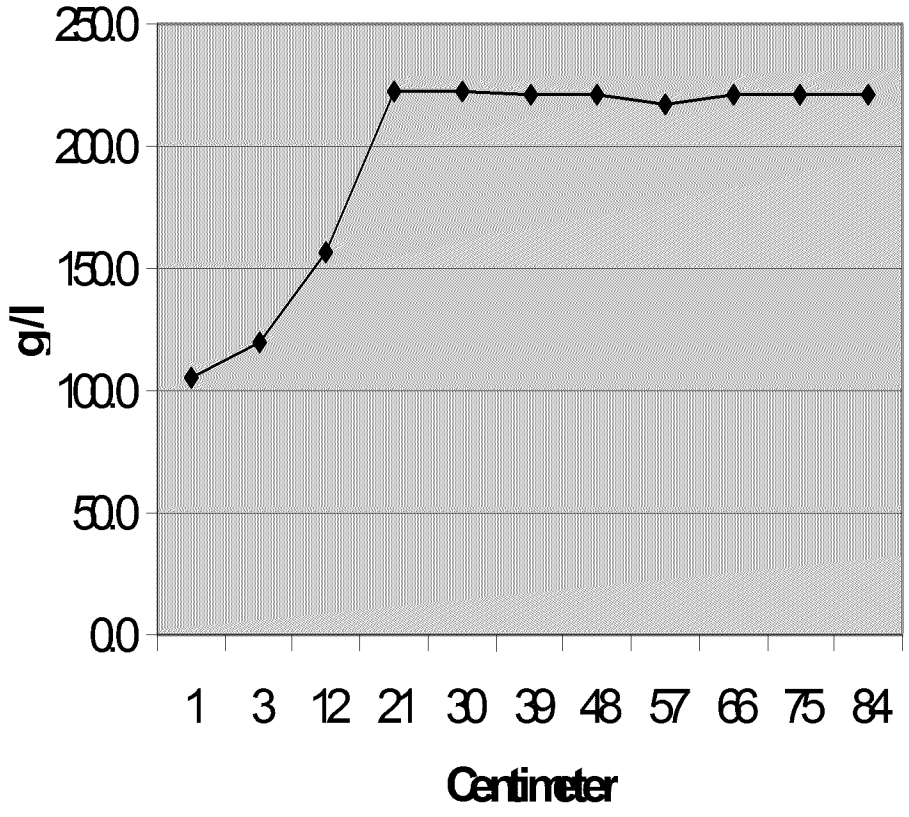
Observational monitoring review
15th April 2005

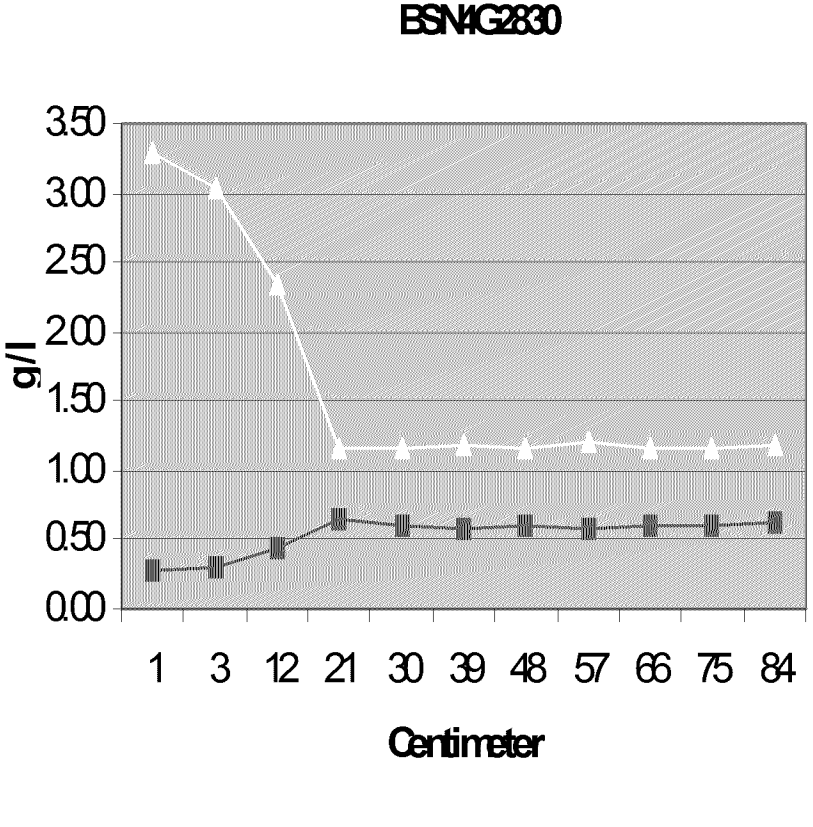
Mike Clapp

1. Knowledge of separation issue in A14380A

- Characterisation of separated formulation – in drum or pack
  - In drum profile
  - Different components
  - Separation with time
- Characterisation of separated formulation – pour off data
  - Pour off data across batches
  - Interpretation of pour off data (drum,pack and pour off analysis)
  - Ease of re-mixing
  - Analysis of bottles returned from SL – 250ml packs only
- Summary of knowledge of material released to Sri Lanka

1. Gradient of concentration of Paraquat, diquat and emetic in a drum





Top

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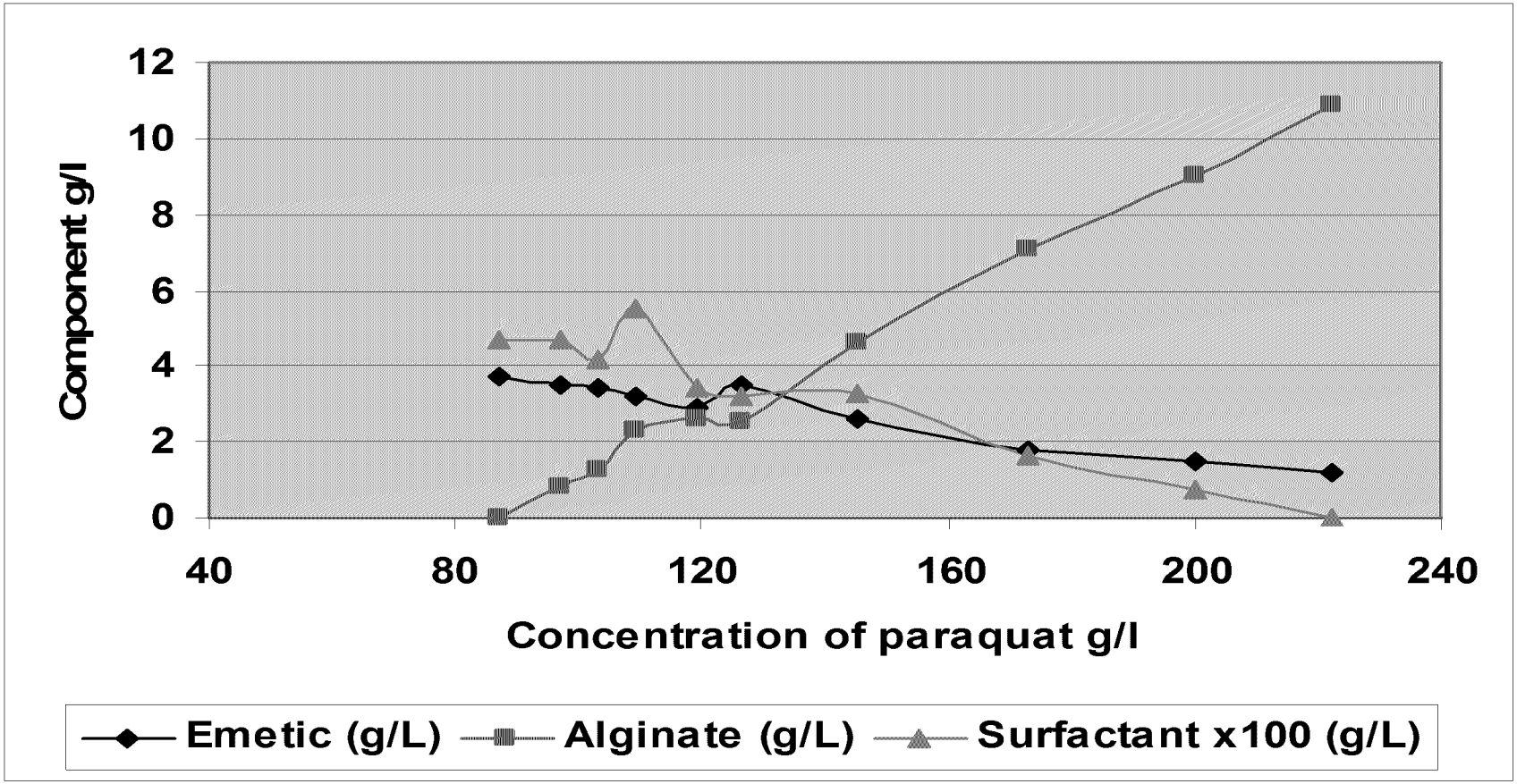
Relationship between different components



The emetic moves with the surfactant

Alginate generally moves with paraquat

But is depleted faster than paraquat

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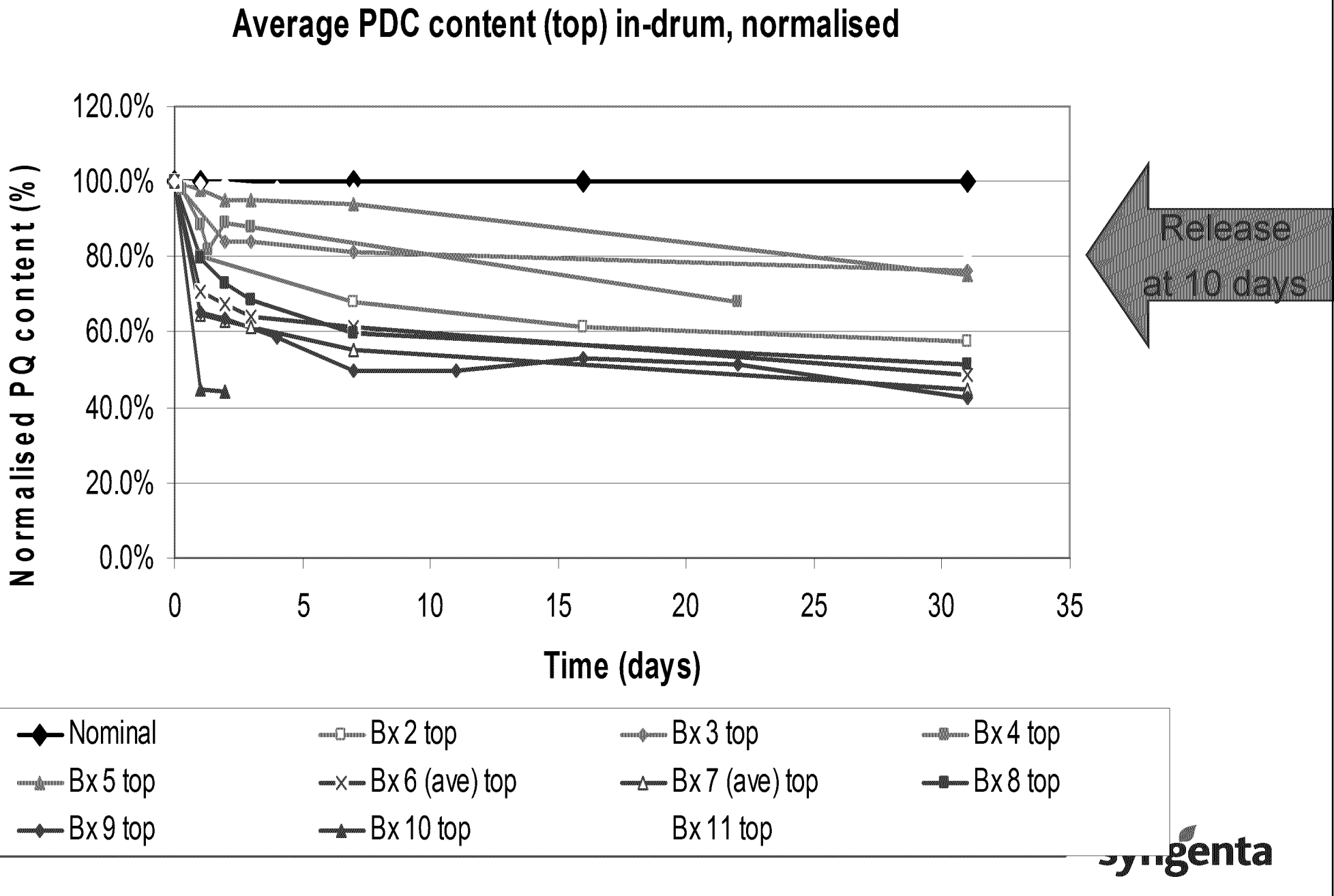
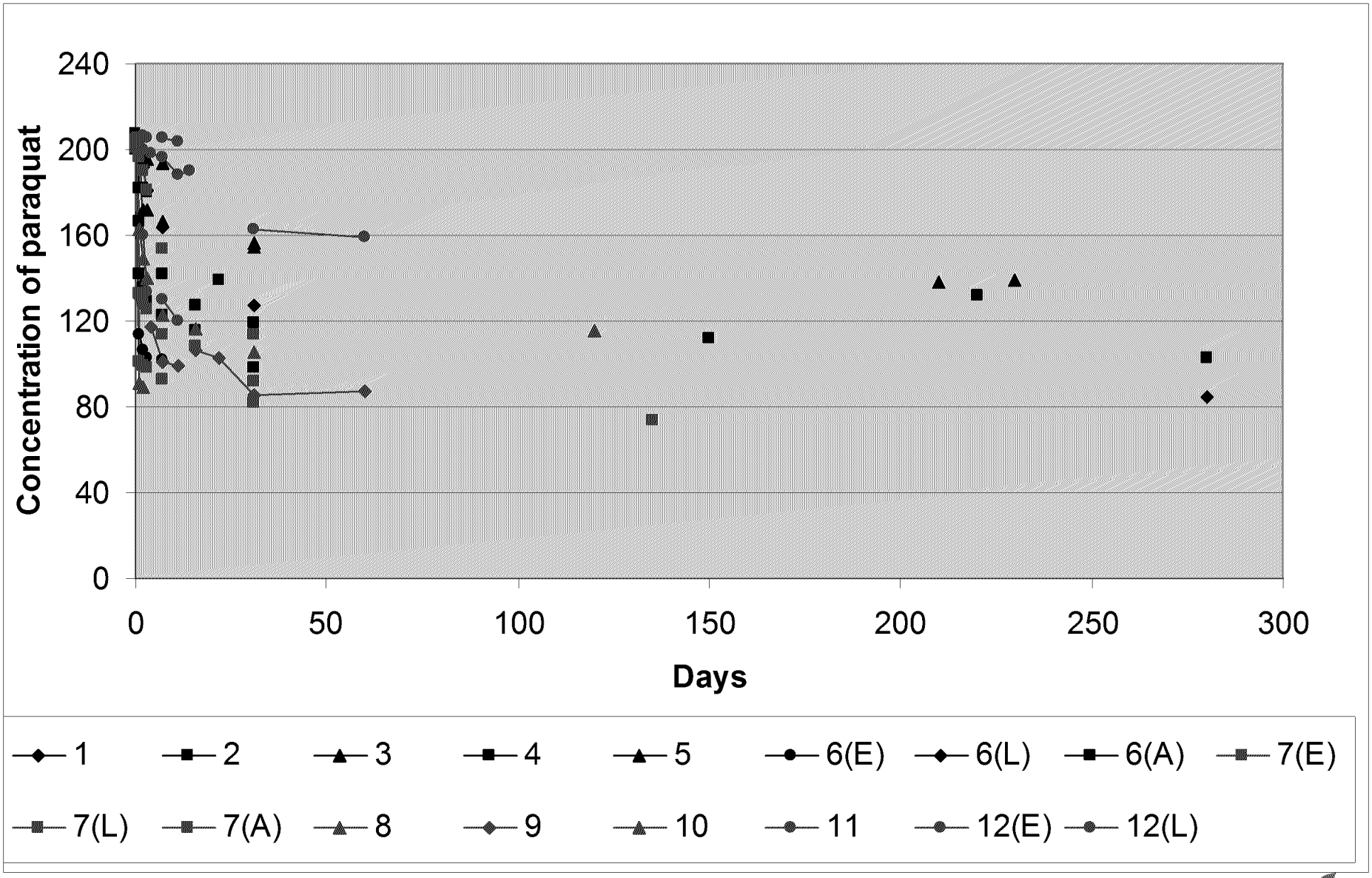
1. Top of Drum Analysis: up to 30 days after manufacture (green, yellow released, red rejected).



1. Effect of longer term storage on paraquat concentration at the top of 200l drum



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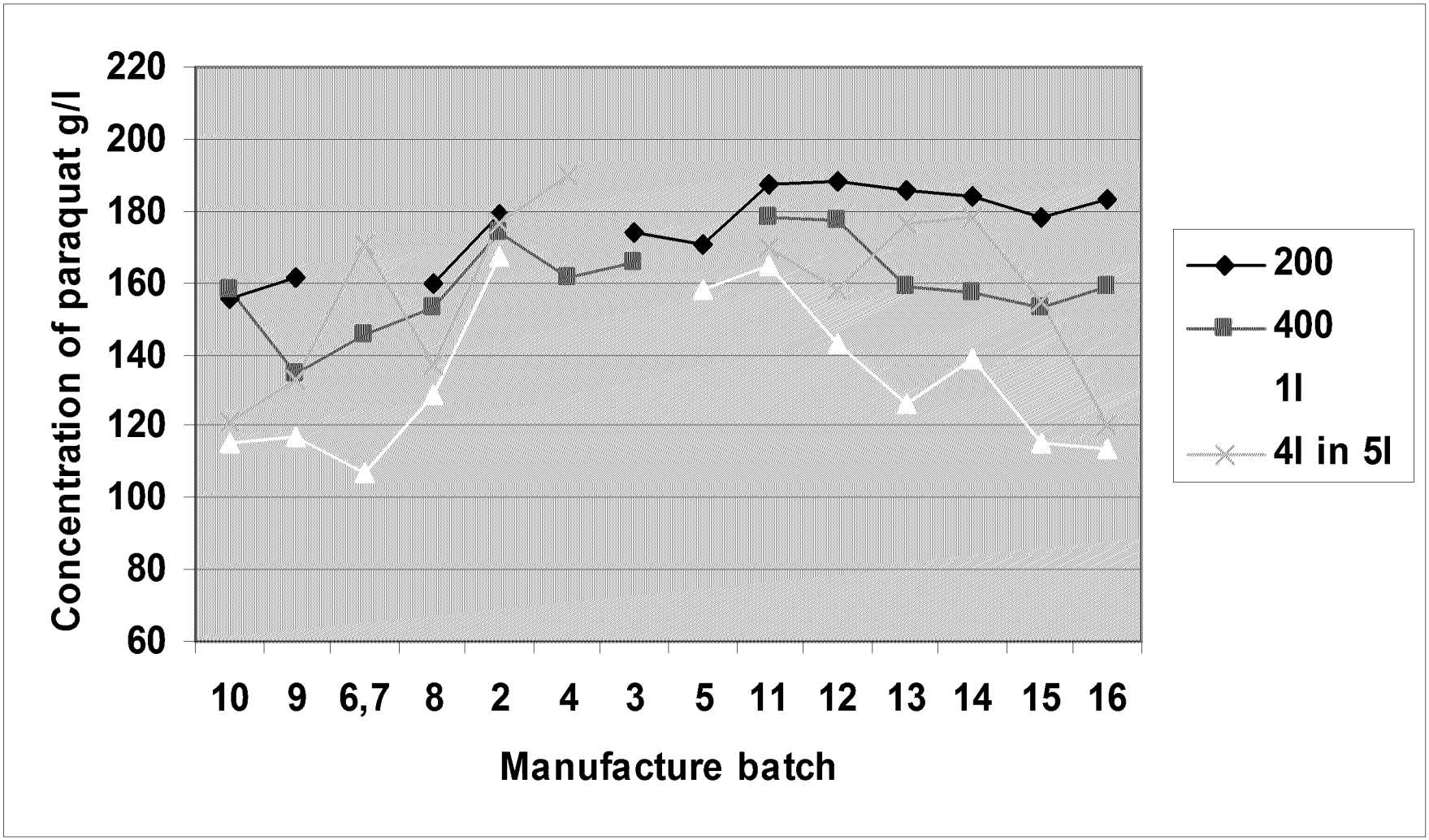
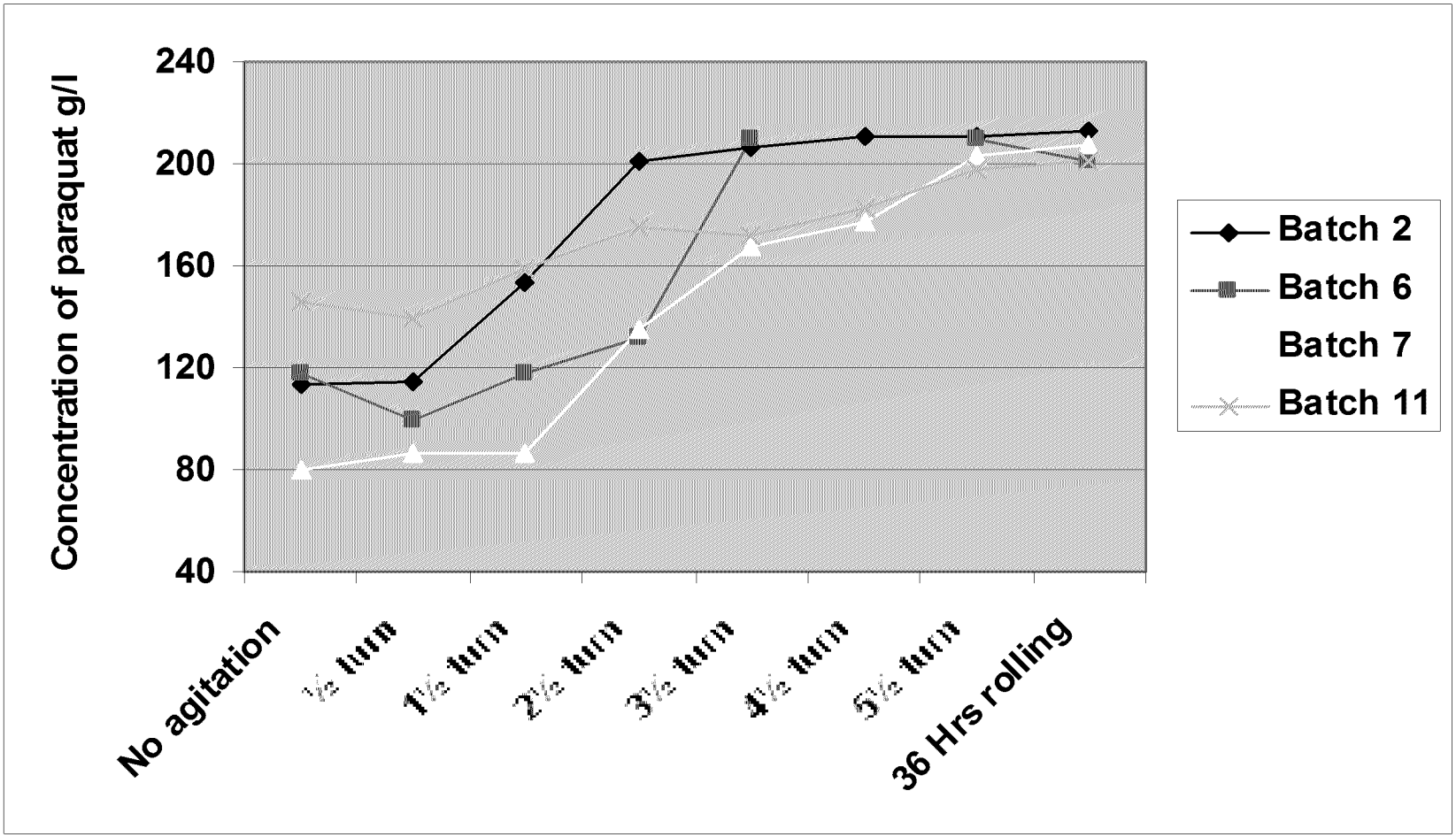
1. Effect of container size on paraquat concentration poured off the top of SL typical pack



Conclusion from drum, pack and pour off analysis

- Incomplete plan to follow for 8-12months – more data to follow
- Batches separate at different rates
- Separation appears independent of pack size
- Pour off data very different to top material:
  - Mixing on pouring – always reflecting less separation
  - More influenced by pack size – smaller pack size more mixing, but appears to be more mixing in 4l in 5l pack than in 1l pack.

1. Ease of remixing four different manufacture batches



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1. Analysis of paraquat concentration (g/l- pour off) in 250ml pack from material released, returned or rejected - at 10days.

	Mean	Range
Released	180.7	170.9 - 188.4
Returned	173.7	162.7 - 189.0
Rejected	158.9	155.8 - 161.1

No significant difference in pour off from material returned from Sri Lanka in 250ml pack at 10 days

1. Summary of knowledge of material supplied to Sri Lanka

1. **Formulation will separate in all packs with time**
2. **Fastest separating batches have not been supplied**
3. **Have not been able to control separation in manufactured batches by service testing**
4. **Formulation ingested from small packs (250 and 500ml) without agitation will be closer to homogenous formulation. (Which is the most frequently used pack?)**
5. **Three to five inversions will remix the formulation**
6. **The likelihood of ingesting formulation without agitation is considered low.**

Sales of AWT from Sept 04 to Dec 2004

Pack Size	# Packs	Litres sold
200ml	54,000	10,800
400 ml	170,000	68,000
1 litre	84,500	84,500
Total		162,500

2. How Safe is a separated formulation?

1. Range of formulations considered
2. Assessment in the rabbit
3. Assessment in the dog

2. Phase separation of A14380A samples available for testing

Paraquat (g/L)	Emetic (g/L)	Alginate (g/L)	Surfactant x100 (g/L)
222	1.18	10.86	0
200	1.5	9	0.72
173	1.8	7.1	1.66
145	2.6	4.6	3.29
126.2	3.51	2.52	3.18
119	2.9	2.58	3.4
109	3.2	2.3	5.54
103	3.4	1.3	4.16
97	3.5	0.83	4.69
87	3.7	0.03	4.71

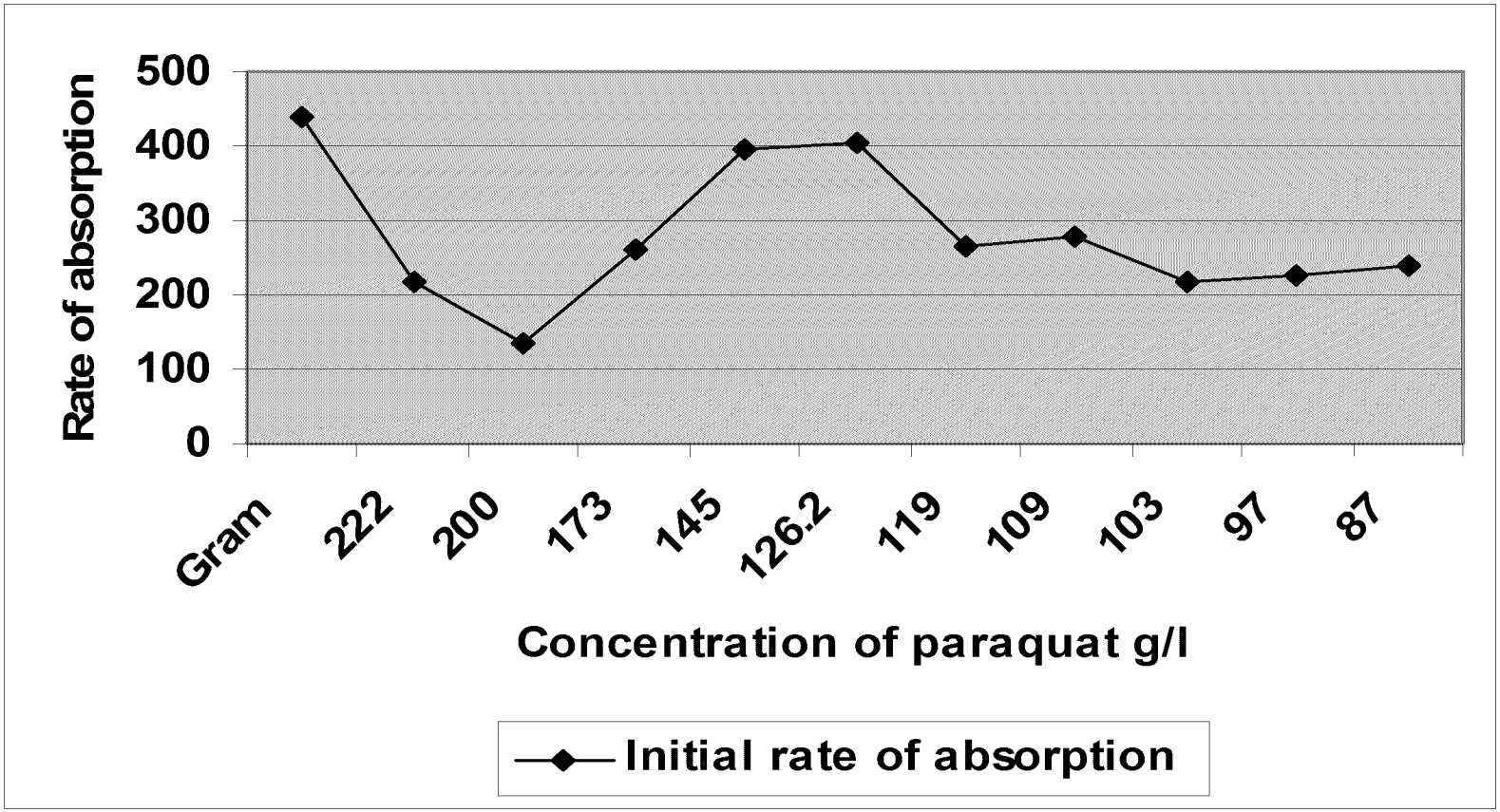
All formulations dosed to rabbit at 40mg paraquat ion/kg.

Plasma profiles determined 4h period after dosing

Initial rate of paraquat absorption, over the first 15 minutes, was calculated.

Estimate

2. Phase separation of A14380A : Comparison of initial rate of absorption proportional to dose volume in the rabbit



Based on the rabbit toxicokinetic studies, 126.2g paraquat ion/l was selected for testing in the dog at equi-volume and equi-dose To a sub-lethal dose of Gramoxone 8mg/kg.

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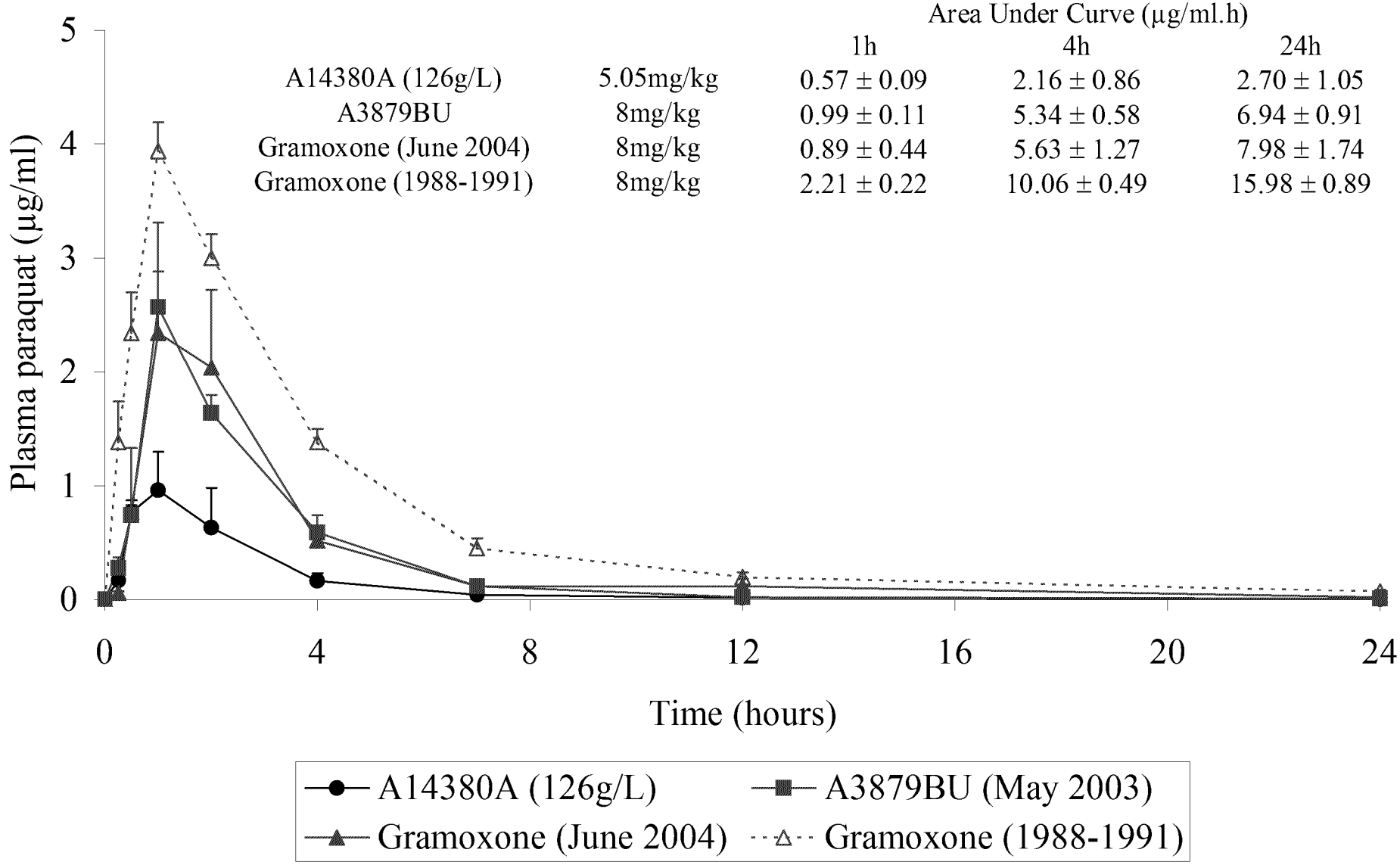
2. Phase separation of A14380A - Dog Studies
Animals dosed at 0.04ml formulation/kg

		Area Under Curve (µg/ml.h)		
		1h	4h	24h
A14380A (126g/L)	5.05mg/kg	0.57 ± 0.09	2.16 ± 0.86	2.70 ± 1.05
A3879BU	8mg/kg	0.99 ± 0.11	5.34 ± 0.58	6.94 ± 0.91
Gramoxone (June 2004)	8mg/kg	0.89 ± 0.44	5.63 ± 1.27	7.98 ± 1.74
Gramoxone (1988-1991)	8mg/kg	2.21 ± 0.22	10.06 ± 0.49	15.98 ± 0.89



Times to emesis: A14380A (126g/L) = 36.3min, A3879BU = 51.3min

2. Summary of safening

- The aim of these experiments was to demonstrate that separated formulation is not more toxic than Gramoxone in the dog.
- The separated formulation (126g/l) which showed the greatest absorption of paraquat per dose volume in the rabbit has been assessed in the dog
- On an equi-volume basis it showed earlier emesis resulting in less absorption of paraquat than Gramoxone
- These dogs will be given the next dose on 19th April

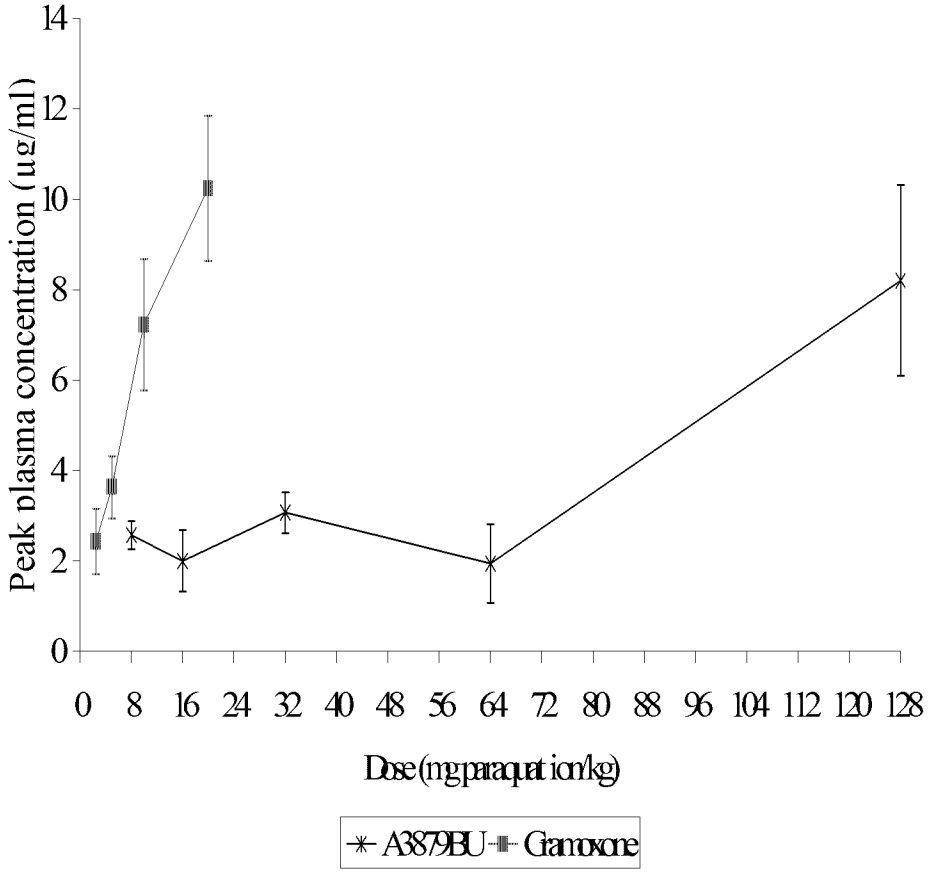
- Preliminary conclusion "At a sub lethal dose of ~44mg formulation/kg in the dog, ingestion of a separated formulation (126g paraquat/l) showed less paraquat absorption than the equivalent dose of Gramoxone."

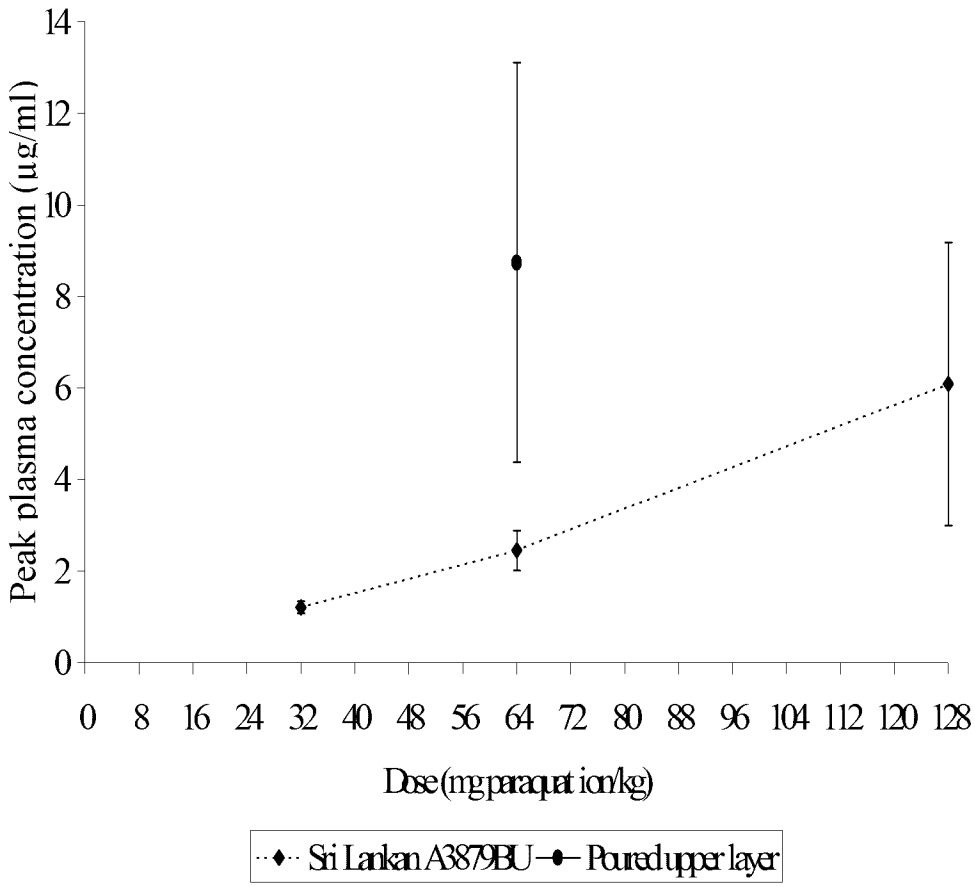
3. Future formulation supply

- In the short term no change – continue to supply material and monitor separation in drums and pour off in pack at 10days.
- A3879BU (bikini) could be considered for introduction late 2005, but no efficacy data and predicted poorer efficacy. Registration based on current product.
- Work ongoing to develop replacement 200g/l formulation (Phoenix) and expect to evaluate lead 4Q'05/1Q'06, if no clear lead back up will be 'stripped 100g/l' (9g/l alginate, 1.5g/l emetic, lower levels alerting agent). Submission 2Q'06.

- If formulation changed then inclusion of alternative biomarker needs to be considered – recommend DEP.

2. Kinetic profile of Gramoxone and A14380A in the dog (peak and 24h AUC show similar patterns)





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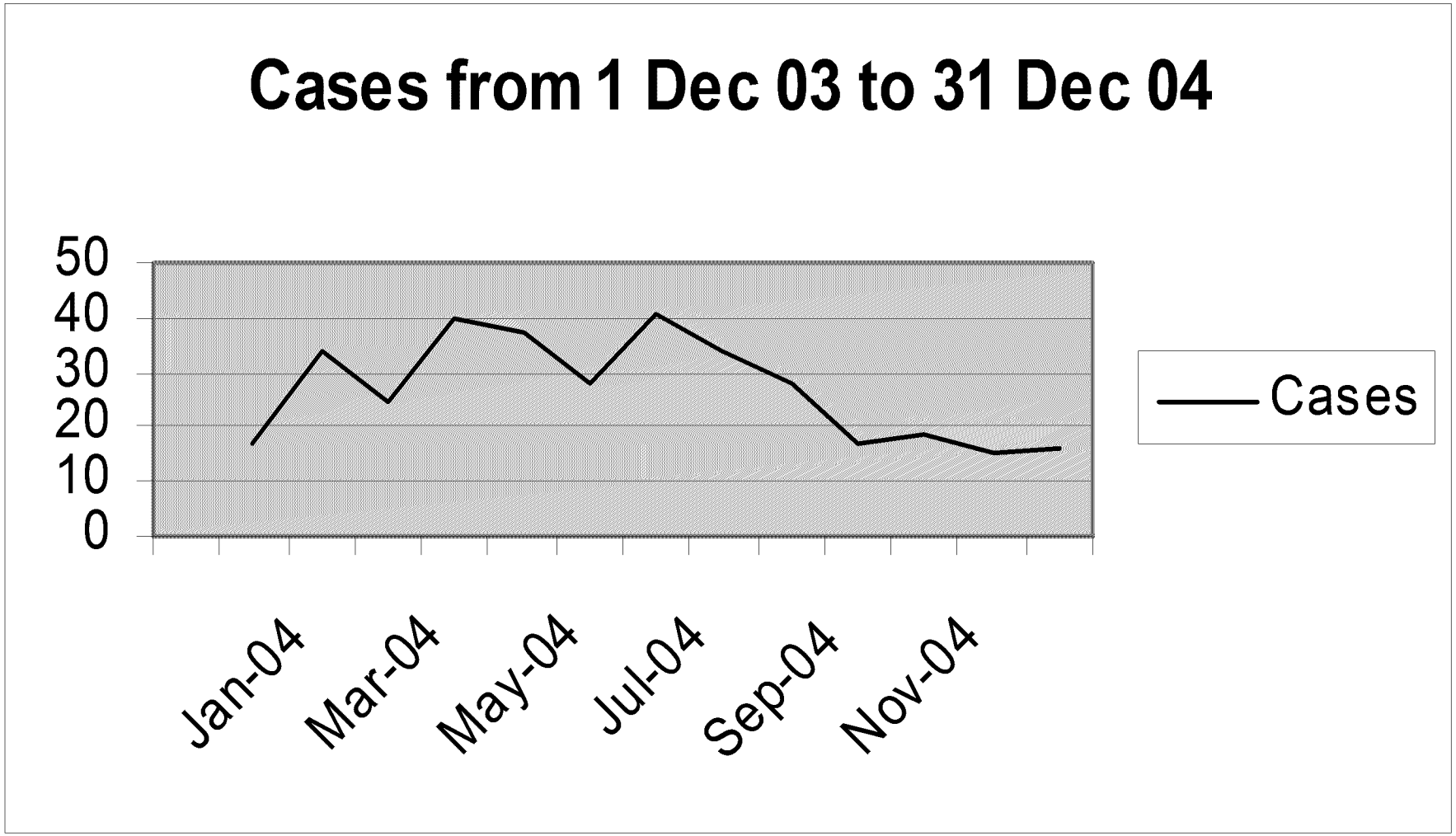
Cases based on Admission Date



Total cases = 341

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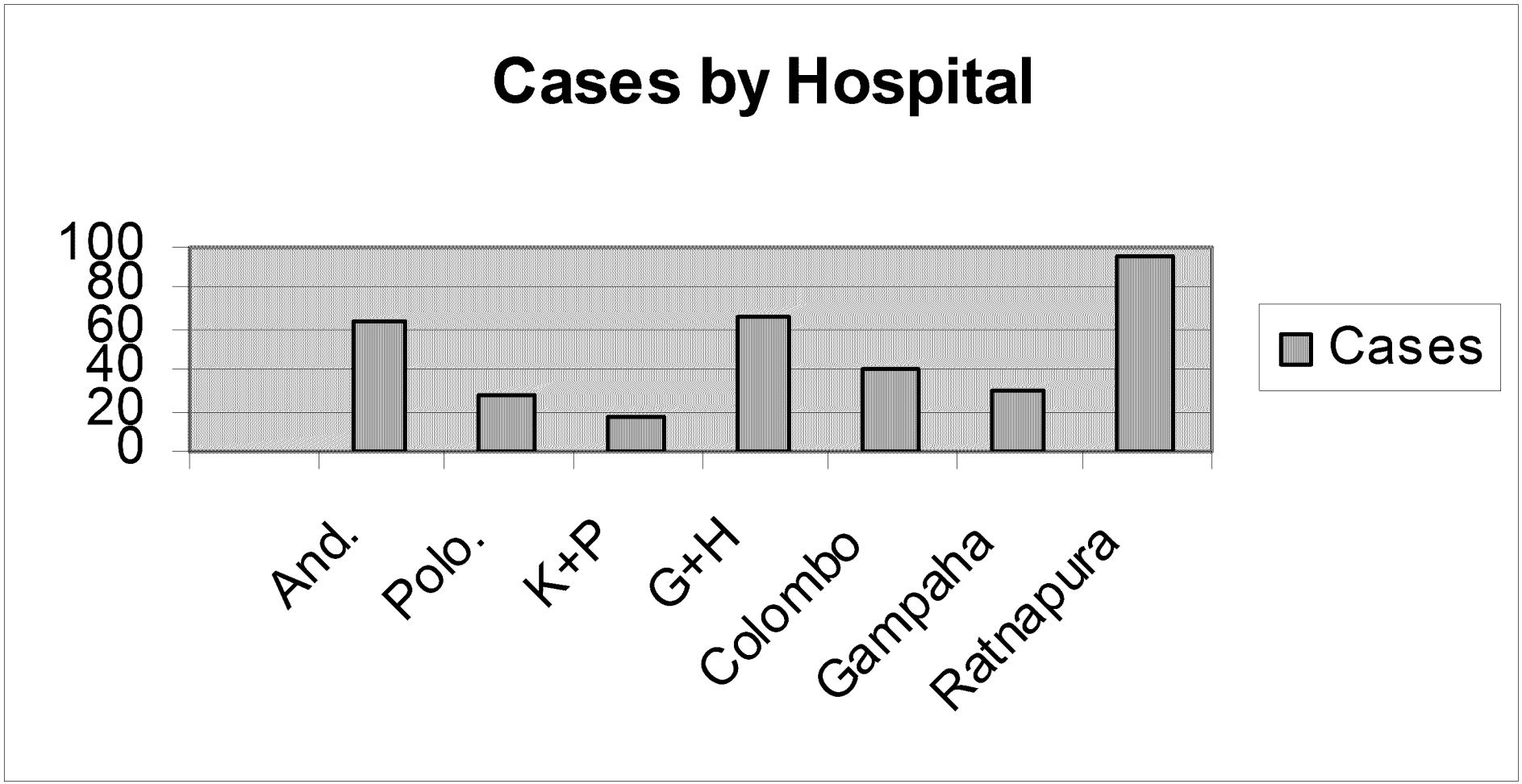
Cases 1 Dec 03 to 31 Dec 04



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Patient Outcome
1 Dec 03 to 31 Dec 04

	And	Polo	K+P	G+H	Col	Gamp	Rat	TOTAL
Died in Hospital	39	11	14	33	29	18	70	194
Died after discharge	1	2	-	11	-	1	3	18
Alive 3 mth after discharge	15	6	-	18	7	5	14	65
Unknown/not found	3	8	4	7	3	7	6	38
Too early	6	2	-	-	-	1	3	12

Characterise survival and relationship with self estimated measure of amount ingested

Identify other factors influencing survival e.g. emesis parameters, absorbent, co-ingestion of alcohol, plasma concentration, sex and age, treatment, absorbent use, body weight, time to start of treatment

Identify whether proportional hazards assumption is met

Compare logistic regression models for 3-month survival with proportional hazards approach

2. Subjects and vital status (13/4/05)

	Andrad May 02 – Dec 04	Polo June 02 – Oct 04	K & P Feb 04 – Nov 04	Galle pilot June 03 – Sep 03	Galle & Hamban Nov 04	Rat Col Gam Dec 03 onwards	Total
Original databases	**137**	**75**	**23**	**25**	**73**	**173**	**506**
Excluded – insufficient data	4	13	5	0	0	8	30
Excluded – exposure before 1/12/03	69	40	0	25	7	0	141
Excluded – duplicated record for patient ref no 87390	-	-	-	-	1	-	1
Non-oral exposure	1	1	0	-	4	8	14
Excluded -exposed after 1/9/04 & not confirmed –ve to Dq	18	0	5	-	3	4	30
Excluded - Lumbini says did not take Pq	-	3	-	-	-	5	8
Included in analysis	**45**	**18**	**13**	**0**	**56**	**150**	**282**
Vital status at 3 months							
Dead	29	12	9	0	40	116	204
Alive	14	3	-	-	8	10	37 [1]
Unknown status	2	3	4	-	8	24	41

[1] Includes two subjects who were alive at 3 months, but died later (one subject ingested 5-10 mls and the other ingested 15-30mls).

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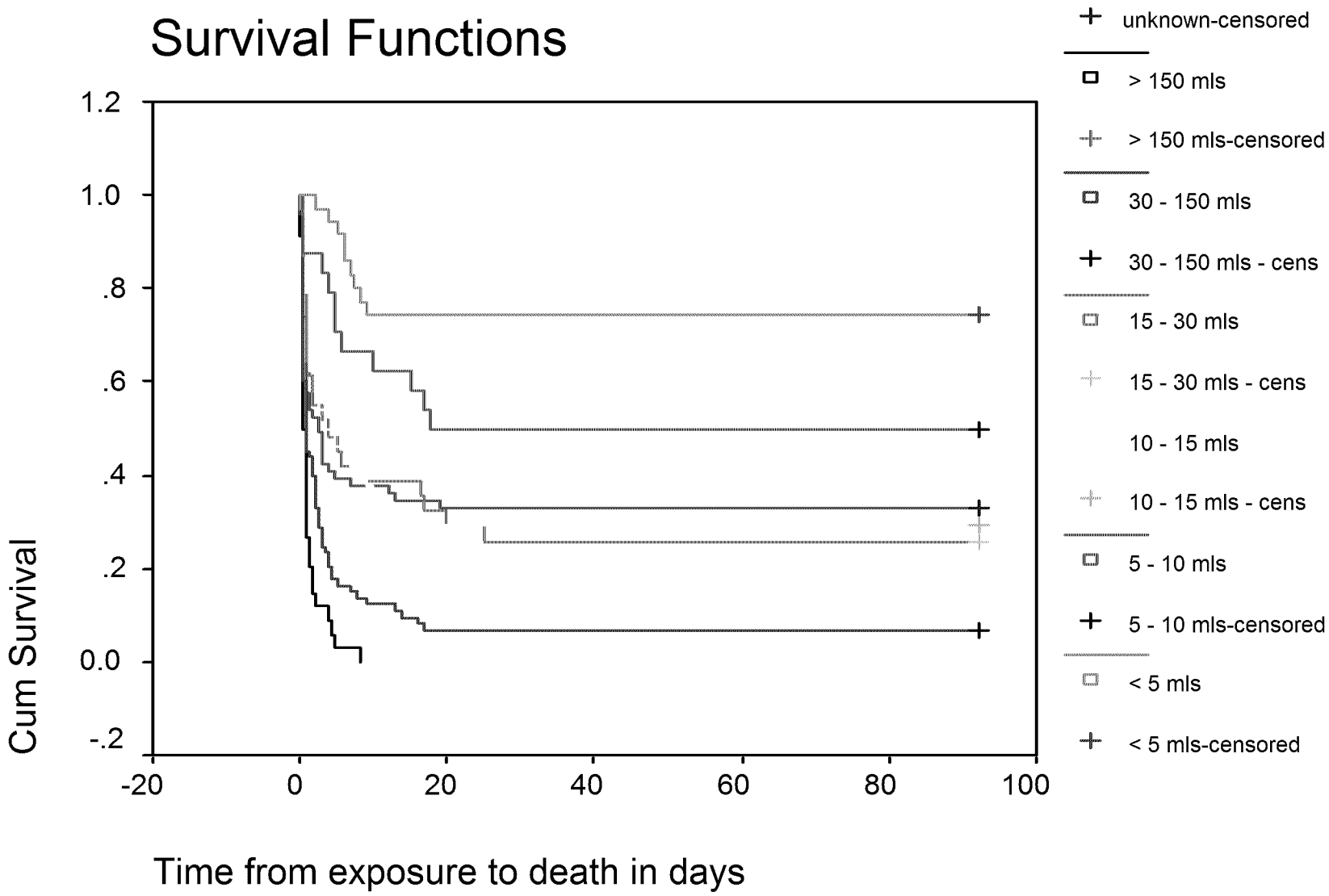
3. Survival curve by amount ingested



4. Vital status at 3 months by amount ingested

Crosstab

			OUTCOME2 Outcome 3 months after ingestion			
			1 Died < 3 months	2 Alive at 3 months	3 Unknown status at 3 months	Total
AMOUNT3 Amount ingested	1 < 5 mls	Count	9	8	18	35
		% within AMOUNT3 Amount ingested	25.7%	22.9%	51.4%	100.0%
	2 5 - 10 mls	Count	12	7	5	24
		% within AMOUNT3 Amount ingested	50.0%	29.2%	20.8%	100.0%
	3 10 - 15 mls	Count	17	4	3	24
		% within AMOUNT3 Amount ingested	70.8%	16.7%	12.5%	100.0%
	4 15 - 30 mls	Count	23	3	5	31
		% within AMOUNT3 Amount ingested	74.2%	9.7%	16.1%	100.0%
	5 30 - 150 mls	Count	68	1	4	73
		% within AMOUNT3 Amount ingested	93.2%	1.4%	5.5%	100.0%
	6 > 150 mls	Count	34	0	0	34
		% within AMOUNT3 Amount ingested	100.0%	.0%	.0%	100.0%
	7 unknown	Count	41	14	6	61
		% within AMOUNT3 Amount ingested	67.2%	23.0%	9.8%	100.0%
Total		Count	204	37	41	282
		% within AMOUNT3 Amount ingested	72.3%	13.1%	14.5%	100.0%

5. Results of Cox PH regression analyses to find predictors of survival.
Hazard Ratio = Exp(b)

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
AGEM	.018	.005	10.947	1	.001	1.018	1.007	1.029
SEXM	.097	.201	.234	1	.629	1.102	.744	1.633
WEIGHTM	.023	.012	4.028	1	.045	1.024	1.001	1.047
AMOUNTG			51.026	3	.000			
AMOUNTG(1)	1.206	.205	34.736	1	.000	3.340	2.236	4.987
AMOUNTG(2)	1.658	.261	40.237	1	.000	5.248	3.144	8.758
AMOUNTG(3)	.995	.248	16.044	1	.000	2.705	1.662	4.403
VOMIT15B	.437	.169	6.732	1	.009	1.549	1.113	2.155
RX4HRS	.324	.202	2.568	1	.109	1.382	.930	2.054
FULLERS	.576	.280	4.234	1	.040	1.779	1.028	3.078
CHARCOAL	1.467	.553	7.038	1	.008	4.337	1.467	12.819
ANTIEMY	-.096	.222	.189	1	.664	.908	.588	1.402
CYCOPHY	.614	.322	3.635	1	.057	1.849	.983	3.477
IVFLUIDY	-.302	.383	.620	1	.431	.739	.349	1.568
DIURETY	.037	.280	.017	1	.895	1.038	.599	1.797
PREDNISY	-.439	.211	4.321	1	.038	.645	.426	.975
LAVAGEY	.329	.217	2.291	1	.130	1.390	.908	2.129

AMOUNTG(1) = amount ingested 30 – 150 mls (73 patients) AMOUNTG(2) = amount ingested > 150 mls (34 patients)
AMOUNTG(3) = amount ingested unknown (61 patients) Reference category for amount ingested is 0-30 mls (114 patients)
Vomit15b = Vomited within 15 mins of ingestion (106 patients)
Rx4hrs = Treated in hospital within 4 hours of ingestion (180 patients).

6. Analysis conclusions

72.3% known to have died within 3 months – likely to increase to 75-77% when FU complete

Strong relationship with estimated ingestion amount

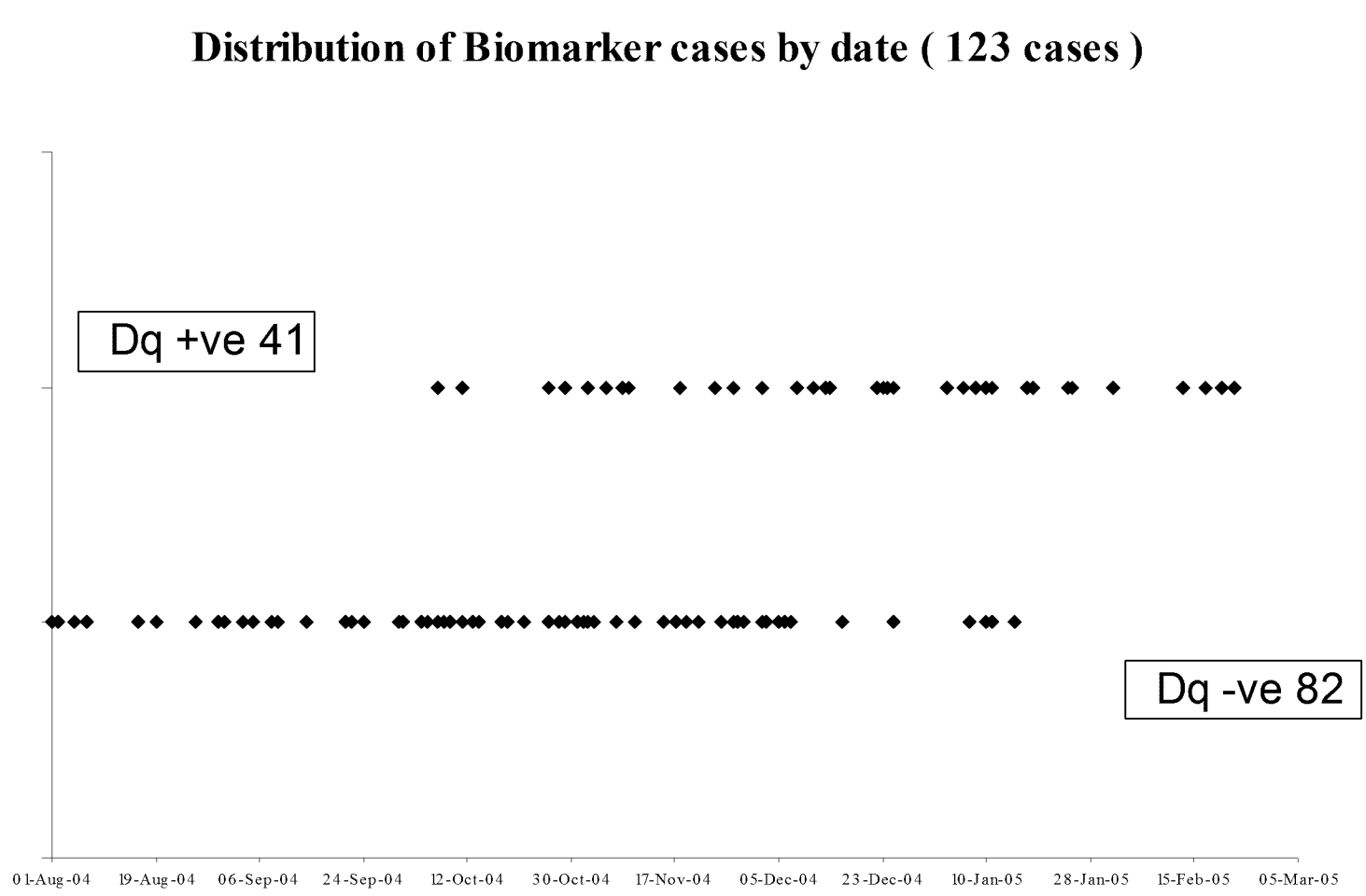
Proportional hazards assumption is met for all factors tested, but further work needed to look at departures in residual plots

PH model gives similar results to logistic regression but makes more efficient use of data and deals better with unequal FU periods and lost to FU

Not vomiting in first 15 minutes and age<50 are the strongest predictors of survival (after ingestion)

Power is unlikely to be lower than calculated as there is a higher proportion of subjects in the 0-30ml group than expected

Distribution of Biomarker Cases by Date (123 cases)



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Messages to SAP
Manufacturing and Supply Challenges (1)

Syngenta believes Inteon technology is a significant advancement in product safety. This is supported by laboratory work in dogs and rabbits

There have been manufacturing challenges in making a consistent product

Careful QC has ensured that batches with unacceptable profile have not been submitted to the SL market

"Worst Case" product scenarios have been modelled and tested in the lab; even this material is considered to be equivalent or better than existing Gramoxone

Messages to SAP
Manufacturing and Supply Challenges (2)

Phasing is more significant in large pack size (1L and 4L); there is better mixing during pour off in small packs. 200ml and 400ml packs account for approx 75% of small-holder packs (200ml – 1L)

The SL trial with the existing product should continue, but is unlikely to show the optimal benefits of Inteon technology

The current Inteon product will not be the final product marketed in SL or ROW – work continues to optimise the safening qualities

The intention is to register and market the optimised formulation as soon as it has been developed

Proposal is to continue the trial in SL with optimised product (with different biomarker)

Questions for SAP

Consider impact of formulation issues on the survey

- On the basis of current knowledge, should we continue and/or extend the survey

Review and discuss results from descriptive study

- Does the analysed data from the comparative study indicate we have the right parameters to analyse and interpret the descriptive study?
- Should we modify any parameters?
- Has the prolonged phase in of Inteon had any impact on the survey?

Messages for the SAP

- Consider publication strategy implications

Additional Issues for Discussion with SAP

Case Definition

Data quality and repatriation

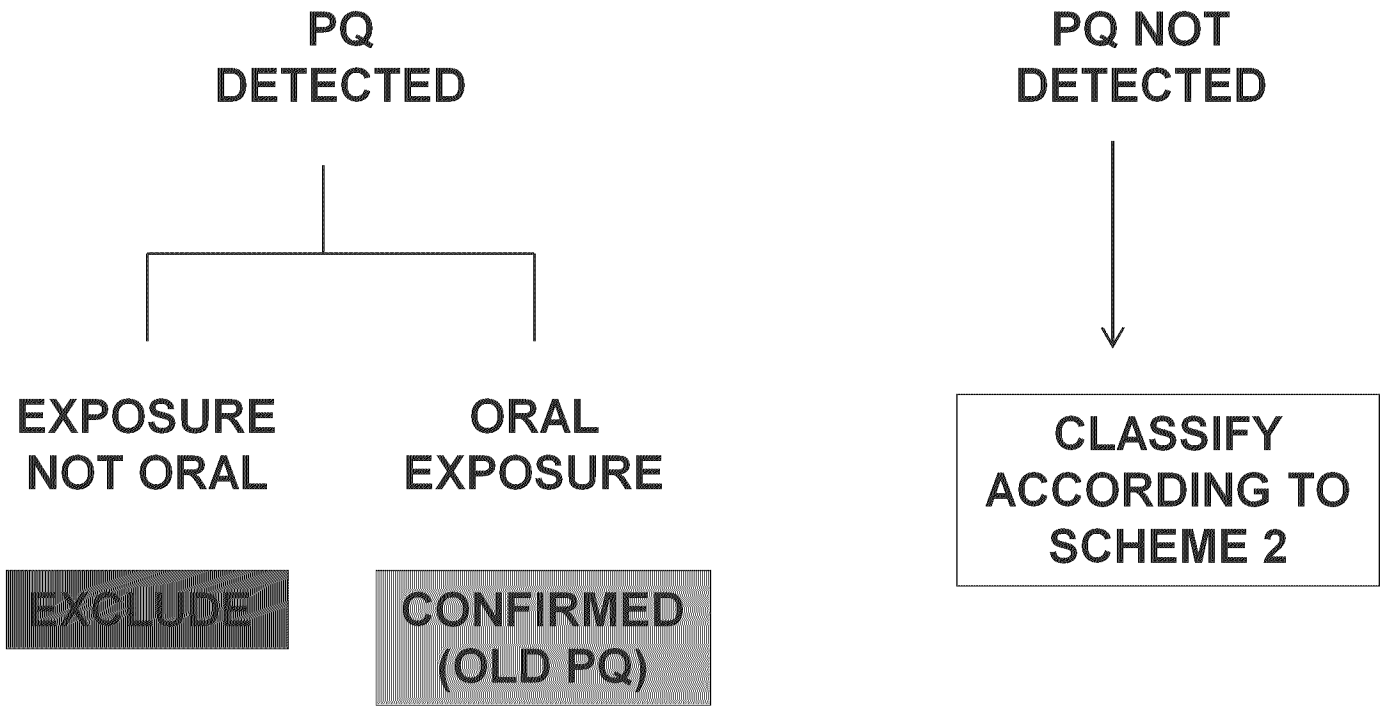
Agree tolerances on parameters

Who does the stats? Who drafts report?

Statistical treatment of discharged patients with no follow up

Treatment and non-referrals of patients from base hospitals

1. Inclusion criteria for suspected paraquat cases where plasma/urine sample is available (pre 1 Sep 2004)



Database:

- All Galle cases from June 03 → 1 Sep 04
- All cases from Nov 03 from other hospitals → 1 Sep 04
- Specifically excludes pre Nov 03 data from Polonnaruwa and Anuradhapura

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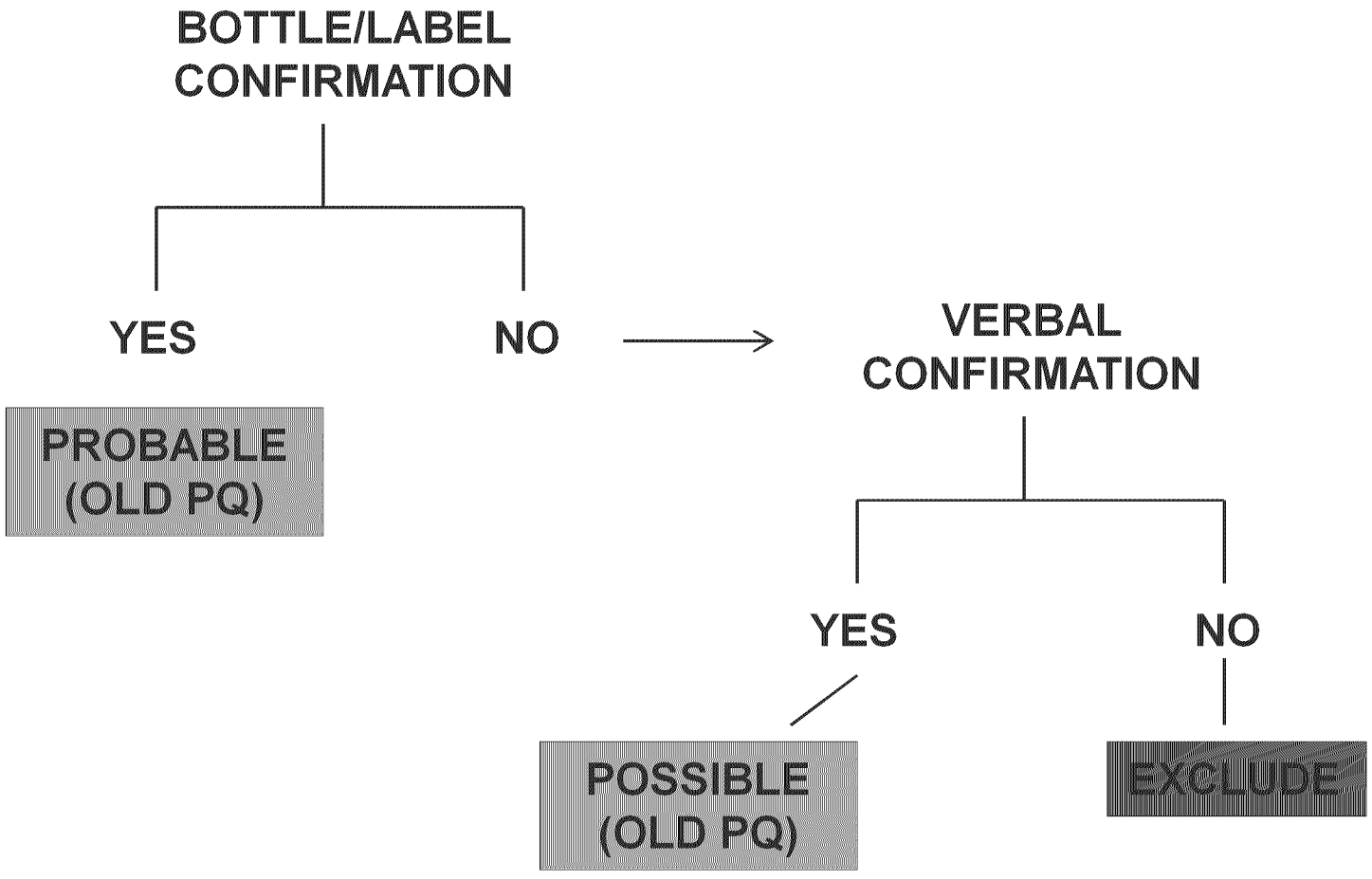
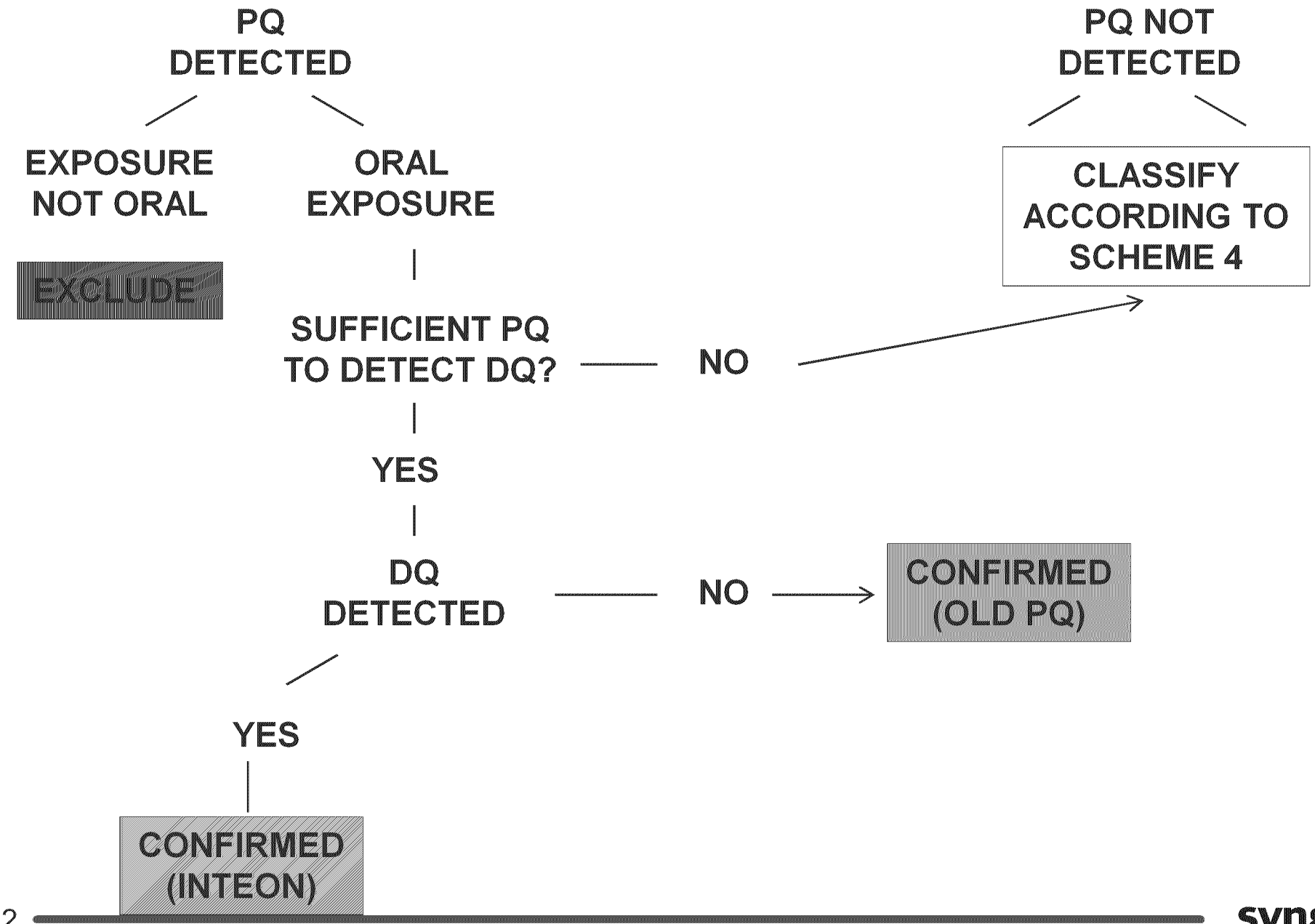
2. Inclusion criteria for suspected paraquat cases where NO plasma/urine sample is available (pre 1 Sep 2004) or where no pq was detected in the sample



3. Inclusion criteria for suspected INTEON cases where plasma/urine sample is available (post 1 Sep 2004)



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4. Inclusion criteria for suspected INTEON cases where NO plasma/urine sample is available (post 1 Sep 2004) or where pq is below LOD or dq would be too low to be detected