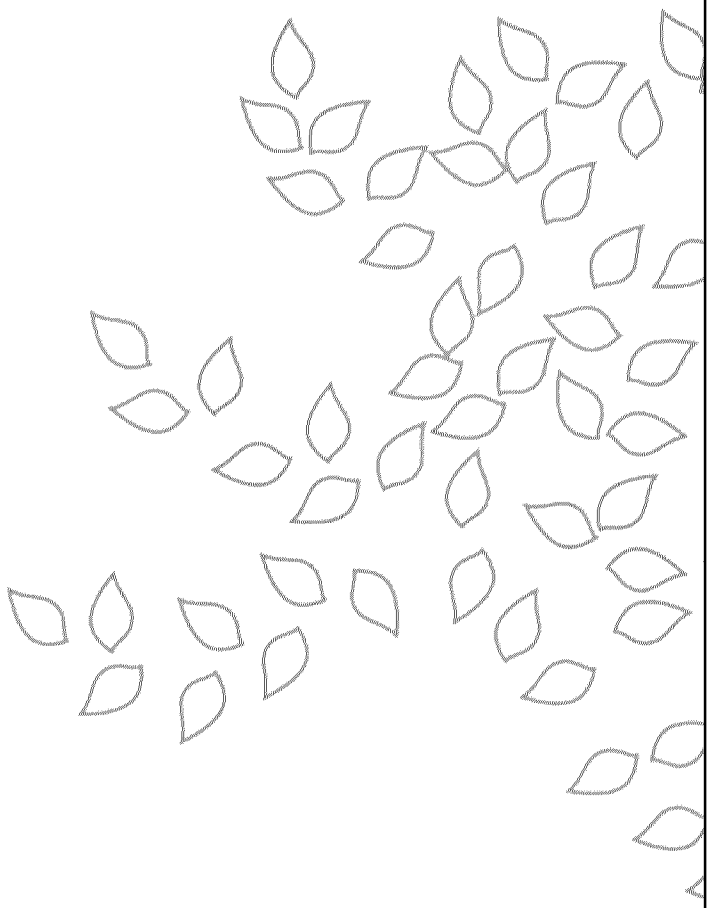
Update on INTEON - the new safer formulation for paraquat

Why Inteon?



Gramoxone Inteon

Ingredients

- Alginate: Acid triggered gel
- New odorant: (Less offensive)
- ➢Active ingredient: Paraquat
- ➢Green dye
- ➢Emetic: Induces vomiting
- ➢Purgative: Enhance excretion

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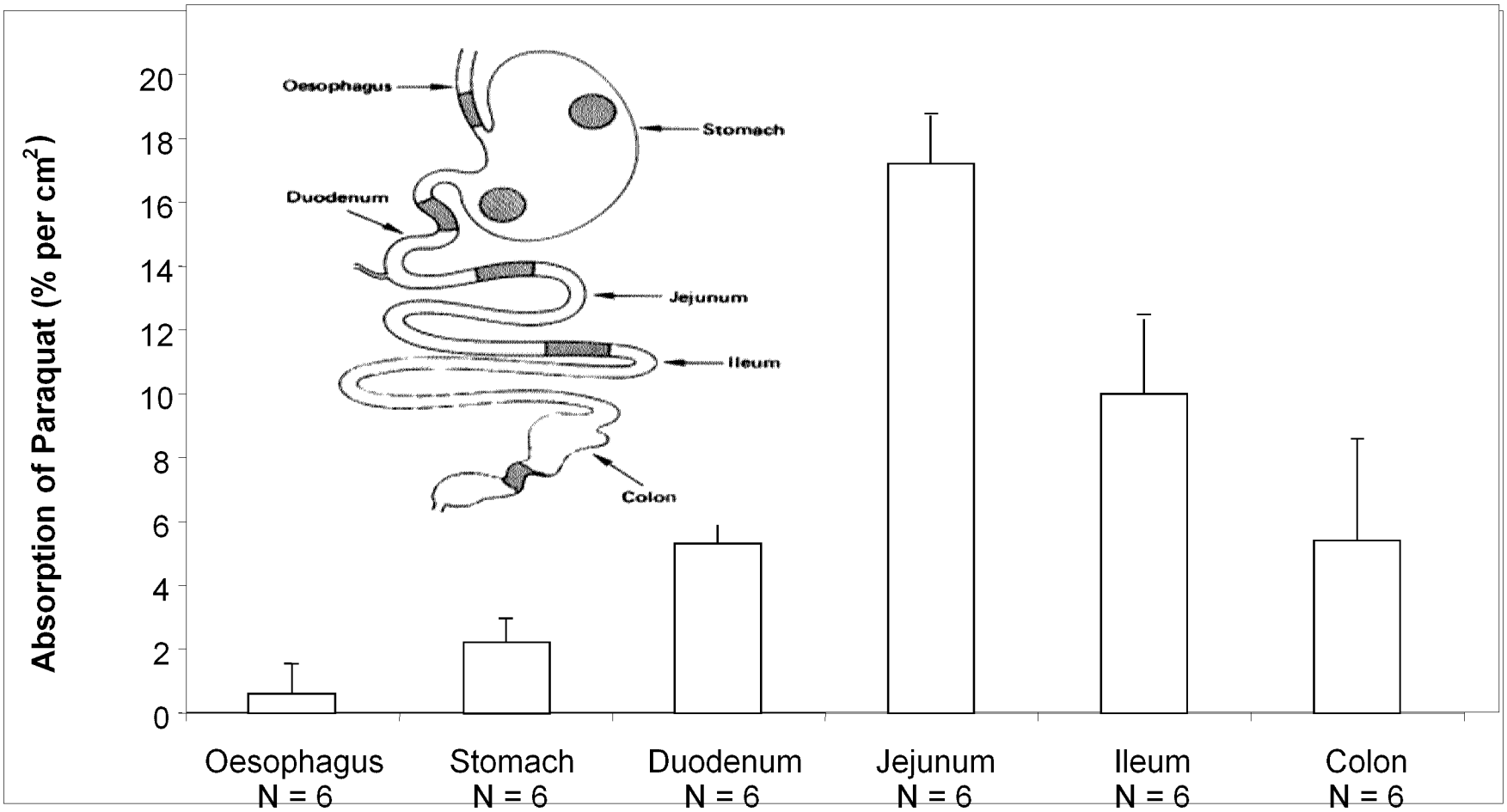
Paraquat is primarily absorbed via the small intestine



Heylings JR *Toxicol. Appl. Pharmacol* 107, 482 - 493, 1991

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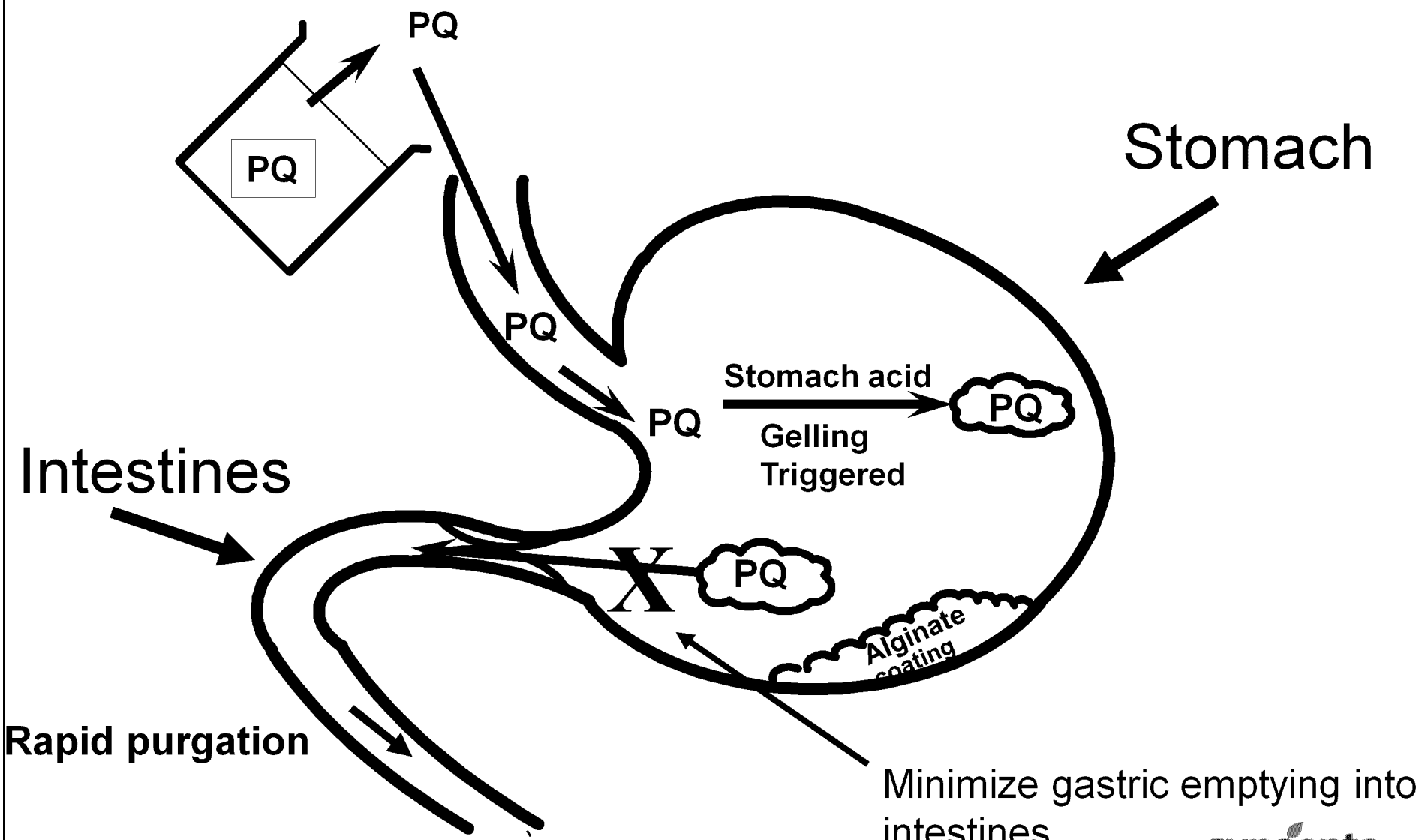
Alginates in Gramoxone Inteon

- **Natural gelling agents (Seaweed extract)**
  - Commonly used in food and pharmaceutical industries
- **Acid triggered gelling**
  - Immediately forms into a gel only at very low pH (e.g., 1 - 3)
  - Gel minimizes/slows dispersion and passage into the small intestines
    - Allowing more time for emetic to work
    - Providing more productive emesis
  - Does not adversely effects agricultural performance

Gramoxone Inteon – scientific rationale



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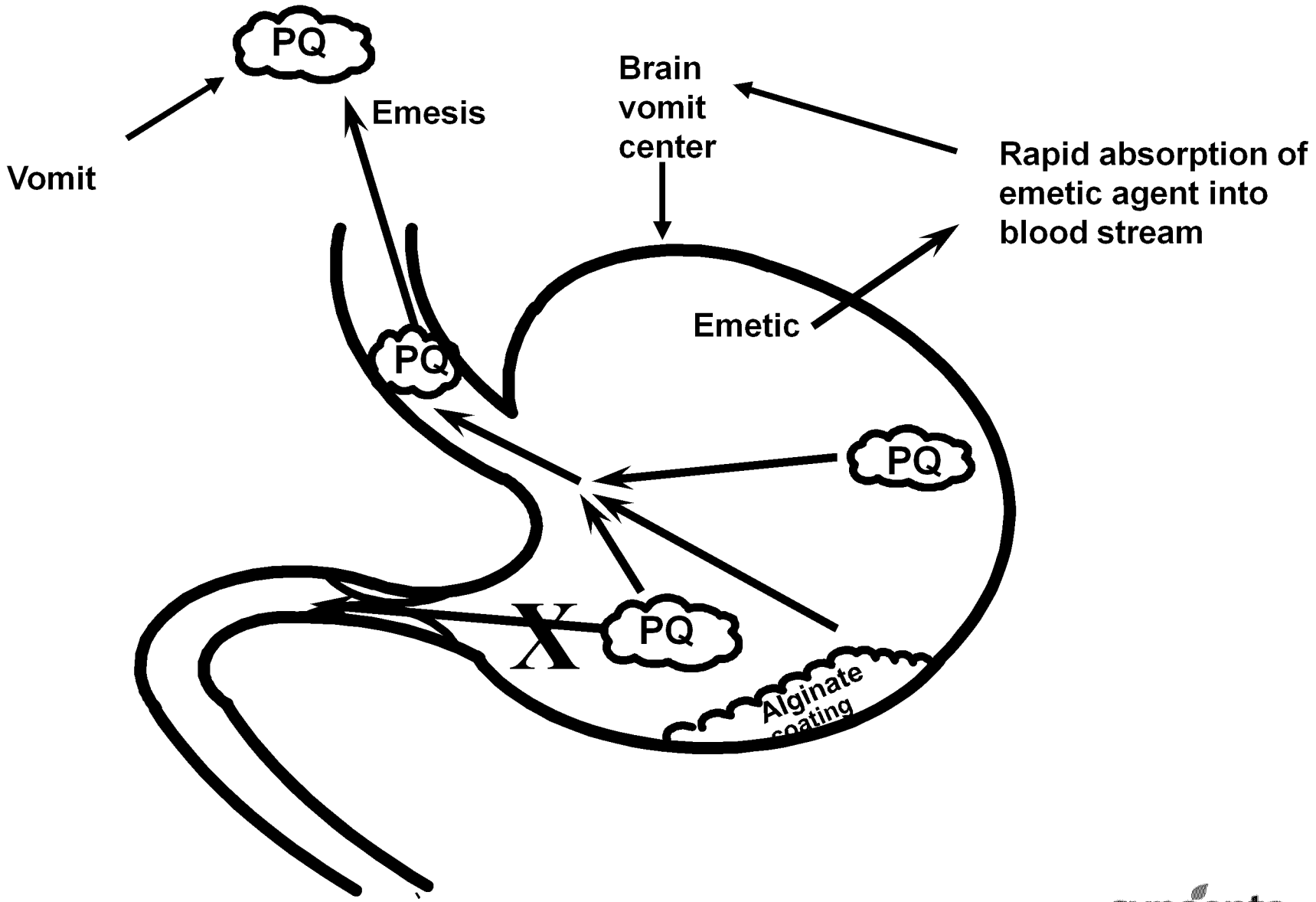
Gramoxone Inteon – scientific rationale



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Gramoxone Inteon

An improvement in oral toxicity
- experimental evidence

Formulation Terms Used

Gramoxone	200 g/l	Non Inteon	Global, not reg. in US
Gramoxone US	360 g/l	Non Inteon	US Voluntary cancellation
Inteon	200 g/l	Inteon	Global, not reg. in US
Inteon US	240 g/l	Inteon	Registered in US

Requirement for use of the dog

Gelling

+

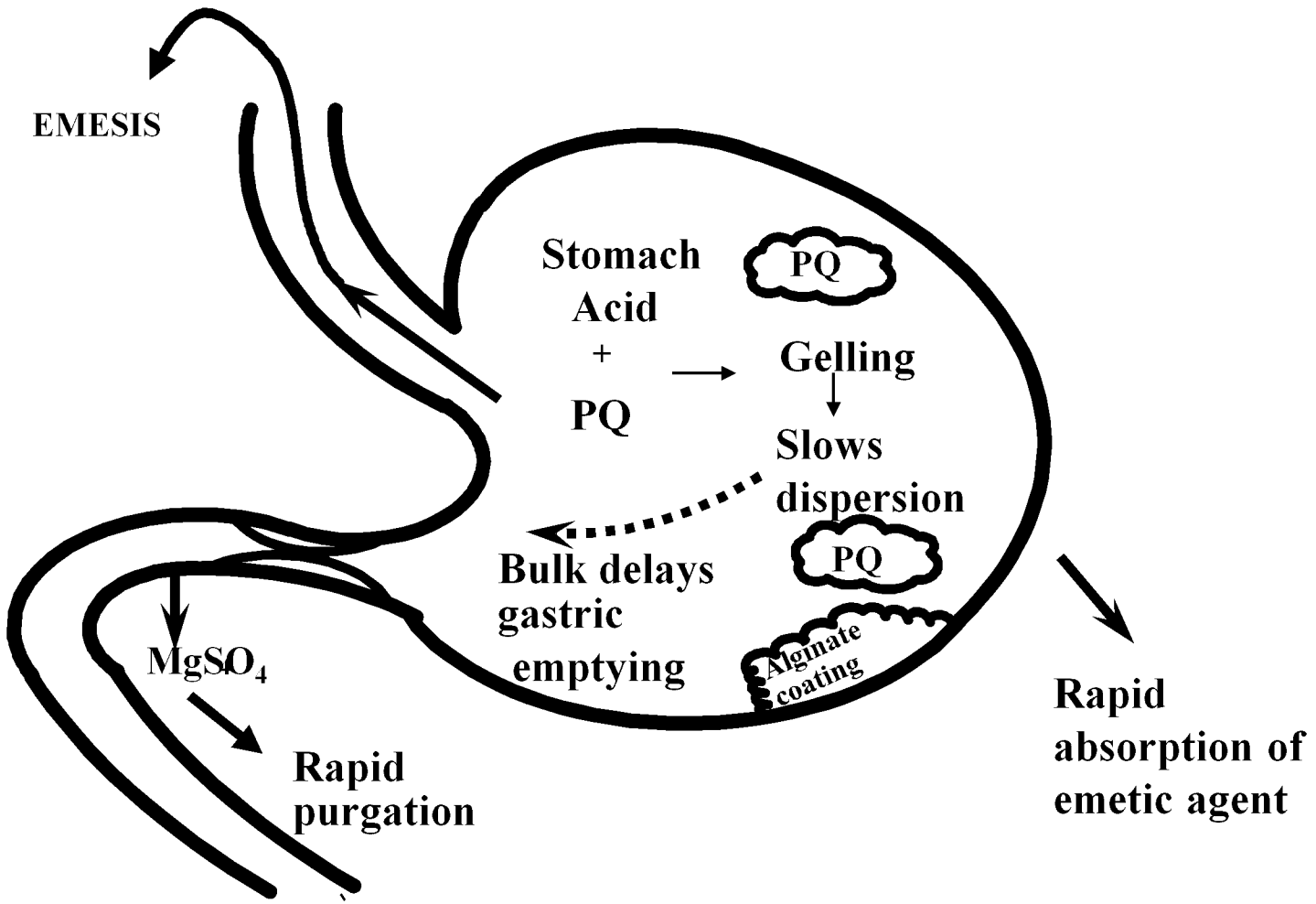
Emesis

+

Purgation

=

Safening



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Evidence in the dog – existing non-Inteon Gramoxone baseline

Gramoxone data based on 200g paraquat/l with built in wetters

- Widdop et al (1977) - literature - showed mortality at 10mg paraquat/kg
  - 6/6 dogs died
  - plasma kinetics measured

- Syngenta data (1988) confirmed median lethal dose (MLD) in dog to be 12mg paraquat/kg for Gramoxone formulation
  - plasma kinetics measured

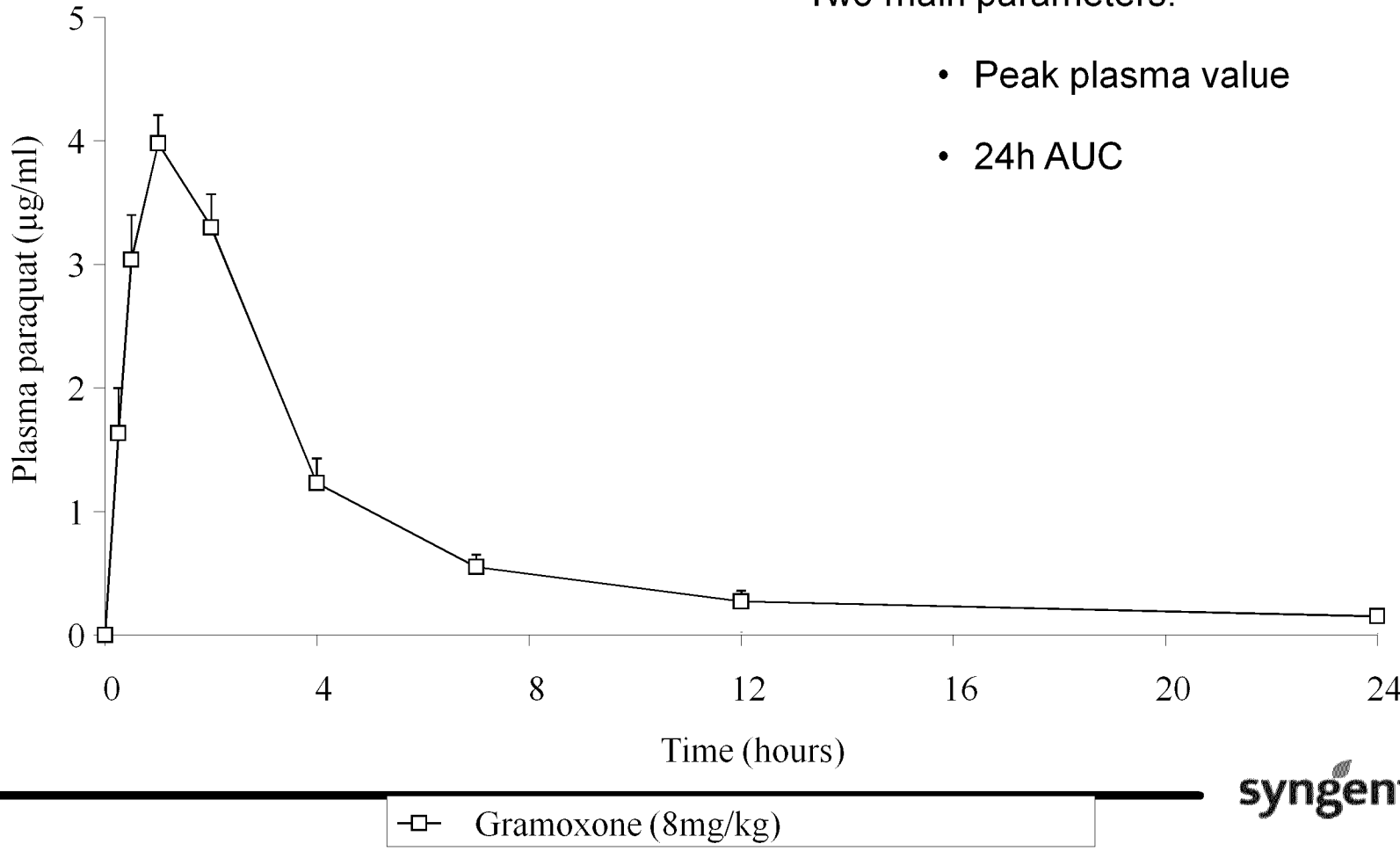
Evaluation of paraquat absorption from formulations

Paraquat Absorption in the Dog

Plasma paraquat following an oral dose of paraquat

Two main parameters:

- Peak plasma value
- 24h AUC



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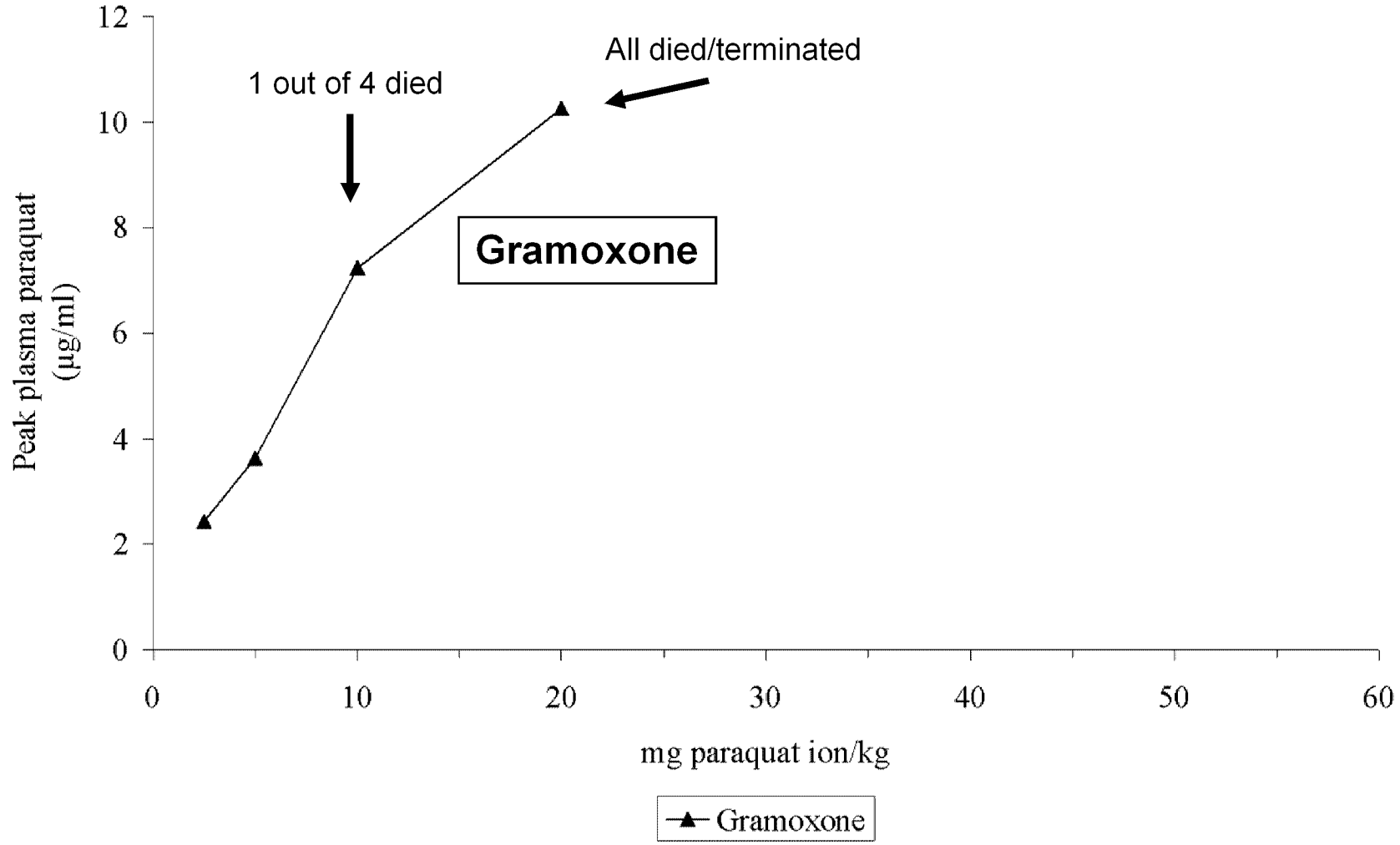
Gramoxone: peak plasma paraquat levels in dogs (existing data - 1988 study)



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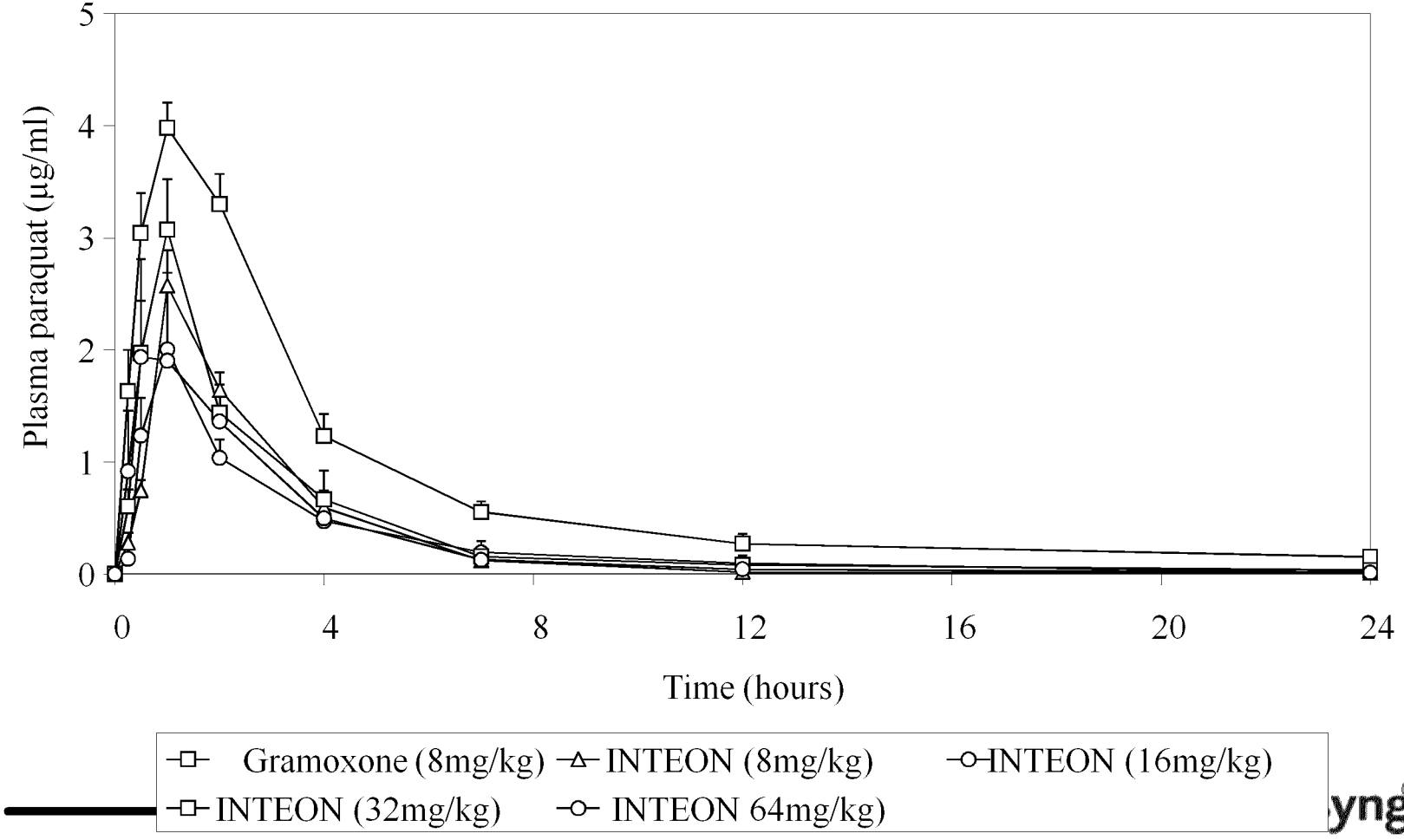
Evaluation of paraquat absorption from formulations
Paraquat Absorption in the Dog

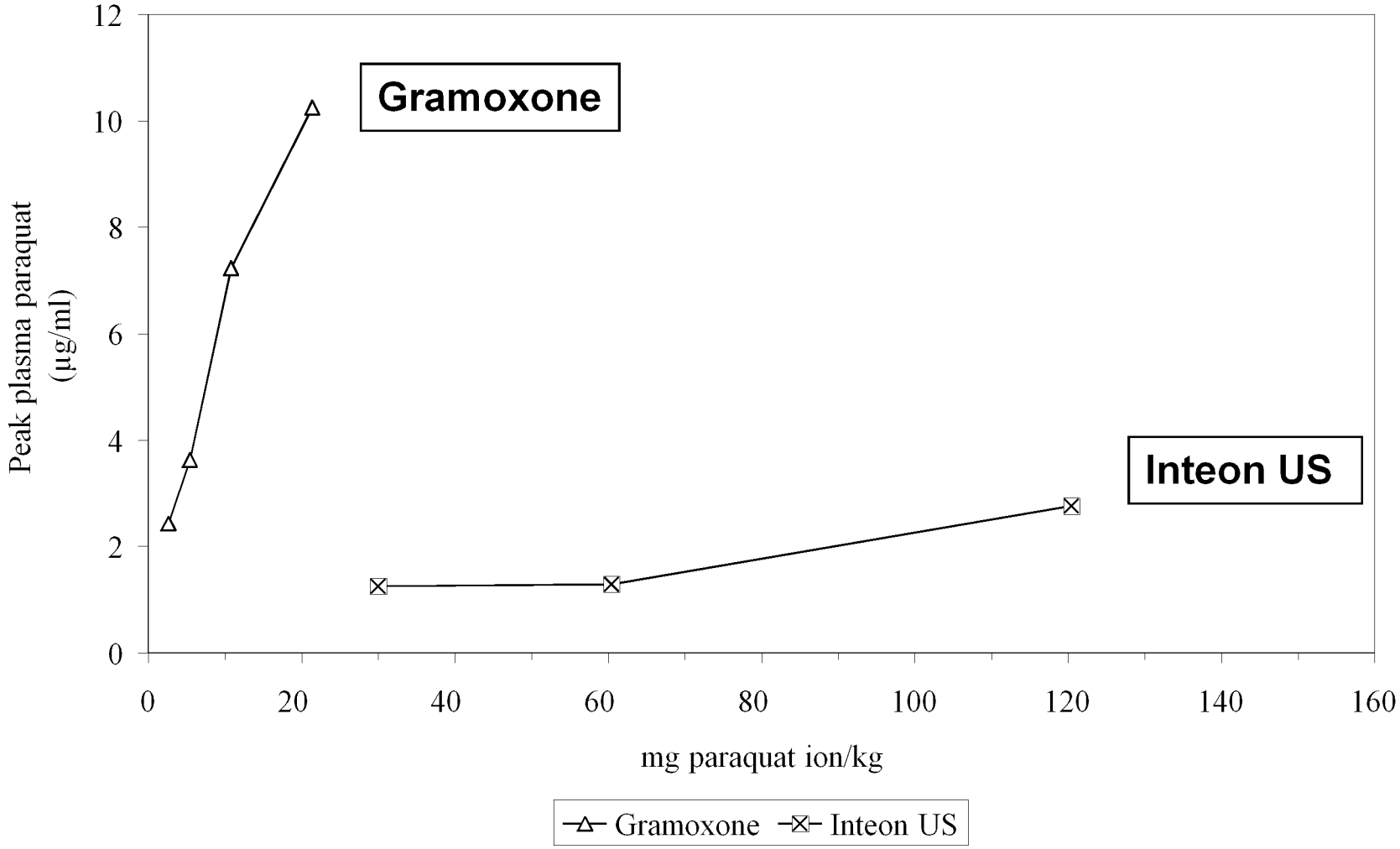
Plasma paraquat following an oral dose of Gramoxone INTEON 8-64mg/kg paraquat ion



Gramoxone control data was generated at CTL between 1987 and 1991. Mean of 7 independent groups of dogs (n = 3 each). The blood levels shown (in black) are well tolerated in this species with no acute toxicity.

How does this relate to a lethal dose in dogs? This is kinetic study but we use a criteria of a peak plasma paraquat level of 10µg/ml or a 24 hour AUC of 40 µg/ml /h as the criteria for humane termination of test animals since it would lead to overt toxicity.

Evaluation of paraquat absorption from Inteon formulations



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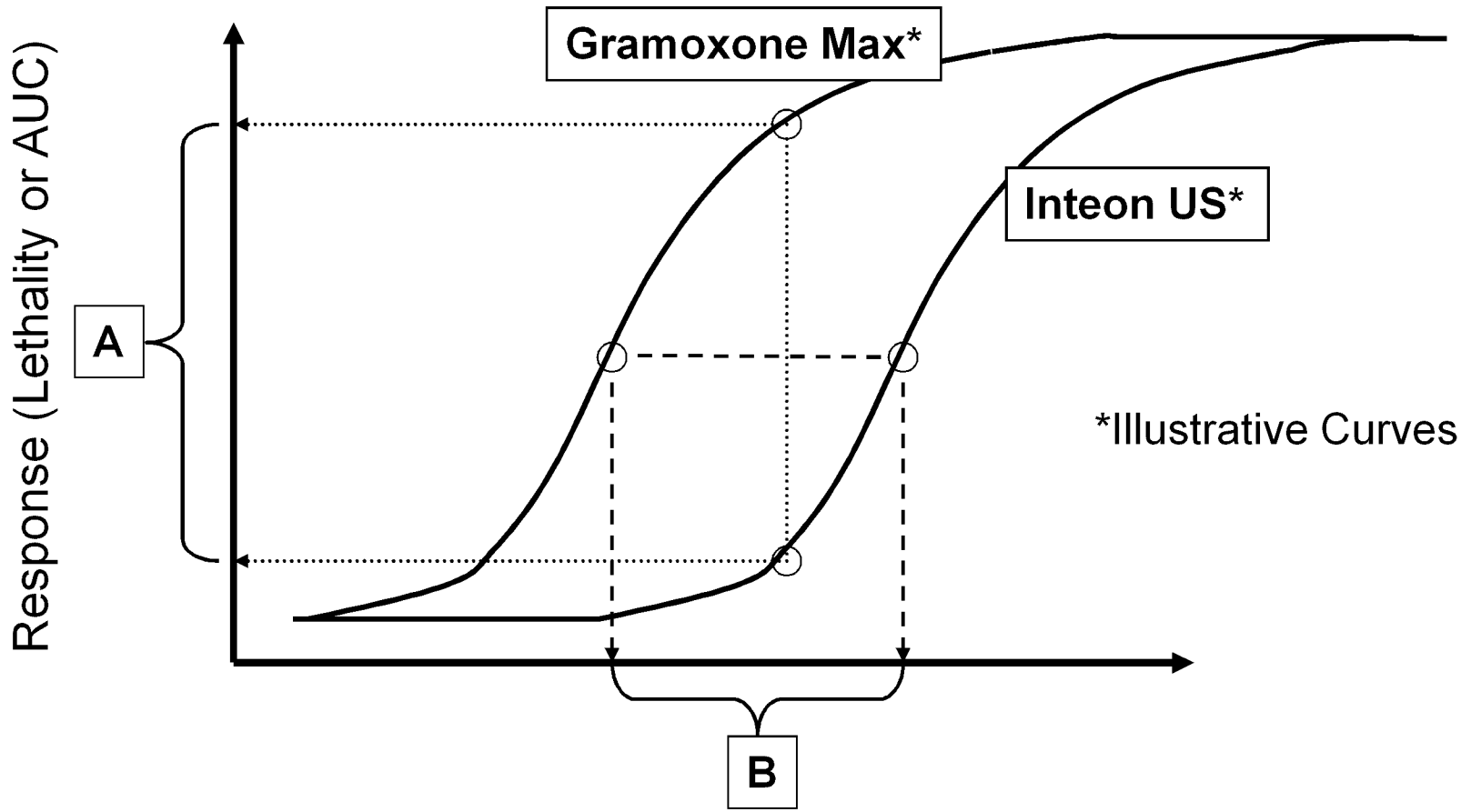
Clear evidence of Inteon US safening in the dog

- All dogs survived Inteon US doses at 32, 64 and 128 mg paraquat ion/kg

- The peak paraquat plasma concentration following dosing with Inteon US at 128 mg/kg was similar to that following dosing with Gramoxone at 8 mg/kg

- Suggested an approximate 10X improvement in oral toxicity in dog with Inteon and Inteon US compared with non-Inteon Gramoxone

Theoretical Dose-Response Comparisons



A= The difference in degree of response at the same unit dose

B= The difference in dose to achieve the same degree of response

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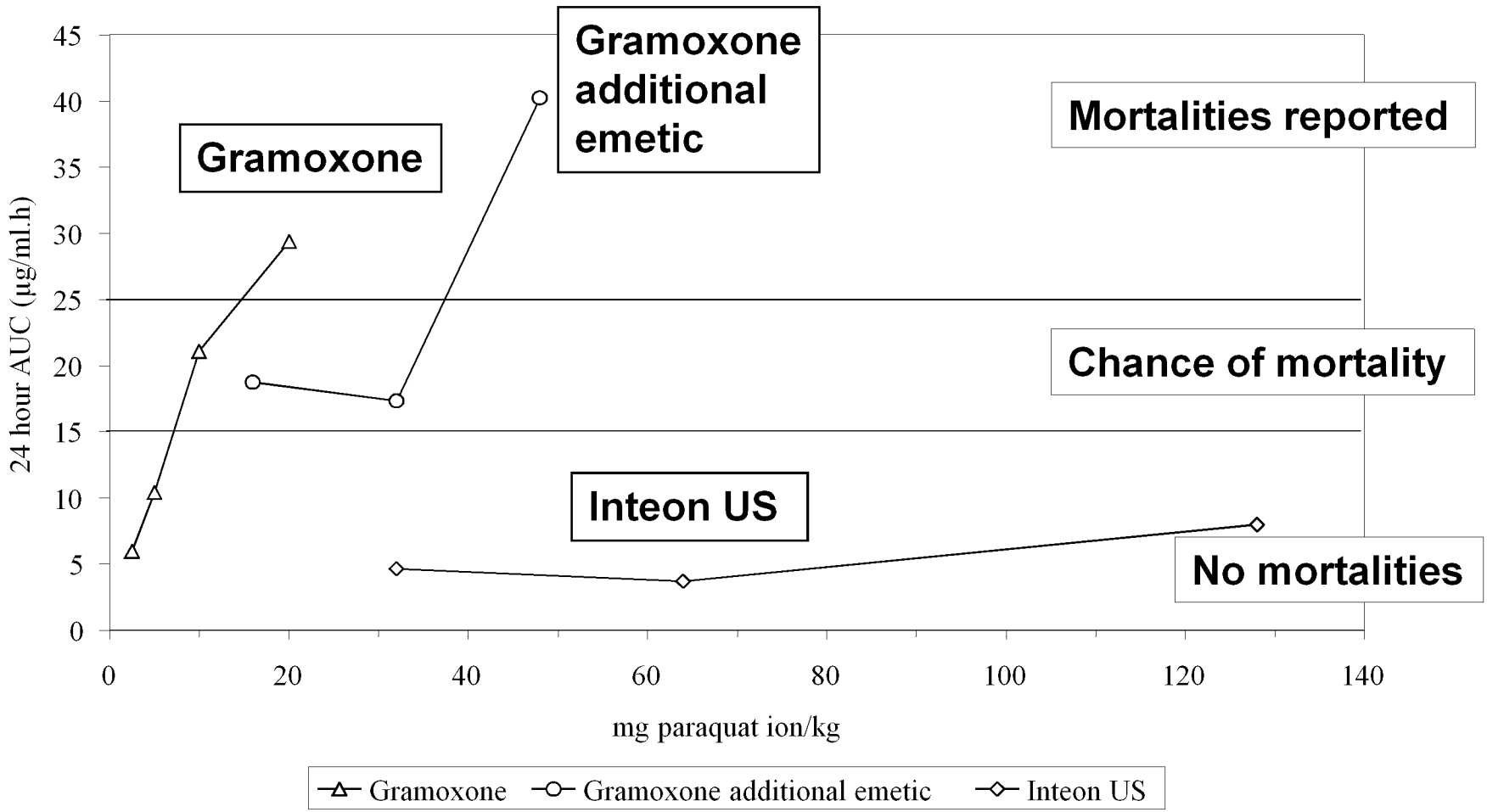
Is improved Inteon safety just due to increased emetic?



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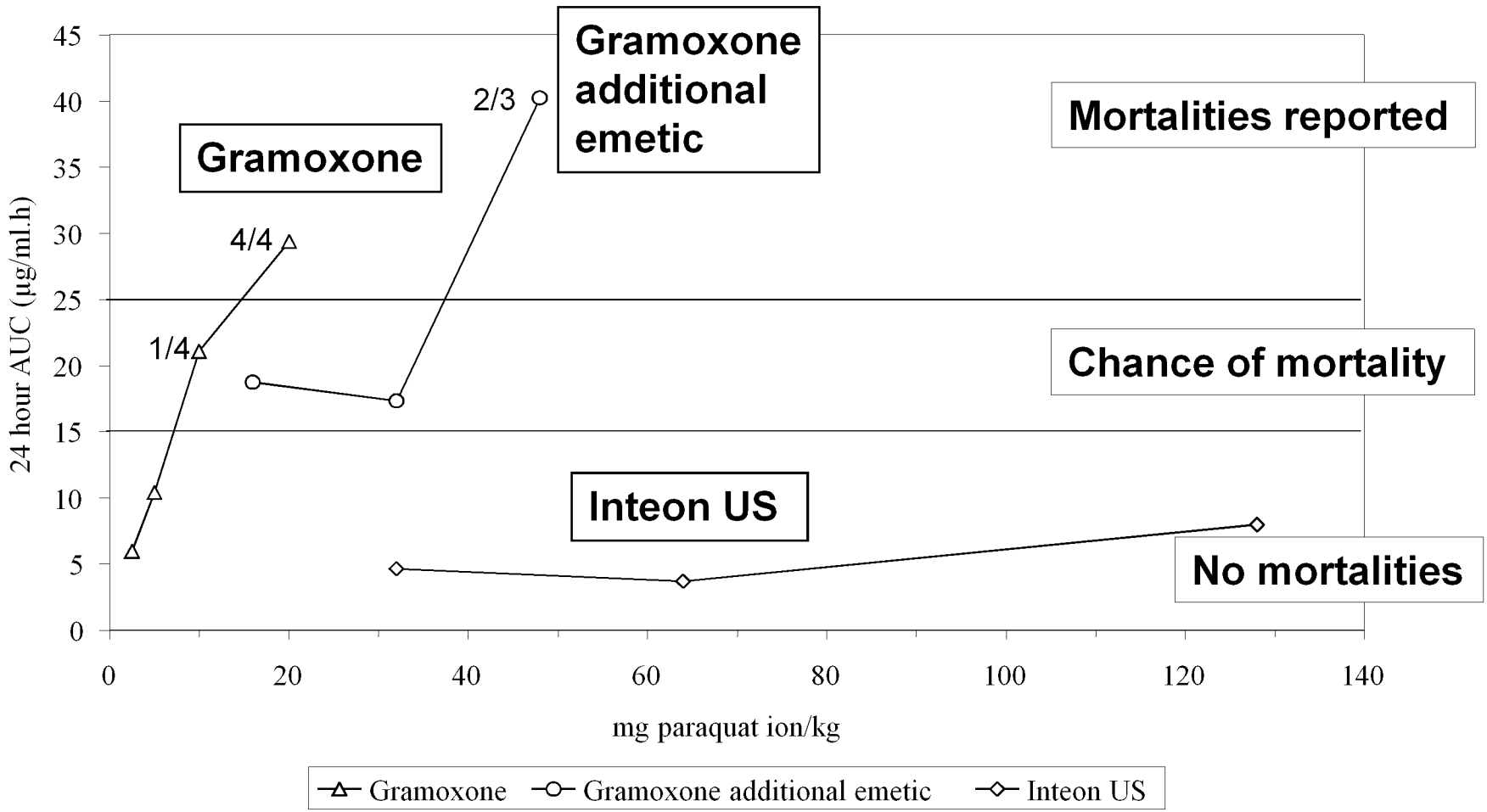

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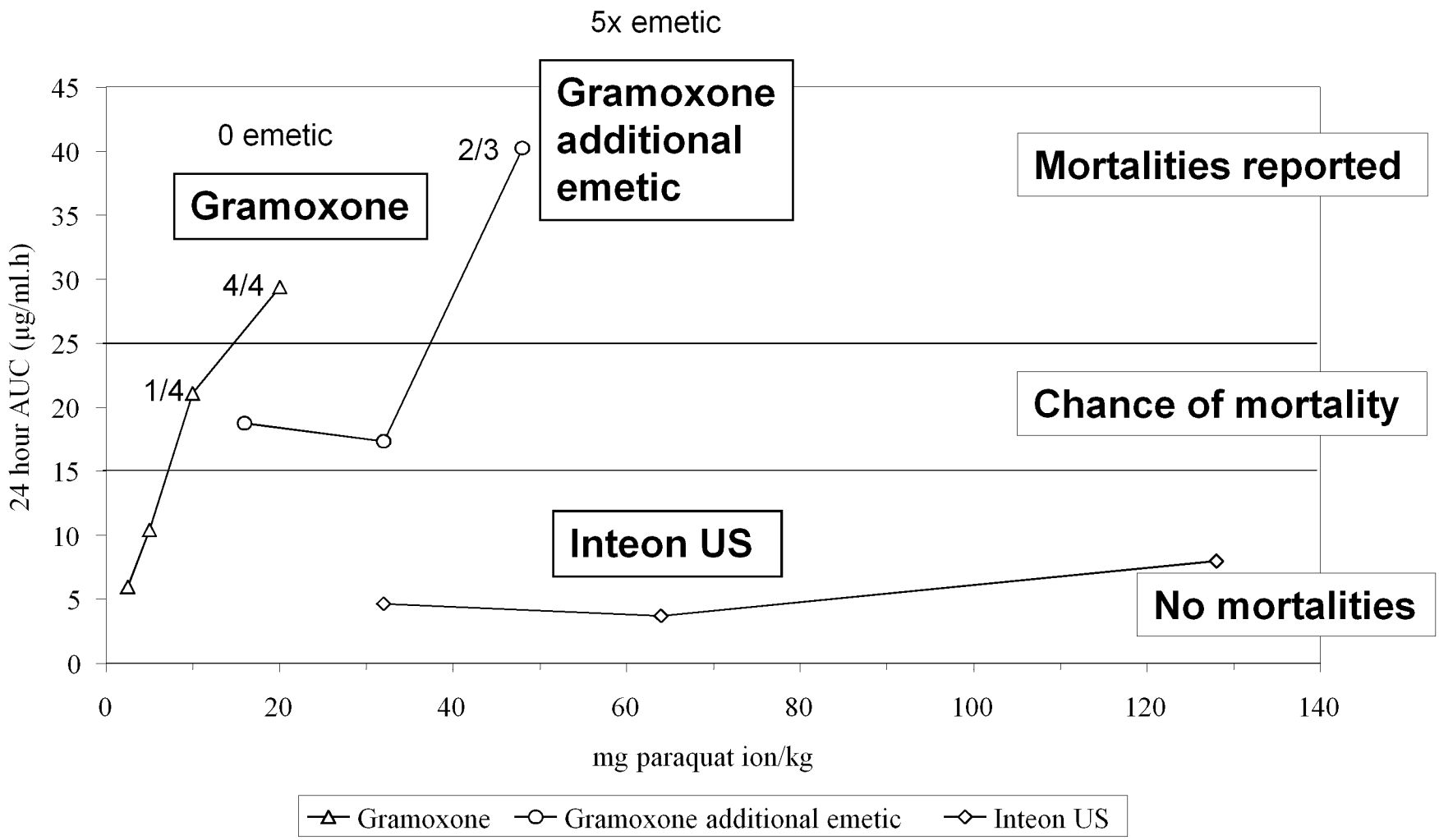

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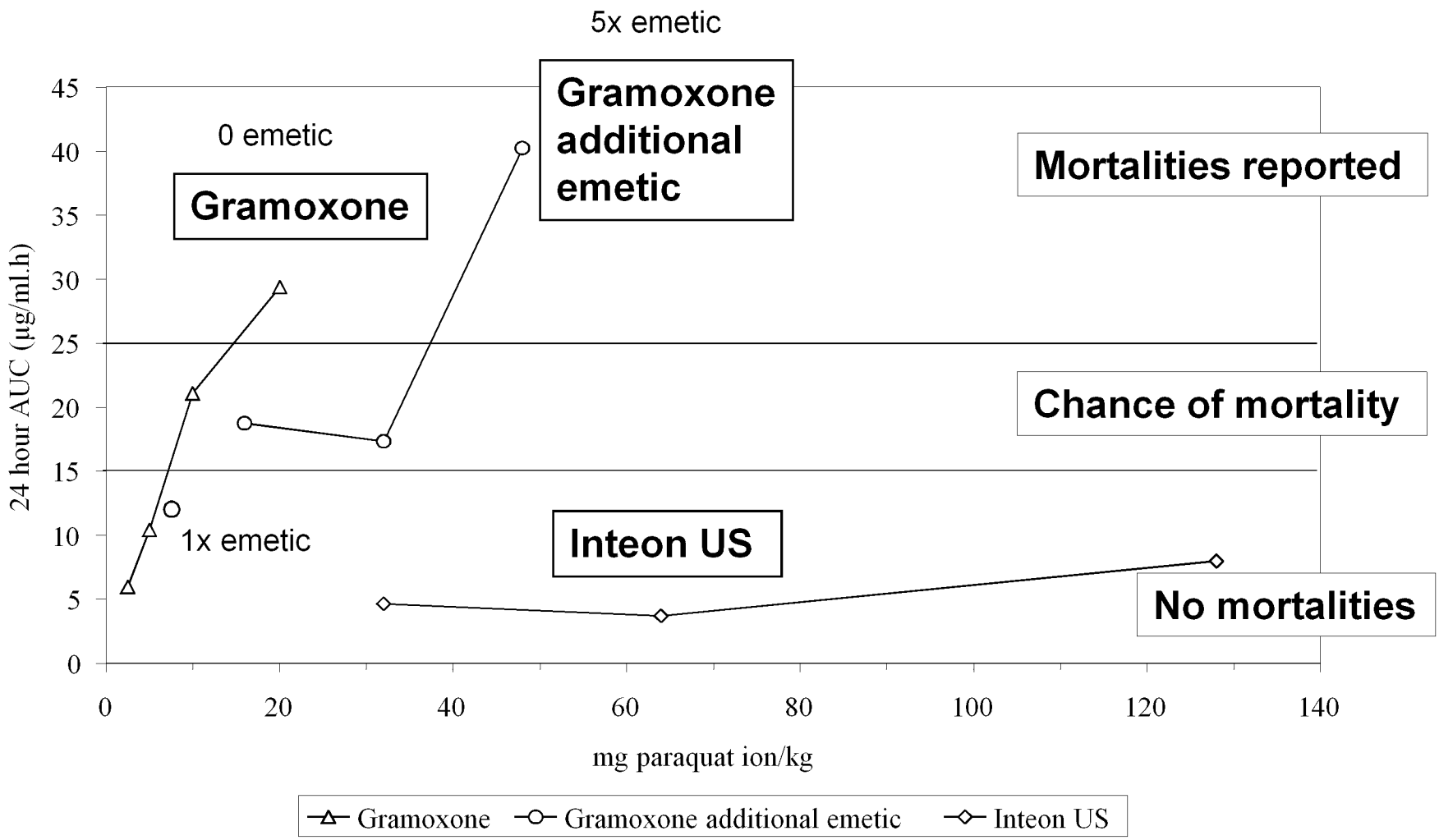
Estimation of degree of safening



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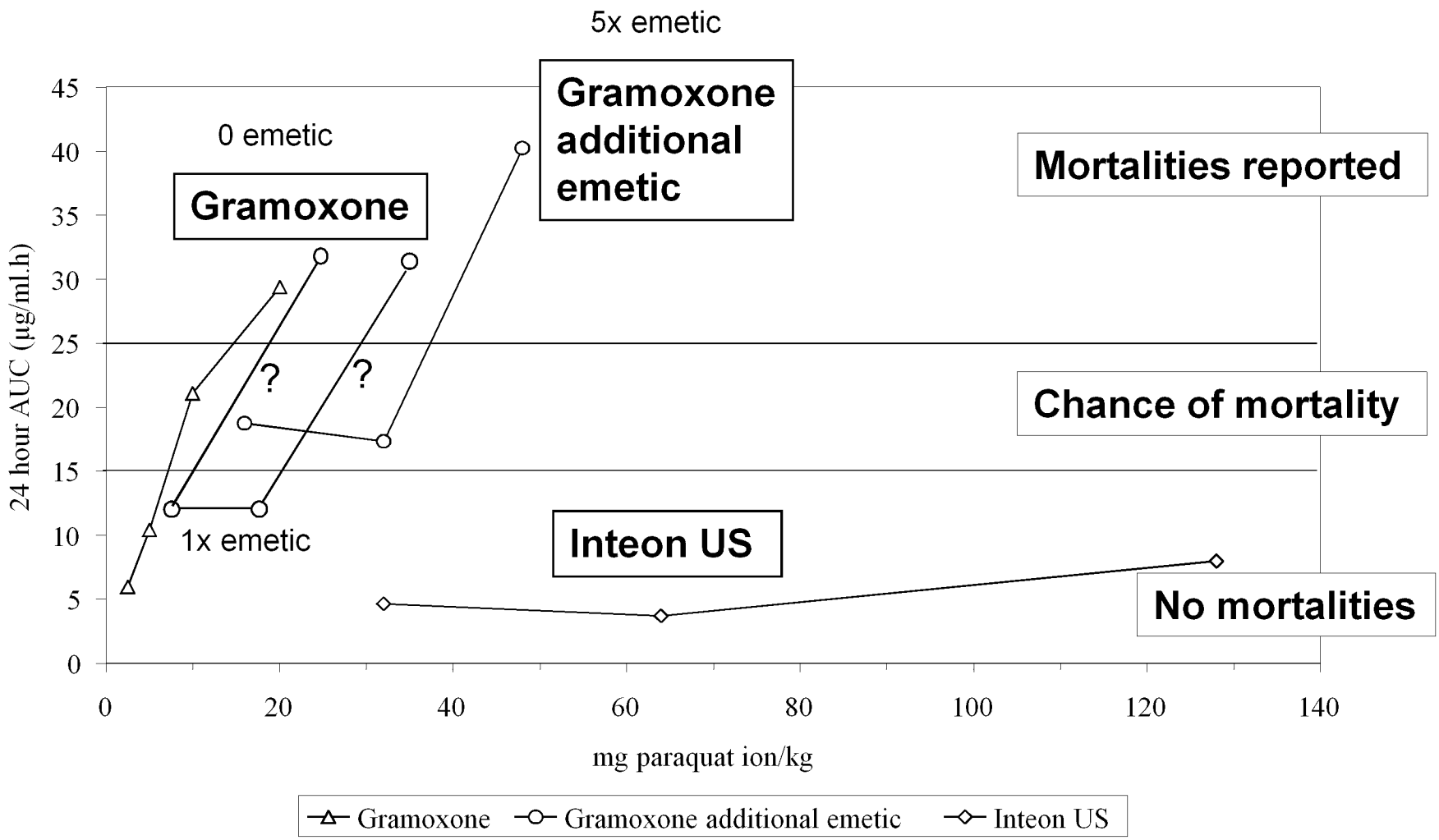
Estimation of degree of safening



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Clear evidence of Inteon US safening in the dog

- All dogs survived doses of Inteon US up to 128 mg/kg
- Even at 128mg/kg, the plasma paraquat level indicated limited paraquat absorption
- The data indicate a clear expected reduction in toxicity with Inteon US compared with existing non-Inteon Gramoxone formulations
- Further studies to allow a better quantitative estimate of the level of reduction in toxicity of the Inteon formulations are being planned

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Baseline studies in the dog for evaluation of the toxicity of Inteon and non-Inteon Gramoxone formulations

Proposals

Main study elements

Objective

Formulations to evaluate

Study details

Study placement

Timing

Main study elements

Objective

Objective for single oral dose studies over a range of formulation doses

- Determine kinetic data on paraquat absorption
- Determine acute toxicity (lethality) - minimum lethal dose

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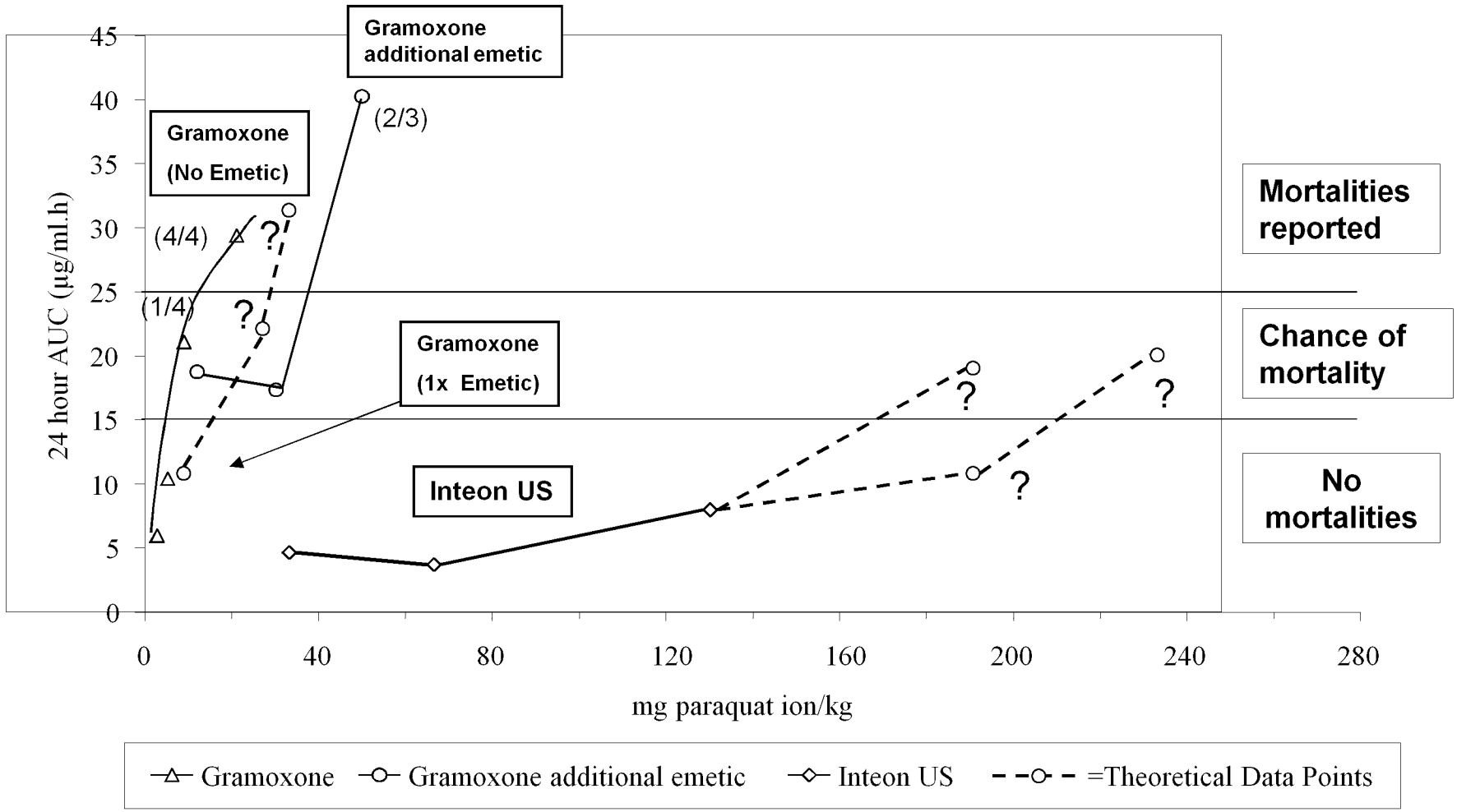
Comparison of 24h plasma paraquat AUC levels in dog (illustrative)



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Formulations to evaluate

	Non-Inteon		Inteon	
	US Gramoxone Max	Global Gramoxone	US Gramoxone Inteon	Global Gramoxone Inteon
Paraquat Concentration	360g/l	200g/l	240 g/l	200g/l
Emetic Concentration	0.5g/L	0.5g/L	1.5g/L	1.5g/L
Built In Wetters	No	Yes	No	No

Main study elements

Study details

Both sexes required?

- Use a single sex; use males

Aim of study: LD50 number or minimal lethal dose

- Determine the shape of the kinetic curve for paraquat absorption together with the minimum lethal dose.

Numbers of animals per dose level

- Proposed to use 4.

Rising doses or concurrent group dosing

- Use rising doses, moving up when reasonable confirmation of the toxicity of the first dose is available (likely 48 hours). Fresh animals per dose level

Main study elements

Study details

Dose levels: number and actual levels

Non-Inteon (USA): Plan for 8, 16, 32 as initial doses

Non-Inteon (Rest of World): Plan for 4, 8, 16 as initial doses

Inteon (USA & Rest of World): Plan for 64, 128 as initial doses

Main study elements

Study details

Means of oral dosing

- Dose by capsule

Endpoints to measure

- As currently done in CTL* - Plasma paraquat kinetics (peak/AUC); clinobs; bodyweight; full gross macropathology; histopathology (incl lungs, kidneys, GI tract)

Endpoint thresholds for requiring termination

- Clinobs or bodyweight thresholds exceeded (detailed limits to be confirmed)
- Measurement of paraquat absorption to be done in real time to advise clinobs frequency

Source of dogs - parity to existing Inteon data

- Beagles of similar weight range to CTL studies (10-12kg). Control potential stress and GI tract factors such as worming, diet, housing

Analysis - parity to existing sensitivity/specificity

- Method validation for PQ analysis in advance on spiked plasma and confirmation the same as results obtained in CTL

Histopathology

- Return tissues as wet tissues or blocks to CTL for histopathology analysis

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*CTL: Central Toxicology Laboratory

Main study elements

Study placement

Laboratory for conducting study

- To be determined

Monitoring of study

- Study monitors with first-hand experience of these studies

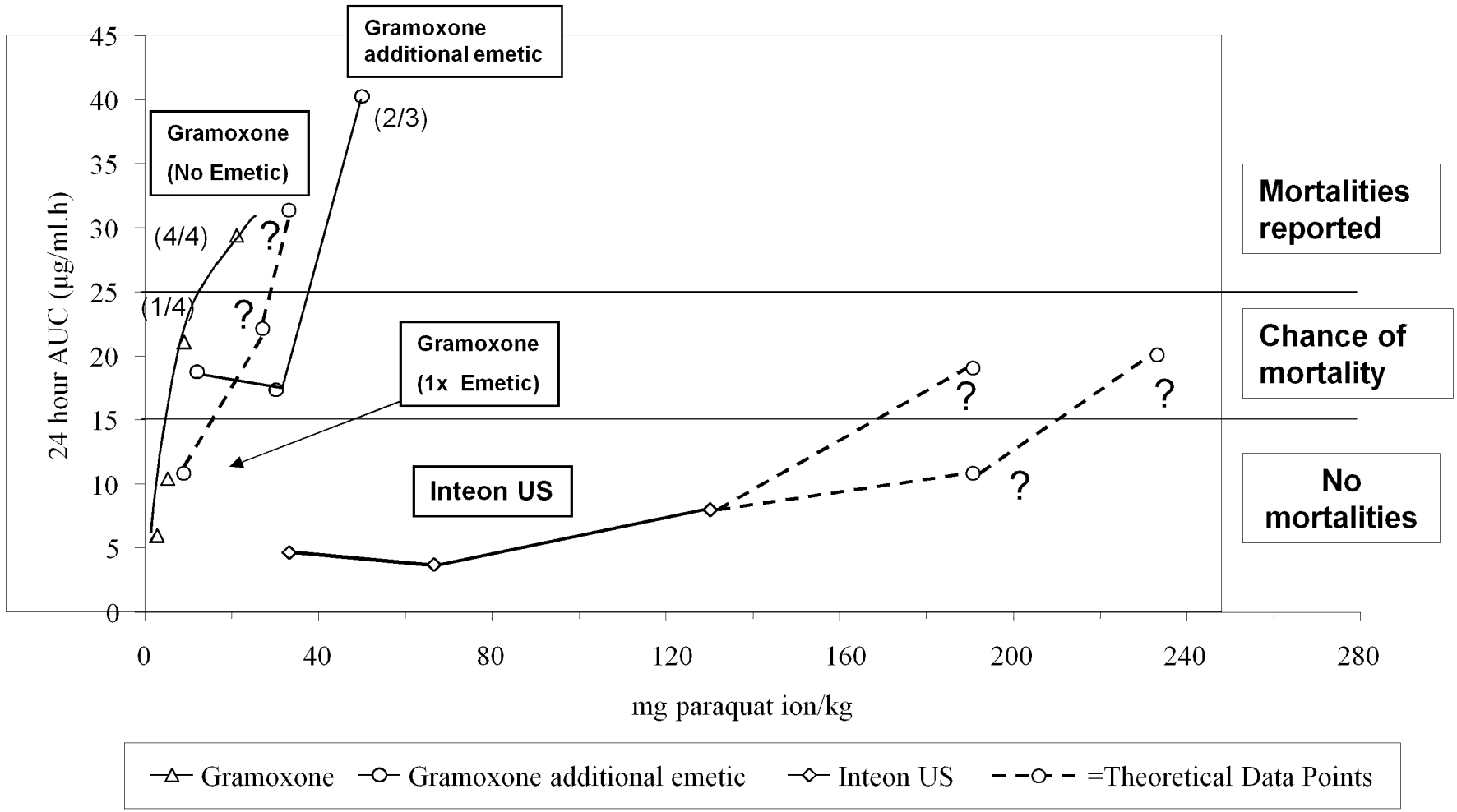
Timing

Planning for animal arrival December

Main study elements: Humane termination criteria

- **Excessive weight loss** and/or extreme emaciation
- **Prolonged absence of voluntary responses to external stimuli**
- **Prolonged anorexia**
- Severe dehydration
- Evidence to suggest irreversible organ failure
- Persistent, difficult, laboured breathing
- Prolonged diarrhoea
- Significant and sustained decrease in body temperature
- Other treatment related effects judged to be indicative of impending death

Comparison of 24h plasma paraquat AUC levels in dog (illustrative)



Sri Lanka Observational Monitoring Survey

Scientific Governance

Steering Group

Responsible for all aspects of the design and conduct of the survey (data capture, analysis, interpretation and reporting)

Dr M Wilks (PI)
Prof R Fernando
Prof PL Ariyananda
Dr M Eddleston
Dr J Tomenson
Mr D Berry

Scientific Advisory Group

To advise the Steering Group on the scientific aspects of survey design, conduct and interpretation

Prof A Dawson (chair)
Prof N Buckley
Dr S Jayamanne
Prof D Gunnell
Prof K Hawton

Commitment to publish results

‘Syngenta commits to present and publish data from the survey in appropriate scientific venues and journals, and will ask the Steering Group to form the core authorship of any future publication of the survey in the scientific literature, seeking the advice and contribution of the Science Advisory Group as appropriate.‘

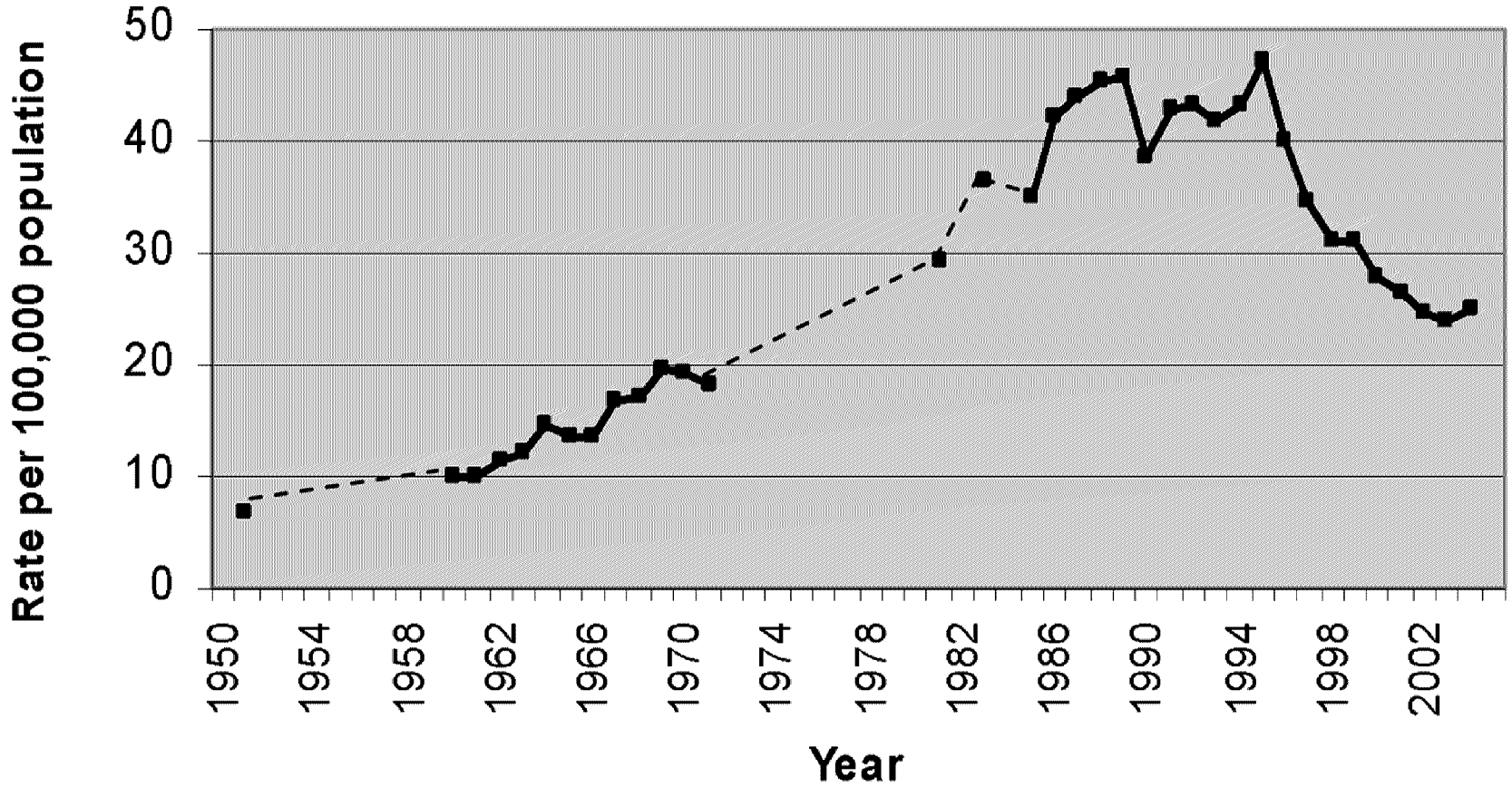
It was an important consideration for the study team and SAP that Syngenta committed to publish the results of the survey.

Survey outline

Objective

- Initially, set up to investigate circumstances of paraquat self-harm incidents
  - Amount ingested; time from exposure to treatment; body weight; time to death ; follow up of survivors after discharge from hospital
- Objective modified to compare the outcome of poisoning cases following the introduction of INTEON® with the standard paraquat formulation.
  - Analytical marker was added to INTEON® to differentiate between old and new formulations

Suicide rates in Sri Lanka from 1950 - 2004



Source: National Poisons Information Centre

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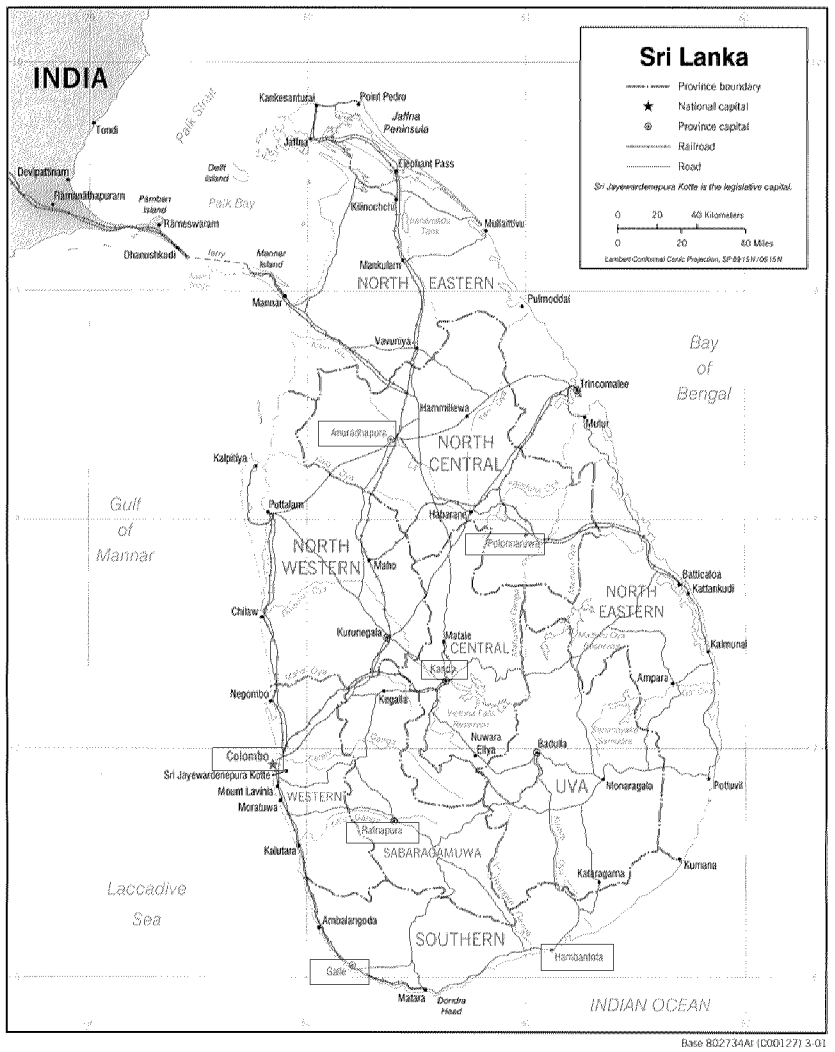
Mortality rates of poison admissions at Anuradhapura General Hospital, Sri Lanka (2.4.02 – 13.1.03)

	# Admissions	# Deaths	Mortality Rates (%)
Oleander	350	25	7.1
Organophosphate	277	39	14.1
Other Pesticides	141	6	4.3
Medicines	101	1	1.0
Carbamates	57	4	7.0
Hydrocarbons	44	0	0
Paraquat	45	21	46.7
Unknown	56	3	5.4
Unknown Pesticides	93	9	9.7
Organochlorines	5	3	60.0
Acid	3	0	0
Alkali	4	0	0
TOTAL	**1176**	**111**	**9.4**

Sri Lanka Observational Monitoring Survey - overview

- 9 hospitals involved
- ~ 350 Gramoxone cases (06/03 – 08/04)
- Introduced Inteon 09/04, later discovered formulation separation problem
- Closed to new cases 01/26/06, at that time 224 confirmed INTEON ingestions (predominantly intentional)
- Criteria for survival: patient alive 3 mo. after release from hospital - end 04/06
- Independent experts met May 2006
- Summary of findings available



Base 8Q2734At (C00127) 3-01

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Survey methodology

Data collected from 9 hospitals

ACCESS questionnaire

Key Parameters

- Amount ingested; time of exposure, time to treatment. Outcome and treatment. Use of Fuller's Earth/charcoal
- Differentiation between Gramoxone and INTEON® formulation
- Plasma paraquat concentration
- Vomiting data
- Body weight, sex, age
- Follow-up of survivors

Power calculation: 210 cases with ingestion of standard product and 210 with INTEON® would give 90% power to detect a x 2-fold reduction in toxicity

Survival by amount ingested

Amount Ingested	Old Product (n=297)			Confirmed or Probable Inteon (n=289)		
	Alive	Unknown	Total	Alive	Unknown	Total
< 5 mls	26 (70.3%)	2	37	22 (68.8%)	1	32
5-10 mls	6 (33.3%)	0	18	17 (68.0%)	0	25
10-15 mls	7 (29.2%)	0	24	19 (44.2%)	0	43
15-30 mls	4 (12.9%)	1	31	18 (40.9%)	2	44
30-50 mls	2 (9.1%)	0	22	6 (20.0%)	1	30
50-100 mls	1 (3.8%)	0	26	5 (16.1%)	0	31
100-150 mls	1 (4.0%)	1	25	1 (7.1%)	0	14
> 150 mls	0	0	38	1 (3.6%)	0	28
Unknown	29 (38.2%)	2	76	13 (31.0%)	0	42
Total	76 (25.6%)	6	297	102 (35.3%)	4	289

Summary and Conclusions

Summary

The overall survival rate is increased from 25.3% to 35.2%

- this is considered clinically significant

All stats analysis indicated that this was a real difference between the two products. The overall reduction in toxicity was approximately 2-fold

The correlation between amount ingested and survival was strong

Patients who have a lethal ingestion of product survive longer with Inteon, allowing more opportunities for intervention medicine

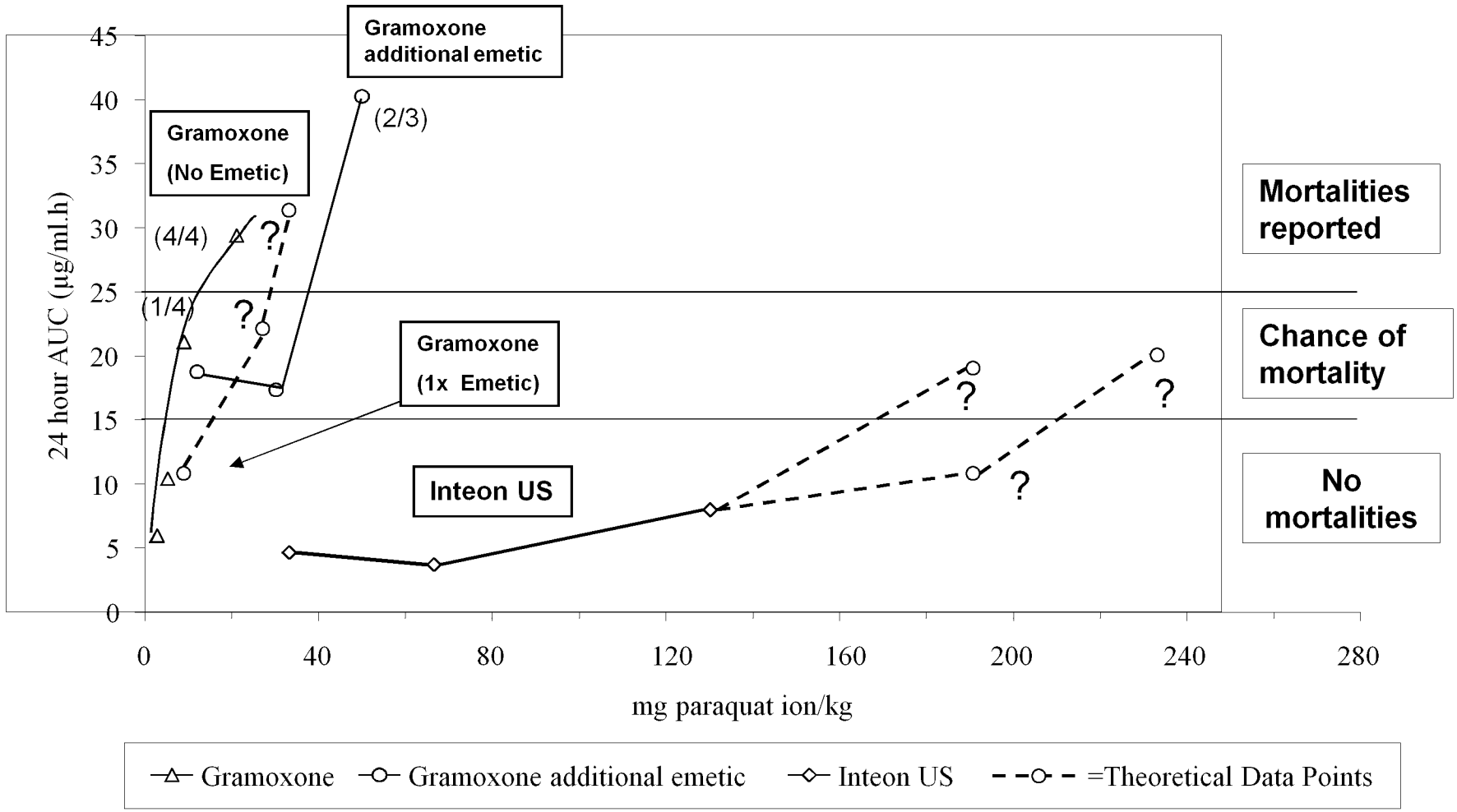
Conclusion

The survey has shown that Inteon® technology significantly improves the survival of patients following paraquat ingestion despite the lack of an optimized formulation

Reporting: Current status

- Presentation made to Asia Pacific Medical Association Meeting in Sri Lanka (5-8 August 2006)
- Draft publication in progress
  - Expected draft for early November, then review by Science Advisory Group (SAG)
  - Approval for release by SAG in November earliest but dependant on agreement and any additional data manipulation required

Comparison of 24h plasma paraquat AUC levels in dog (illustrative)



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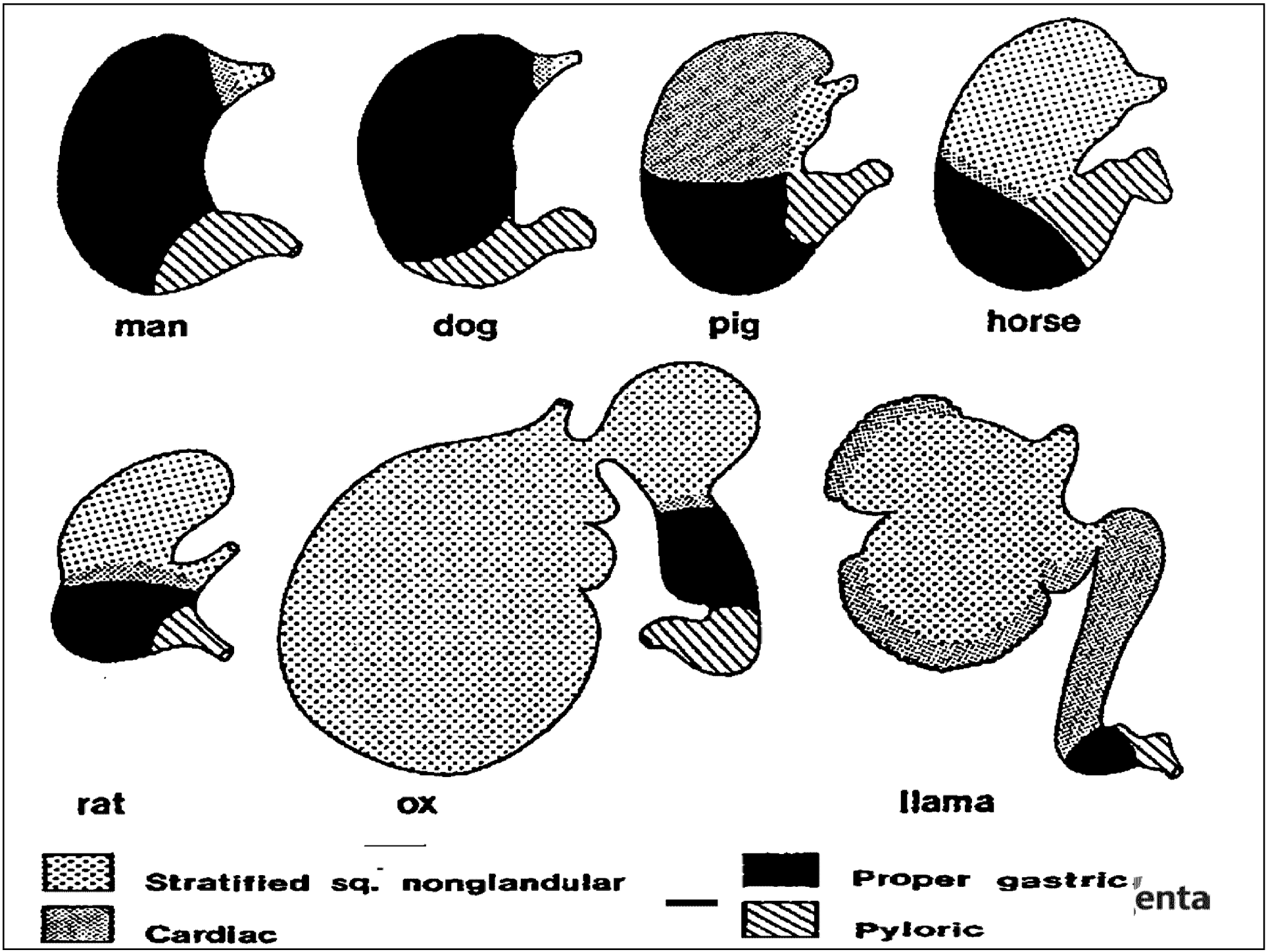
Introduction of Inteon ®

Inteon ® introduced into Sri Lanka Sept 2004. Old product actively removed from distributors and wholesalers.

No change in product label; slightly thicker product due to different surfactants – slightly improved efficacy

Challenges with quality control of formulated product – screening of product to ensure product meets minimum criteria to deliver anticipated safety.

- When left undisturbed, slight phasing of ingredients resulting in surfactant rich top layer with reduced paraquat concentration. Fully homogenised on inversion.
- Alginate associated with lower, paraquat rich (surfactant poor) layer
- Emetic associated with upper, lower paraquat layer
- Increased QC to address possibility of drinking from top layer – increased surfactant would give increased pq absorption
- Only batches that met acceptable profile of paraquat and co-formulants were released for the Sri Lanka market – resulted in approx 50% batches being rejected for use
- Batches air-freighted to Sri Lanka to maintain market commitments



Requirement for use of the dog and issues arising

• Inteon technology requires vomiting as essential for realizing the safety potential

•The dog is a vomiting species

•The dog has good similarity to humans in regard to the stomach and GI tract

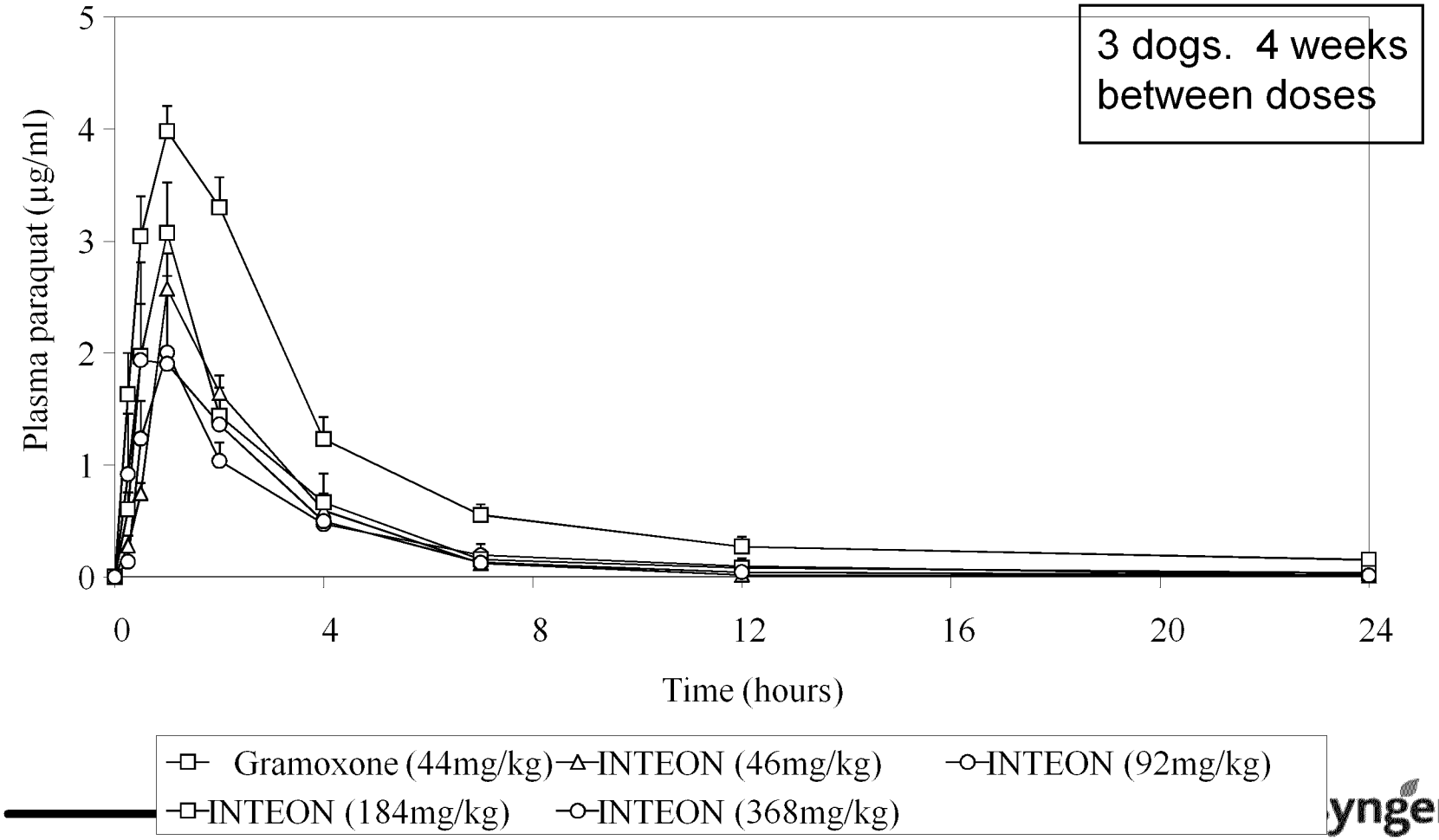
•Need to minimize the use of animals

•Need to minimize the toxicity induced in dogs but retain an evaluation of Inteon against current non-Inteon Gramoxone formulations

•Utilize existing data where possible and non-lethal end-points

Evaluation of paraquat absorption from formulations
Paraquat Absorption in the Dog

Plasma paraquat following an oral dose of Gramoxone INTEON 44-368mg/kg formulation



This chart shows the blood levels of PQ following an oral dose of 200g paraquat ion/l formulation as either Gramoxone or the AWT formulation (A3879BU) in the adult male dog over a range of dose levels.

As with human ingestion (suicide attempts) the increase in dose is achieved by administration of increasing volume and therefore the dose of any component in the formulation would be increased as the dose of paraquat increases, mg/kg bw.

The AWT formulation under identical conditions of dosing etc. caused no toxicity over the dose range 40-320mg formulation per kg bodyweight. There was no toxicity in any animal and no effect on kidney or liver function.

The additional gel, emetic and purgative is more than compensating for the extra PQ given. Consistent with acid triggered gelling in the stomach, the formulation remaining in the stomach longer and more productive emesis.(More of the dose being removed from the body prior to the dose reaching the small intestines.

Emesis occurred at approximately 53mins – low dose and approximately 25 mins high dose.

[Gramoxone contains 0.5g/l emetic, whereas A3879BU contains 1.5g/l, but it is the effectiveness of the emetic and gelling which is important rather than the level of emetic per se.]

Gramoxone control data was generated at CTL between 1987 and 1991. Mean of 7 independent groups of dogs (n = 3 each). The blood levels shown (in black) are well tolerated in this species with no acute toxicity.

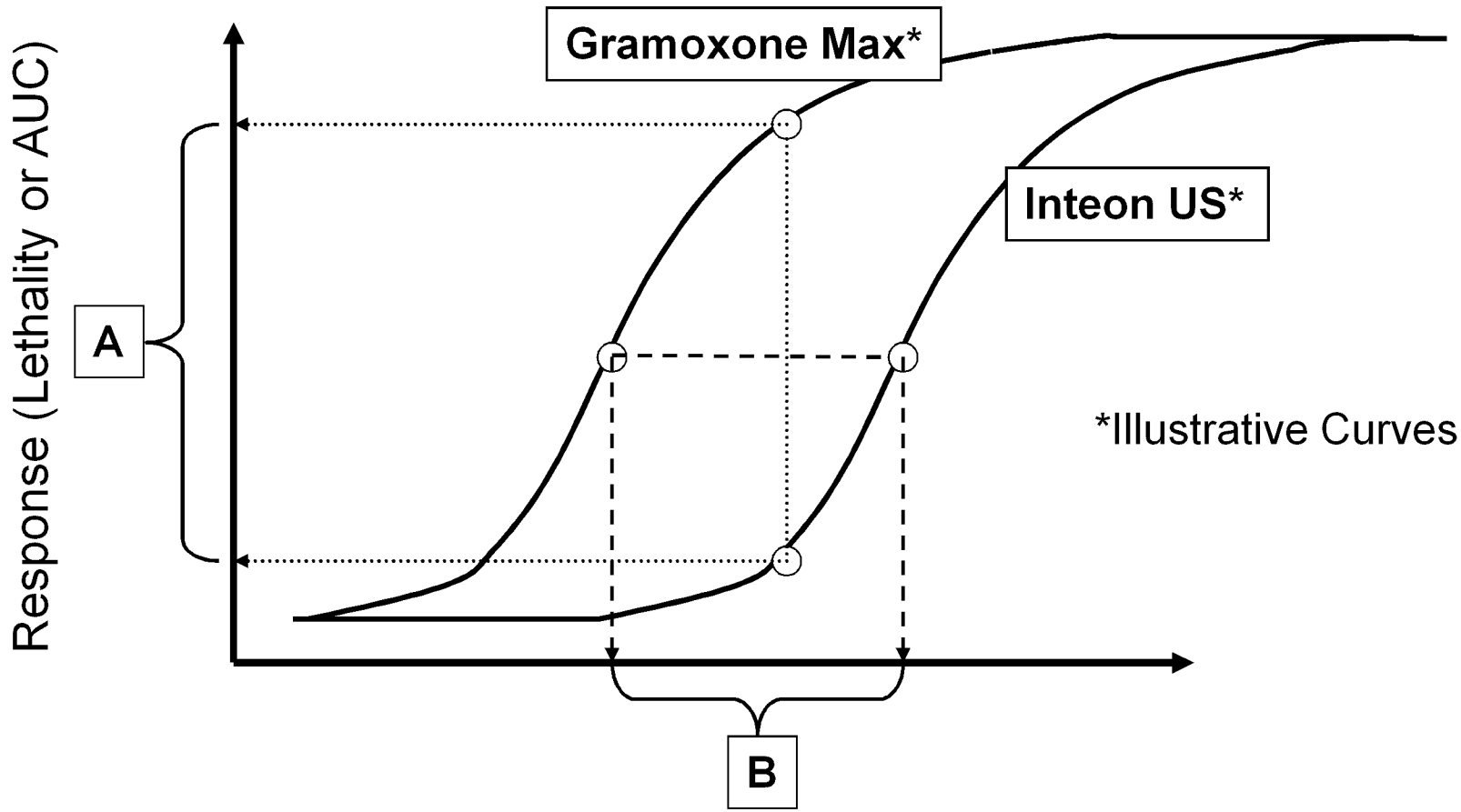
How does this relate to a lethal dose in dogs? This is kinetic study but we use a criteria of a peak plasma paraquat level of 10µg/ml or a 24 hour AUC of 40 µg/ml /h as the criteria for humane termination of test animals since it would lead to overt toxicity.

Evidence in the dog - background

- These data provide the rationale for not testing Gramoxone at doses greater than 8 mg/kg (sub-lethal)

- Higher doses of Gramoxone (e.g., 16, 32, 64, and 128 mg/kg) doses would be expected to result in mortality

Theoretical Dose-Response Comparisons



A= The difference in degree of response at the same unit dose

B= The difference in dose to achieve the same degree of response

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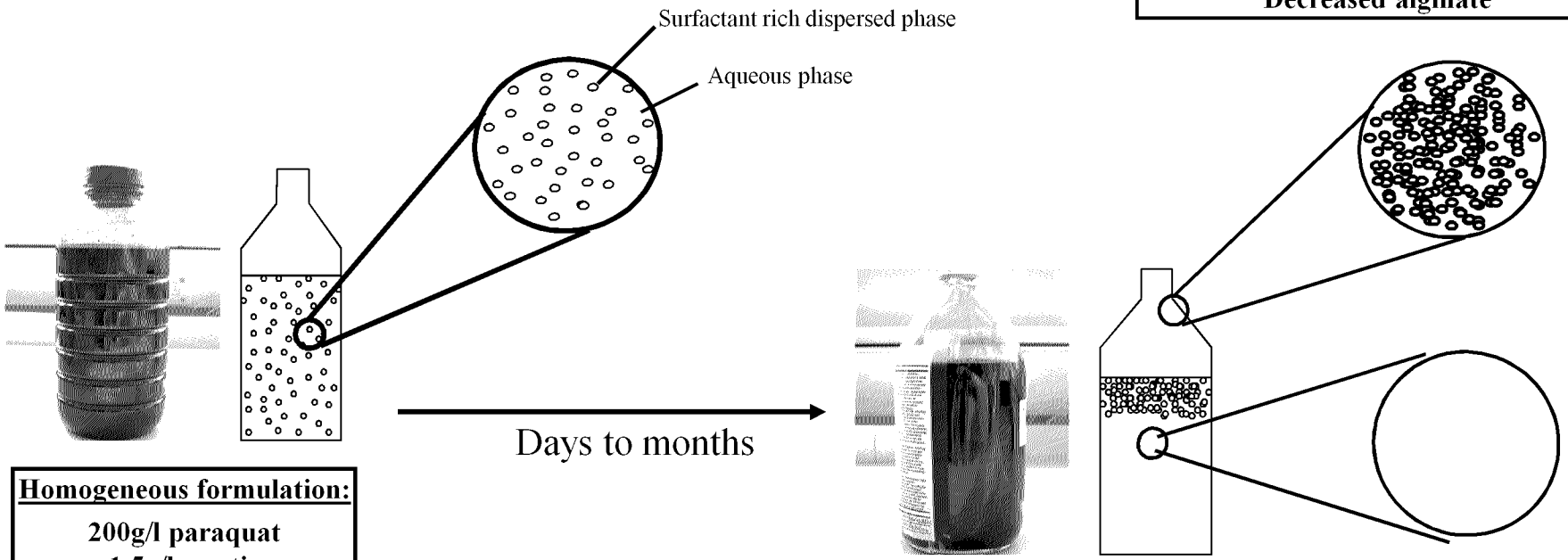
Inteon Sri Lankan formulation: Illustration of formulation separation

Top:

Decreased Paraquat loading
Increased Emetic loading
Greatly increased Surfactant loading
Decreased alginate



Homogeneous formulation:

200g/l paraquat
1.5g/l emetic
9g/l alginate
~100g/l surfactants

Bottom:

Increased Paraquat loading
Decreased Emetic loading
No Surfactant
Slightly increased alginate

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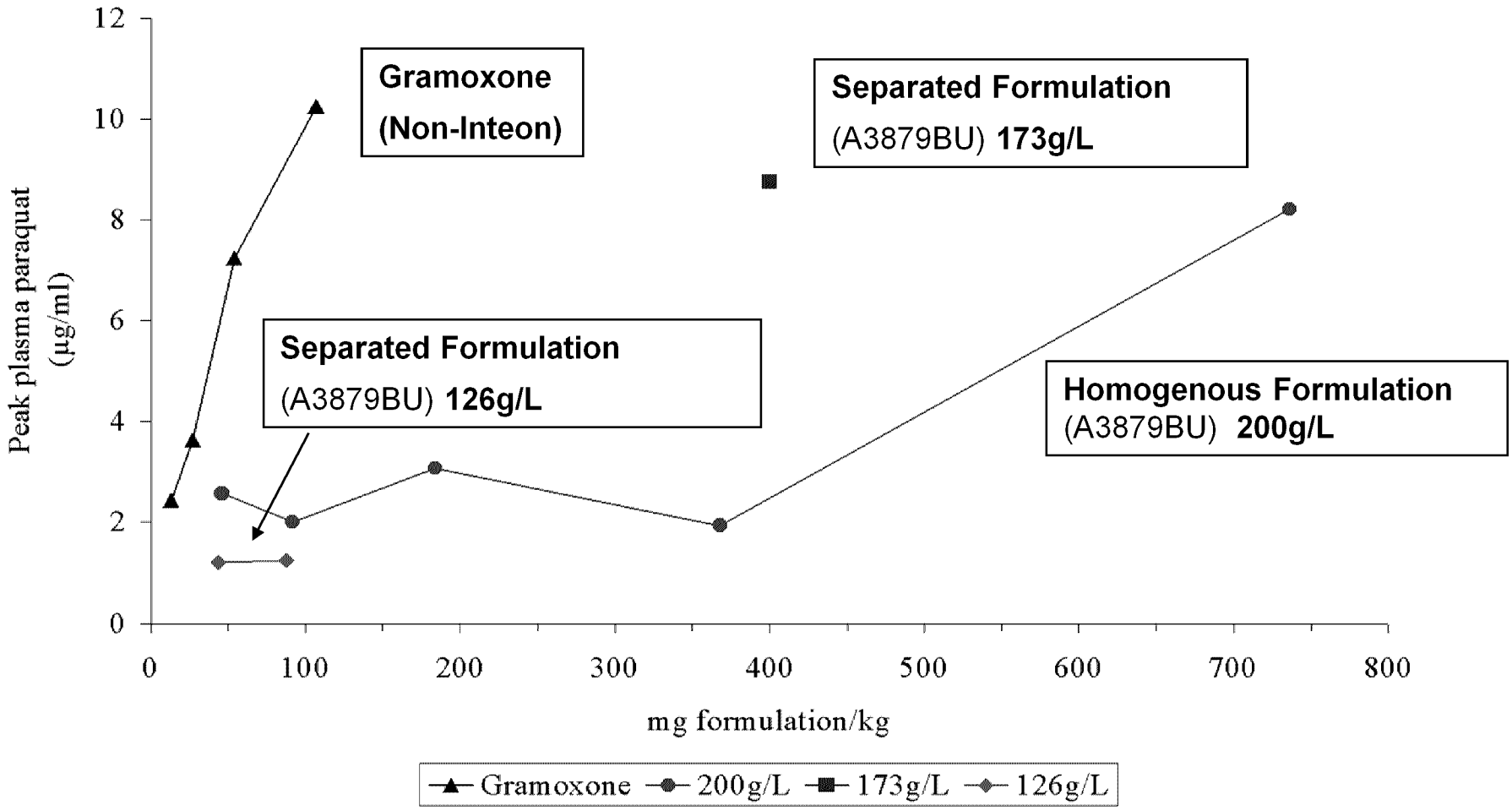
- The analytical profile of bottom phase is very similar to US formulation

- NB – no visual difference between homogeneous and separated formulation (recall demonstration), even in clear packs – and sales packs are essentially opaque (recall demonstration)

Inteon formulation in Sri Lanka: Plasma Paraquat Levels in Dogs



Separated Inteon formulation shows reduced safening but safer than Gramoxone

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Status of the Inteon formulation used in Sri Lanka

Separated Inteon formulation A3879BU

- ✓ It is safer than Gramoxone
- ✓ Not as safe as homogenous Sri Lankan Inteon formulation (A3879BU)
- ✓ Not as safe as the Inteon US formulation (A7813K)

  Inteon US does not separate

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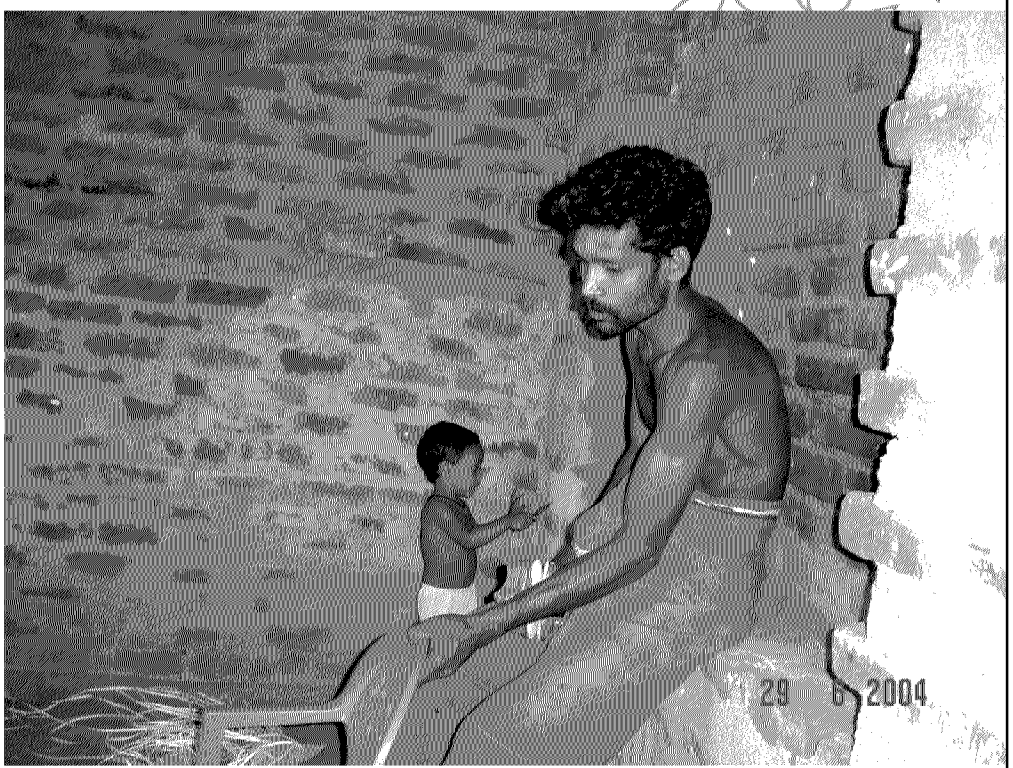
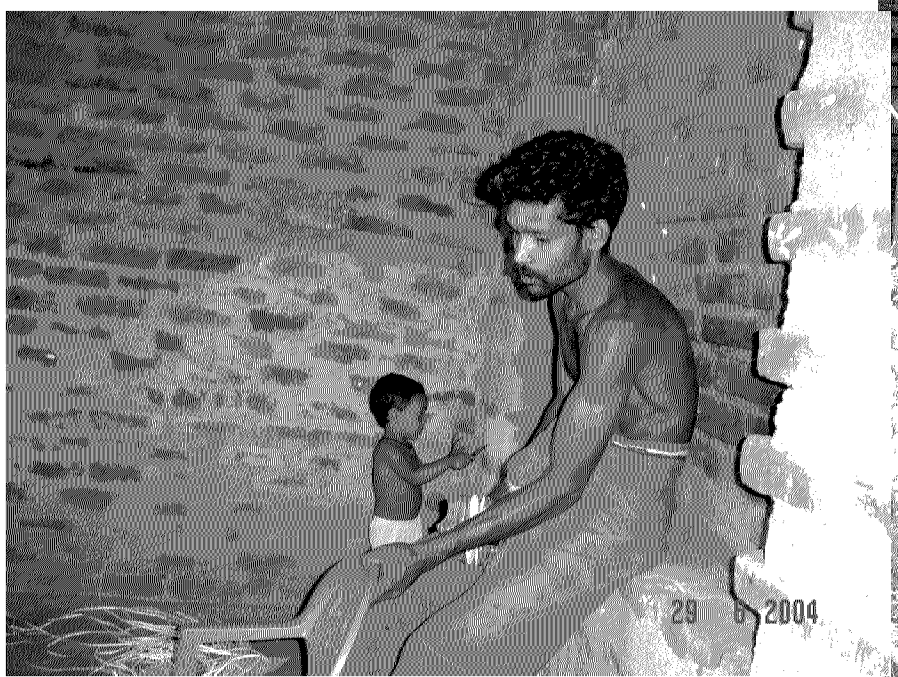
Locking up chemicals to prevent deliberate self-harm: A feasibility study in Hettipola and Lunugamvehera Sri Lanka

A Secure Access project

Visit notes David Scott March 05

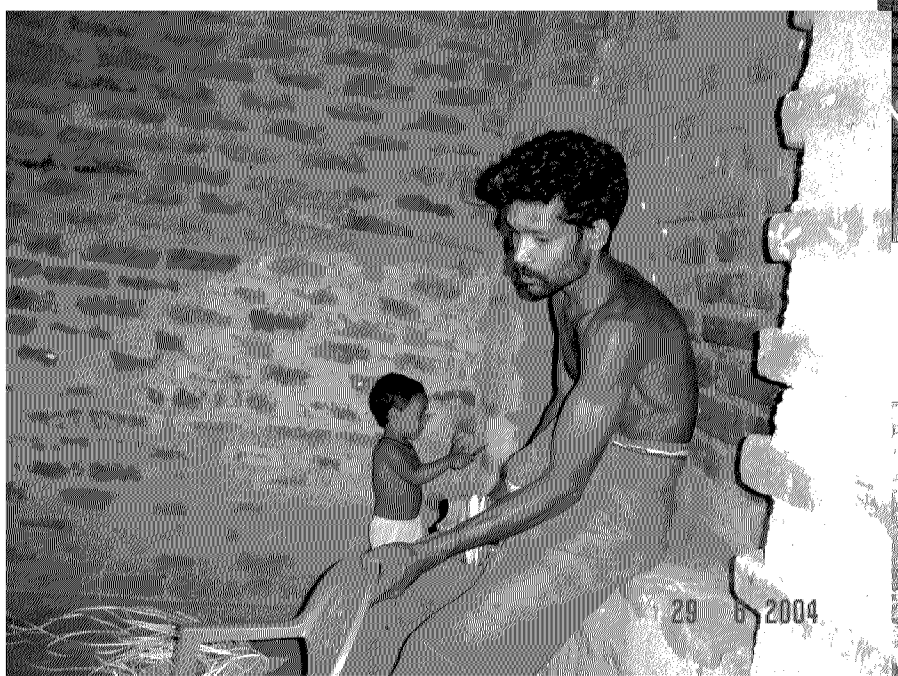


the project

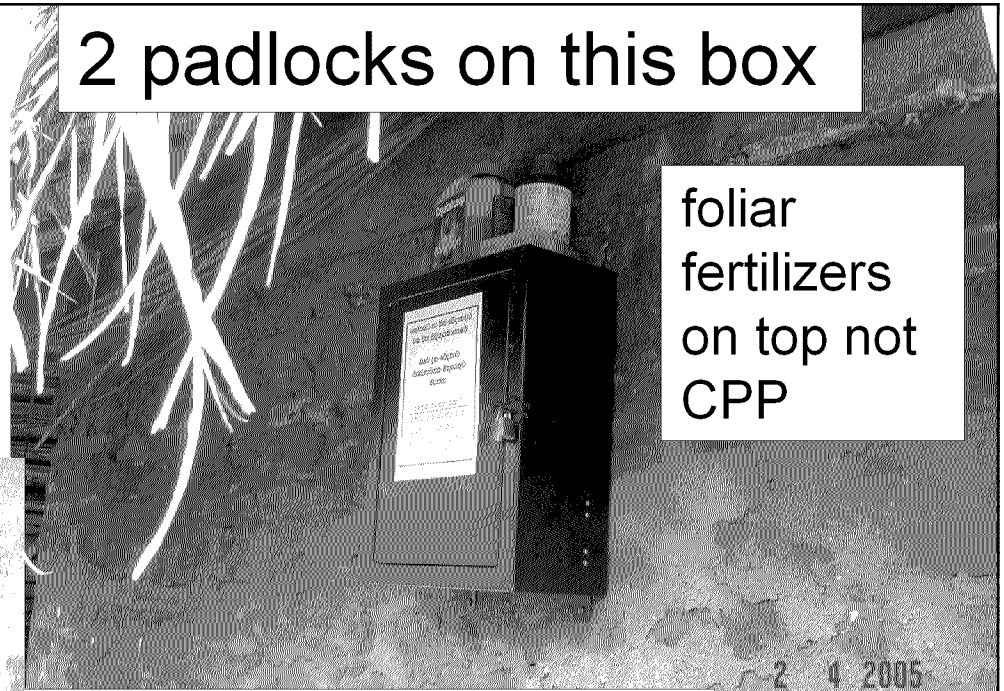


few places to securely store chemicals in simple village houses

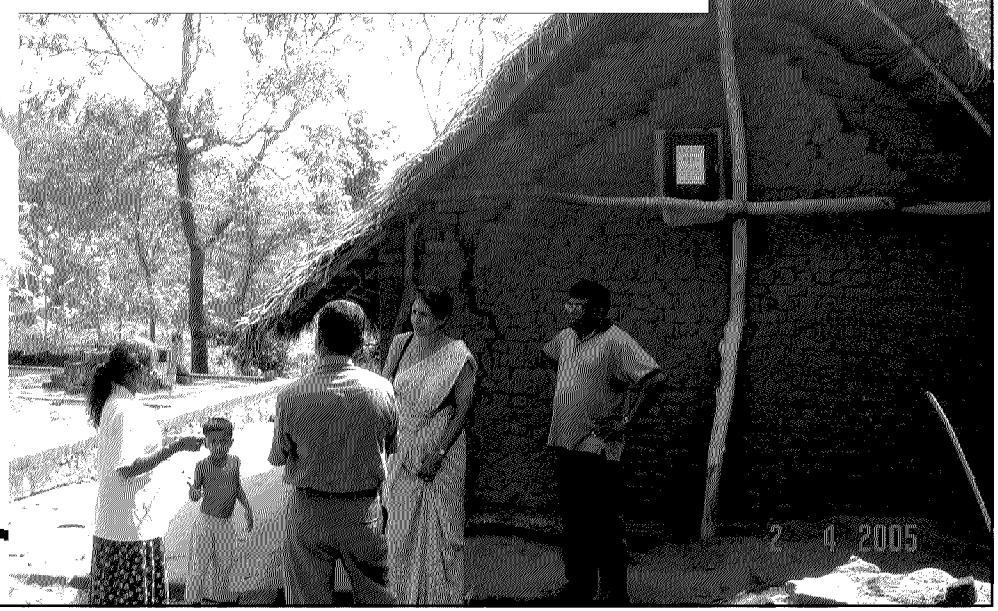
the project



few places to securely store chemicals in simple village houses

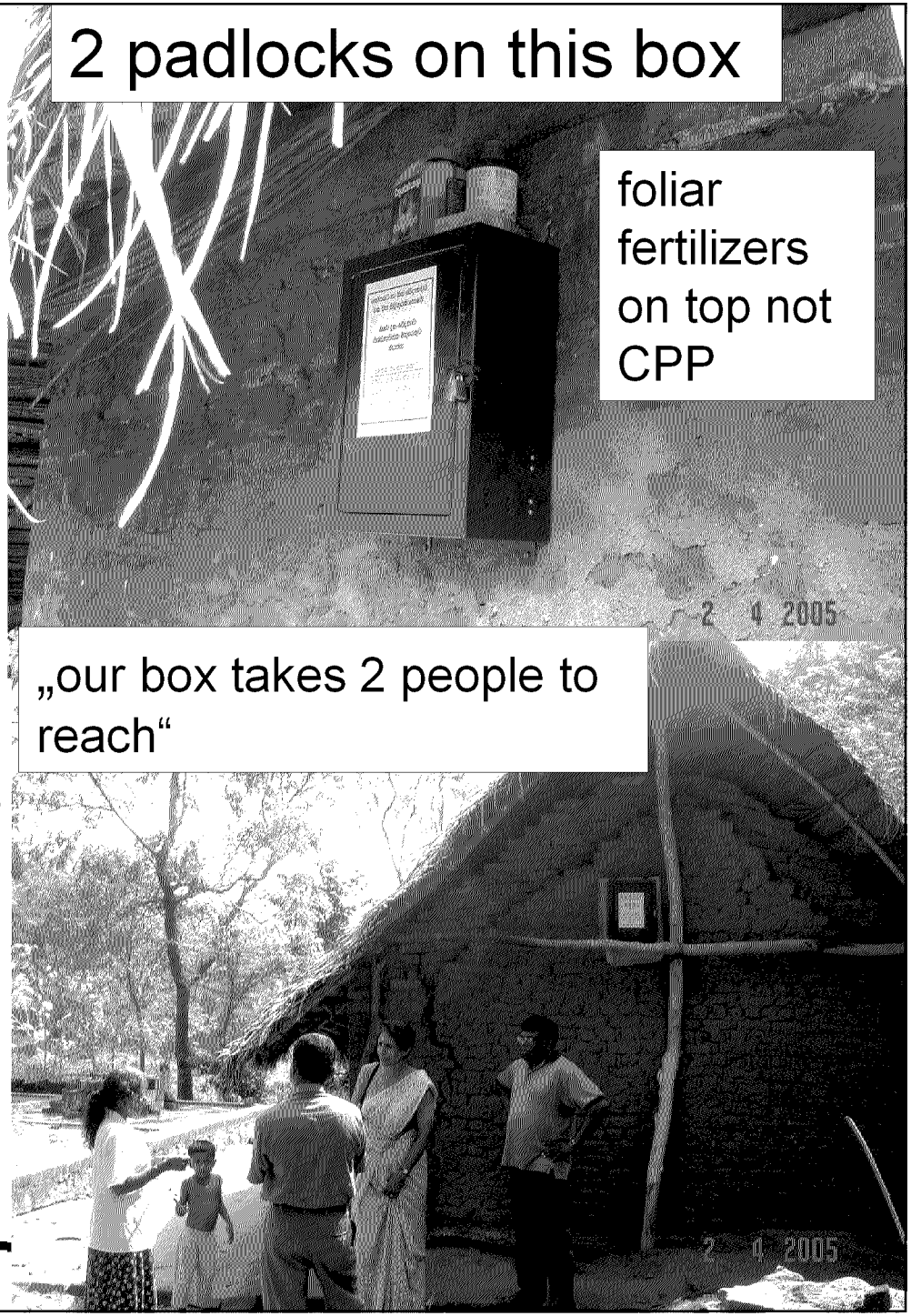


„our box takes 2 people to reach“

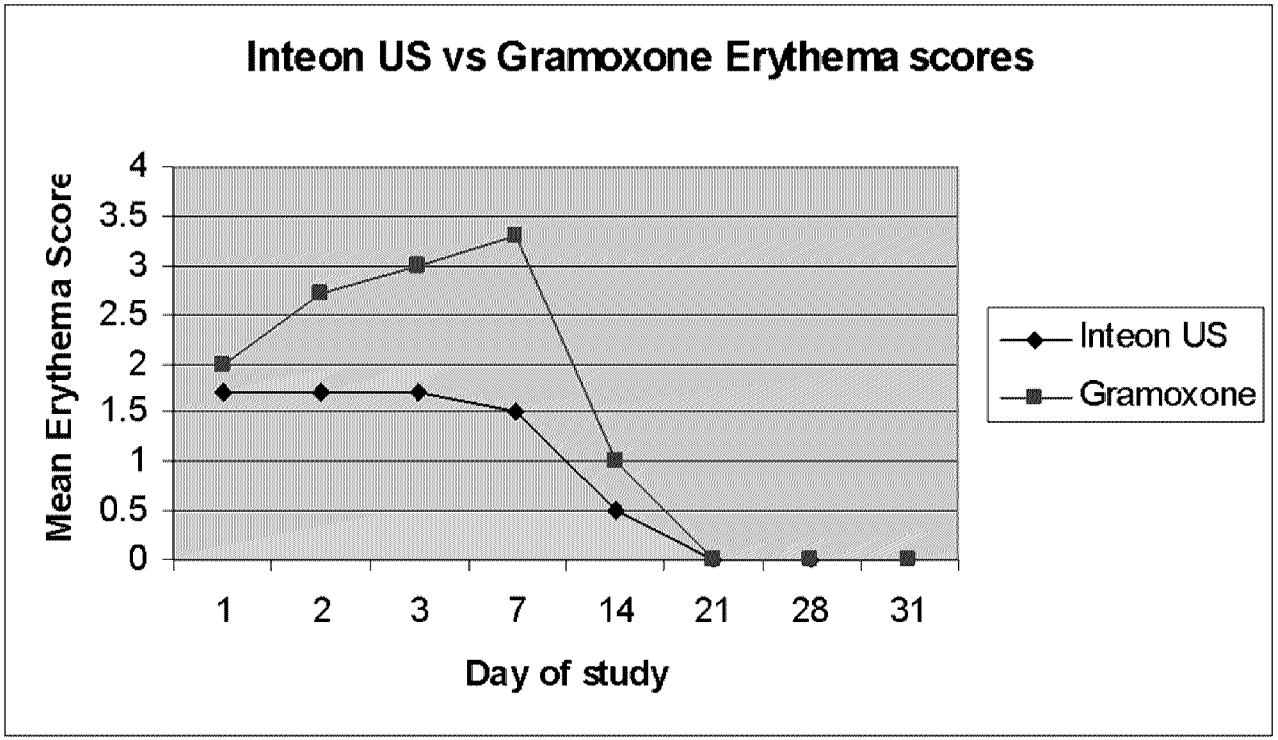


the project

- Conceived by Sumithrayo with support from CIC and Syngenta
- working together to reduce suicide from drinking CPPs by implementing secure access on small holdings
- 100 metal boxes distributed in 2 areas - 2 villages per area –each box cost 2500 rupee
- safety messages on each box – “talk to a friend…..”
- The Sumithrayo volunteer network introduced the project and obtained community agreement to implement
- boxes distributed via a lottery system to willing families thought to have “at risk” members
- some boxes with 1 lock some with 2 locks with separate keys
- Sumithrayo checking on use, experiences and impact of the boxes



Skin Irritation Comparisons



Erythema Scores:

0 No erythema

1 Very slight (barely perceptible)

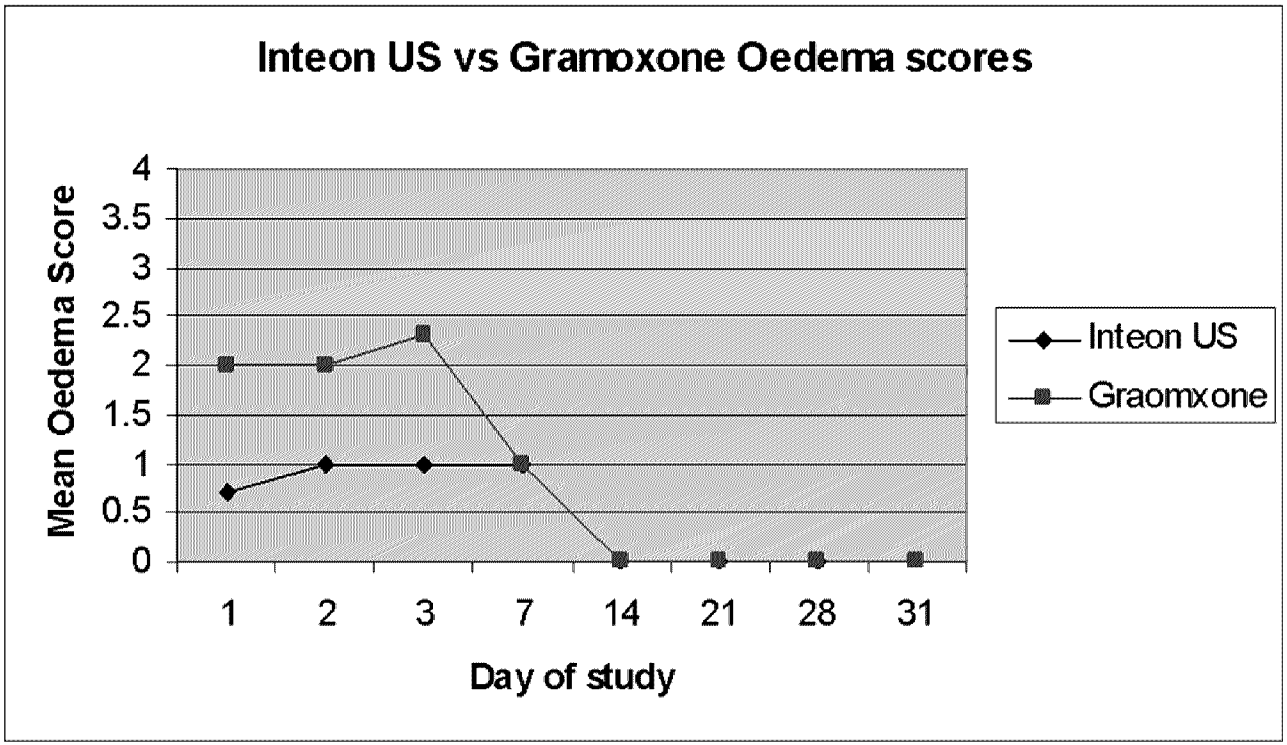
2 Well defined

3 Mod to severe

4 Severe (beet redness)

syngenta

Skin Irritation Comparisons



Oedema Scores:

0 No oedema

1 Very slight (barely perceptible)

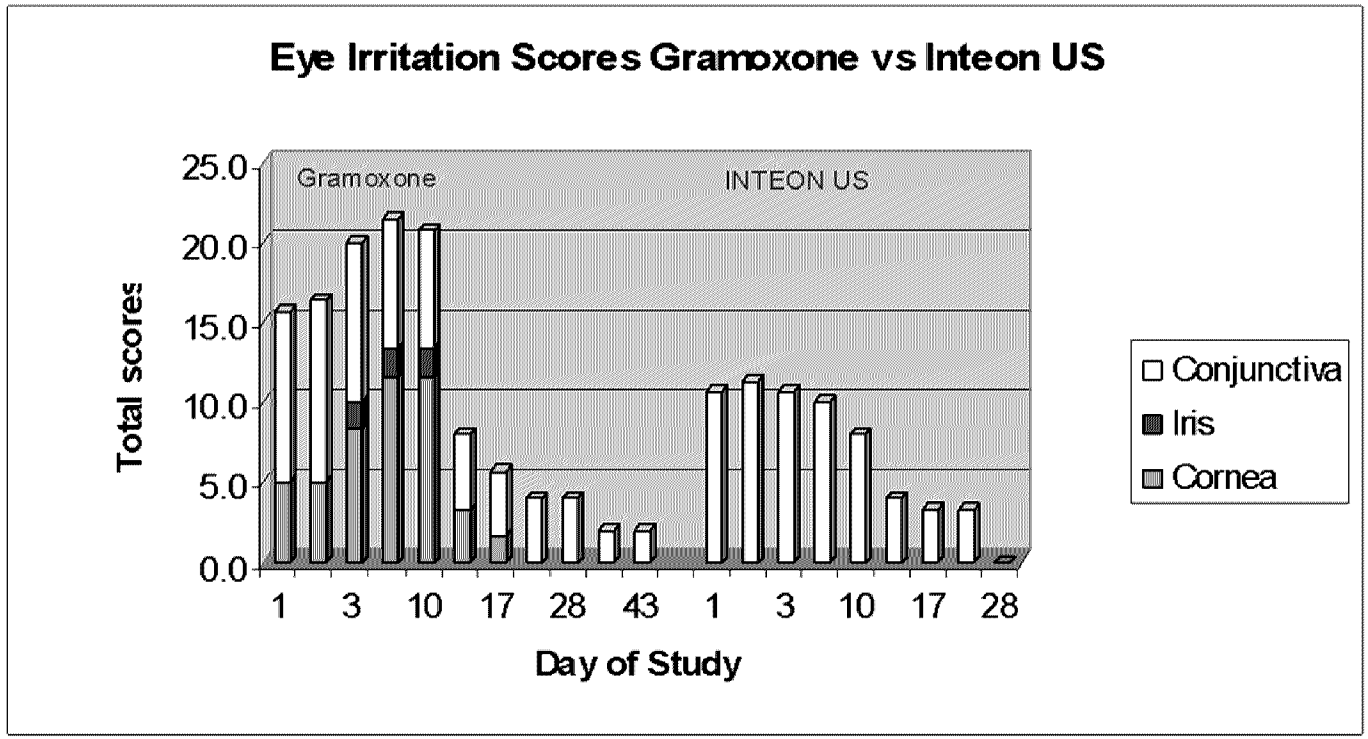
2 Slight (edges of area defined by definite raising)

3 Moderate (raised approx 1mm)

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

syngenta

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

syngenta