Improvement in survival following paraquat ingestion after introduction of a new formulation with INTEON® technology in Sri Lanka

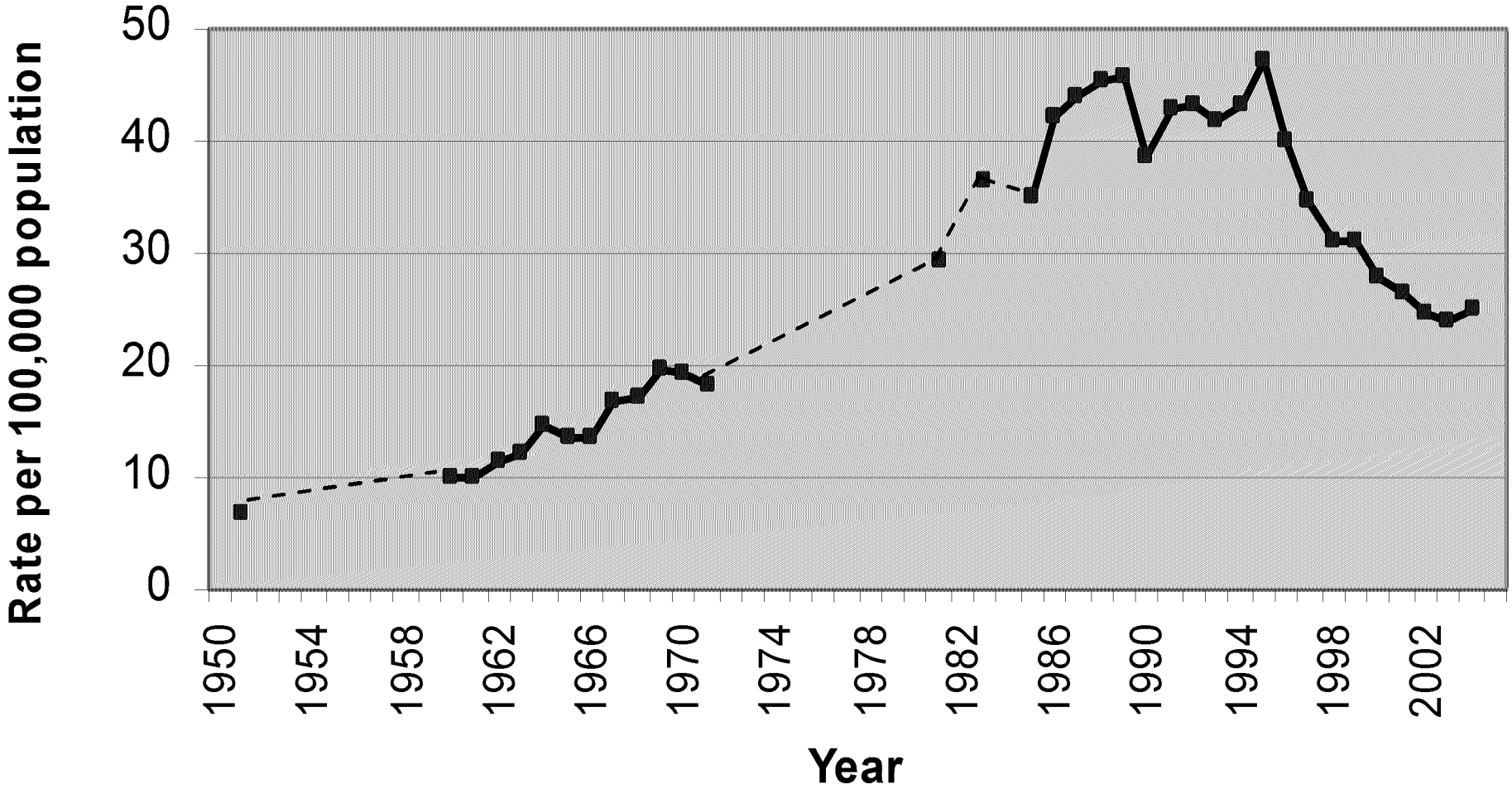
Martin Wilks, Ravindra Fernando, P L Ariyananda, Michael Eddleston, Dave Berry, John Tomenson, Nick Buckley, Shaluka Jayamanne, David Gunnell, Andrew Dawson

Background

- Self harm with pesticides is a significant public health concern in many developing countries.
- Recent studies estimate that as many as 300,000 deaths from pesticide self poisoning may occur in the Asia-Pacific region – accounting for up to one quarter of the world‘s suicides.

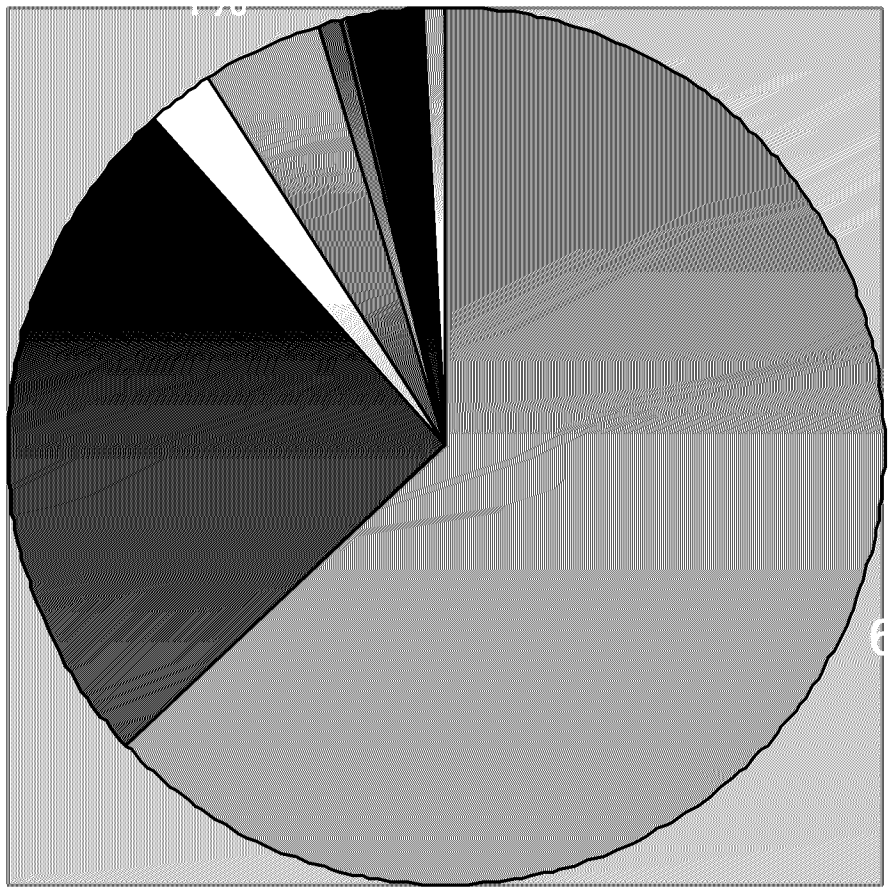
  Phillips, Lancet, 2002, Eddleston, BMJ, 2004
- Strategies to address this problem include
  - Reducing the hazard of pesticide formulations
  - Limiting availability of products for self harm
  - Improving medical management of poisoning

Suicide rates in Sri Lanka from 1950 - 2004



Source: National Poisons Information Centre

Methods used to commit suicide in Sri Lanka (2004)



- Self poisoning
- Hanging
- Drowning
- Self immolation
- Firearm use
- Explosives
- Sharp weapons
- Jumping in front of trains/motor vehicles
- Jumping from a height
- Over dosage of drugs
- Others

Source: National Poisons Information Centre

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**

Paraquat in Sri Lankan agriculture

- Non-systemic, fast acting
- Rain-fast, quickly deactivated in soil
- No tillage preserves soil structure

- No damage to surrounding crops
- Broad spectrum, no weed resistance
- Key crops in Sri Lanka are tea and rice

Paraquat INTEON® technology - what is it?

Acid triggered gel

Emetic

$MgSO_4$

Benefits:

Acid Triggered Gel: Alginate, *Ascophyllum* Seaweed extract: coats skin, reduces irritancy and reduces gi tract absorption

Emetic: more productive emesis

$MgSO_4$: purgative

slightly thicker, less odour

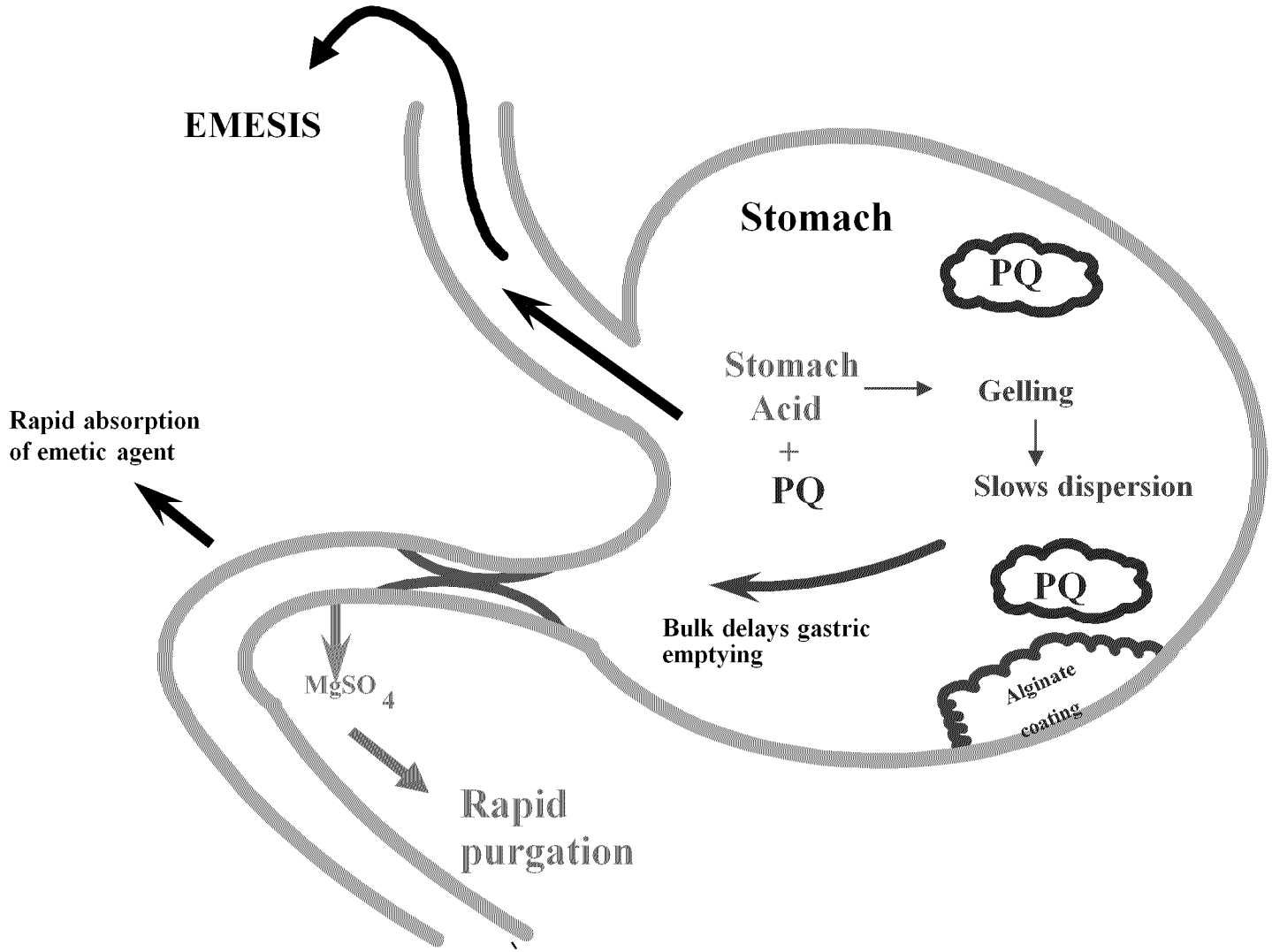
Complex technology, based on optimized package of factors

- Efficacy
- Skin / Eye irritation improvements
- Lowering Ingestion toxicity

Speaker Notes:
3 components which together reduce absorption of pq from the gi tract
Alginate – is used in medical and dietary preparations – bulking agent closes pyloric sphincter. Bulking triggered by pH 3-4 acid in stomach
Emetic – CNS acting emetic (not local irritant) – lipophillic and absorption unaffected by alginate gel. Note – Syngenta formulations have always contained emetic but we have increased concn to give quicker and more effective emesis
Mag Sulphate – any soln that does get through to intestine should be rapidly purgated

In addition to oral safening, animal studies show improved skin and eye irritancy

How does INTEON® work in the G.I. tract?



Gelling

+

Emesis = Safening

+

Purgation

Speaker Notes:
This slide shows a diagrammatic representation of the human stomach.

Each of the 3 processes; gelling, emesis and purgation would in their own right reduce the oral absorption of PQ. Together they would act synergistically and could potentially improve the oral toxicity following oral ingestion.

A key consideration is that a minimally lethal dose of product contains an effective dose of gelling agent, emetic and purgative.

An extensive research programme has investigated the potential of the Inteon technology to deliver such a benefit following oral ingestion.

Survey outline

- Objective
  - Initially, set up to investigate circumstances of paraquat self-harm incidents.
  - 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

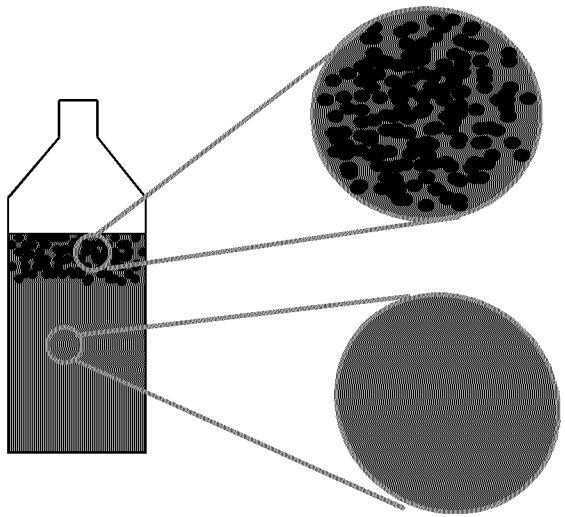
Speaker Notes:
Biomarker was diquat at an inclusion rate of 500ppm – able to detect in plasma and urine at 2ng/ml levels

Governance

- Legal
  - New formulation registered in Sri Lanka following review by PETAC
- Ethical
  - Review and approval by Ethics Committees covering all participating hospitals
- Scientific
  - Establishment of a Steering Committee and independent Science Advisory Panel
  - Commitment to publish results

Introduction of INTEON®

- INTEON® introduced into Sri Lanka Sept 2004. Standard product actively removed from distributors and wholesalers.
- Challenges with quality of formulated product – separation of ingredients into two phases



Paraquat ↓, alginate ↓, emetic ↑, surfactant ↑↑↑

Paraquat ↑, alginate ↑, emetic ↓, no surfactant

- Quality control of batches to ensure product meets minimum criteria to deliver anticipated safety.

Speaker Notes:
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

Survey methodology

Data collected from 9 hospitals

- ACCESS questionnaire
- Key Parameters
  - Amount ingested; time of exposure, time to treatment. Outcome and treatment. Use of FE/charcoal
  - Differentiation between Gramoxone and INTEON® formulation
  - Plasma paraquat concentration
  - Vomiting data
  - Body weight, sex, age.
  - Follow-up of survivors
- Needed approx 210 cases with INTEON® to detect a x2-fold reduction in toxicity.

Speaker Notes:
Data collected over 26 months – new product with Inteon introduced September 2004

Statistical methodology

- Non-parametric analysis methods (Kaplan-Meier survival curve estimates and log rank tests)
- Cox's proportional hazards regression to identify prognostic factors and adjust for possible confounding factors. Covariates included:
  - estimate of ingested paraquat concentrate;
  - sex, age and body weight of subject;
  - treatments received; adsorbent use;
  - time between ingestion and start of medical care.
- Stratification by treatment centre (9 hospitals) used to account for clustering by centre.

Survey subjects

Total cases (1.12.2003 to 26.1.2006)	779
Exclusions non-oral/refusals (38); Kassipu incident (36); duplicates (5); sample with no patient record (4);inadequate information(1)	84
Cases not included during "washout"	62
Cases with standard product excluded since introduction of INTEON, post washout	47
Incidents included with standard product	**297**
Incidents included with INTEON® (195 confirmed with plasma/urine analysis; 94 classified as 'probable' post washout period)	**289**

Speaker Notes:
The 62 cases excluded during “wash-out” … the assumption was that after we had 2 confirmed INTEON cases at a hospital, then all cases after that time where it was equivocal whether the patient had INTEON or standard product (ie ingestion too low to detect biomarker), these would be considered to be INTEON cases. Up to this time, it would be uncertain if they were standard or INTEON cases and thus they were excluded
47 cases excluded after post “washout” – the cohort for the standard cases group was all patients up to introduction of INTEON.

Demographic details

	Standard product (n = 297)		**Confirmed or probable Inteon (n = 289)**	
	Mean (SD)	unknown	Mean (SD)	unknown
Age (year)	**31.0 (13.7)**	-	**29.4 (12.5)**	1
Weight (kg)	**55.0 (8.1)**	65	**56.4 (9.0)**	50
	N (%)		N (%)	
Sex: male	**230 (77.4%)**	-	**233 (80.6%)**	-

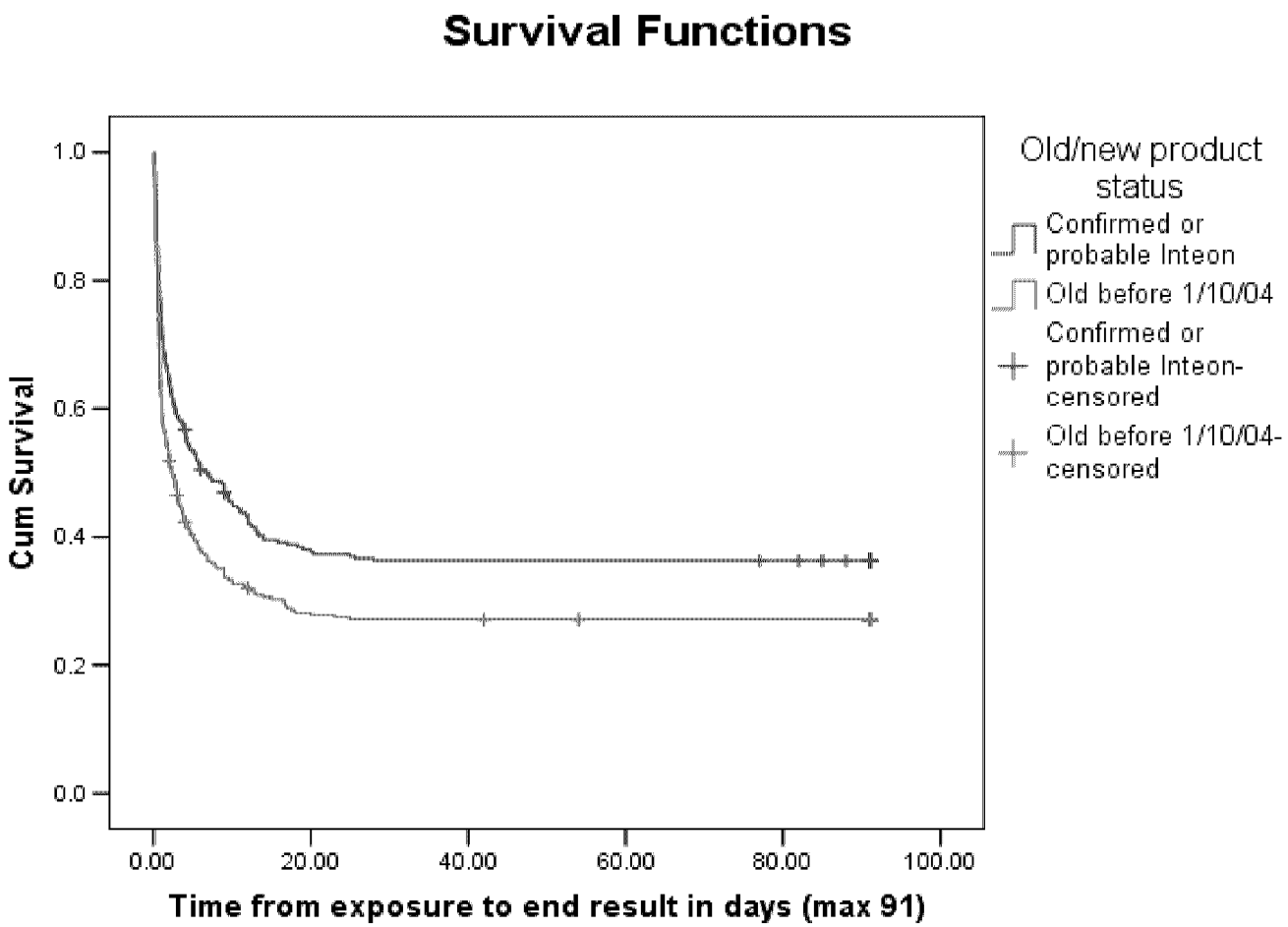
Clinical details

	Standard product (n=297)		Confirmed or probable Inteon (n=289)	
	N (%)	n.k.	N (%)	n.k.
Vomit. w/i 15 min	**113 (38.0%)**	**38**	**158 (54.7%)**	**37**
Treated w/i 4 h	174 (58.6%)	29	157 (54.3%)	26
Fullers Earth	233 (78.5%)	1	209 (72.3%)	17
Charcoal	11 (3.7%)	1	5 (1.7%)	17
Anti-emetic	38 (12.8%)	22	50 (17.3%)	11
Cyclophos.	34 (11.4%)	27	38 (13.1%)	19
IV fluids	277 (93.3%)	3	257 (88.9%)	10
Diuretics	22 (7.4%)	12	28 (9.7%)	20
Prednisolone	**50 (16.8%)**	**23**	**27 (9.3%)**	**19**
Lavage	**162 (54.5%)**	**11**	**115 (39.8%)**	**19**

Survival by Group

		Outcome 3 months after ingestion			
		Dead	Alive	Unknown	Total
Standard product before 1/10/04	Cases	215	76	6	297
	%	72.4%	25.6%	2.0%	100.0%
Confirmed or probable Inteon	Cases	183	102	4	289
	%	63.3%	35.3%	1.4%	100.0%
Total	Cases	398	178	10	586
	%	67.9%	30.4%	1.7%	100.0%

INTEON® and standard product survival curves

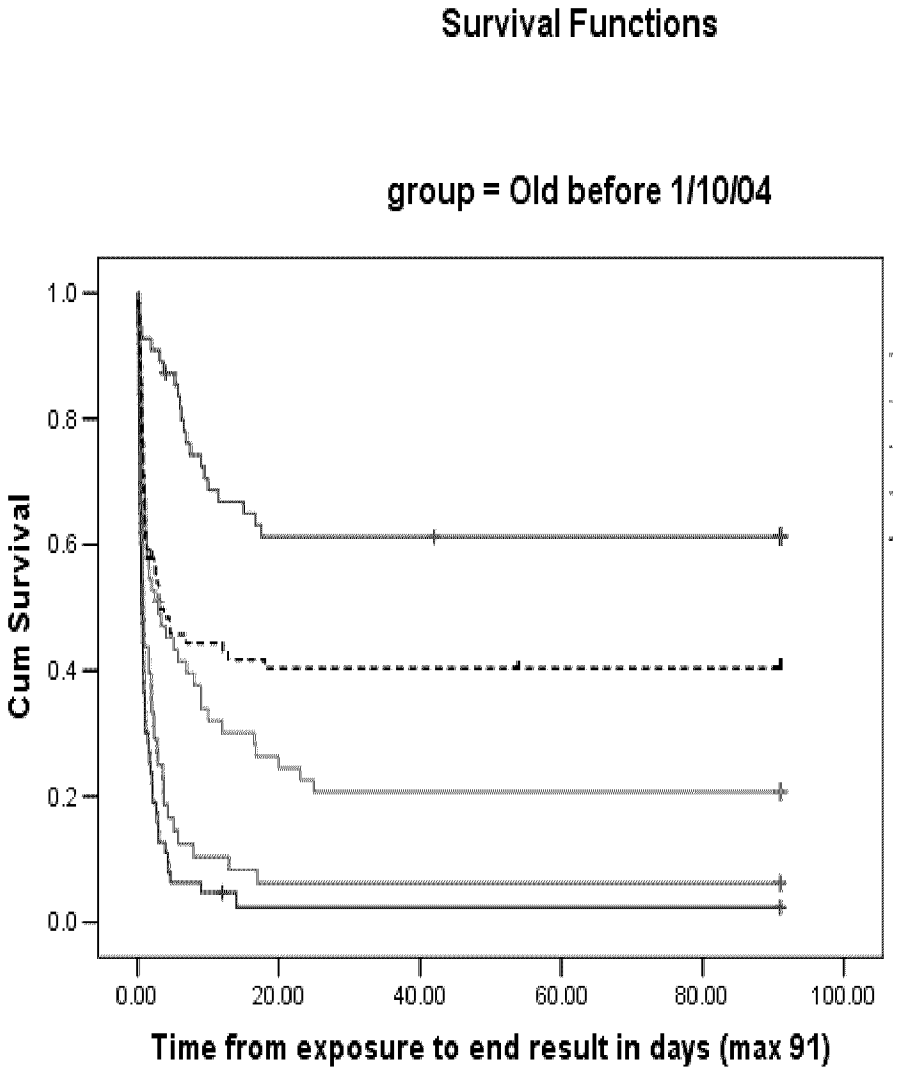


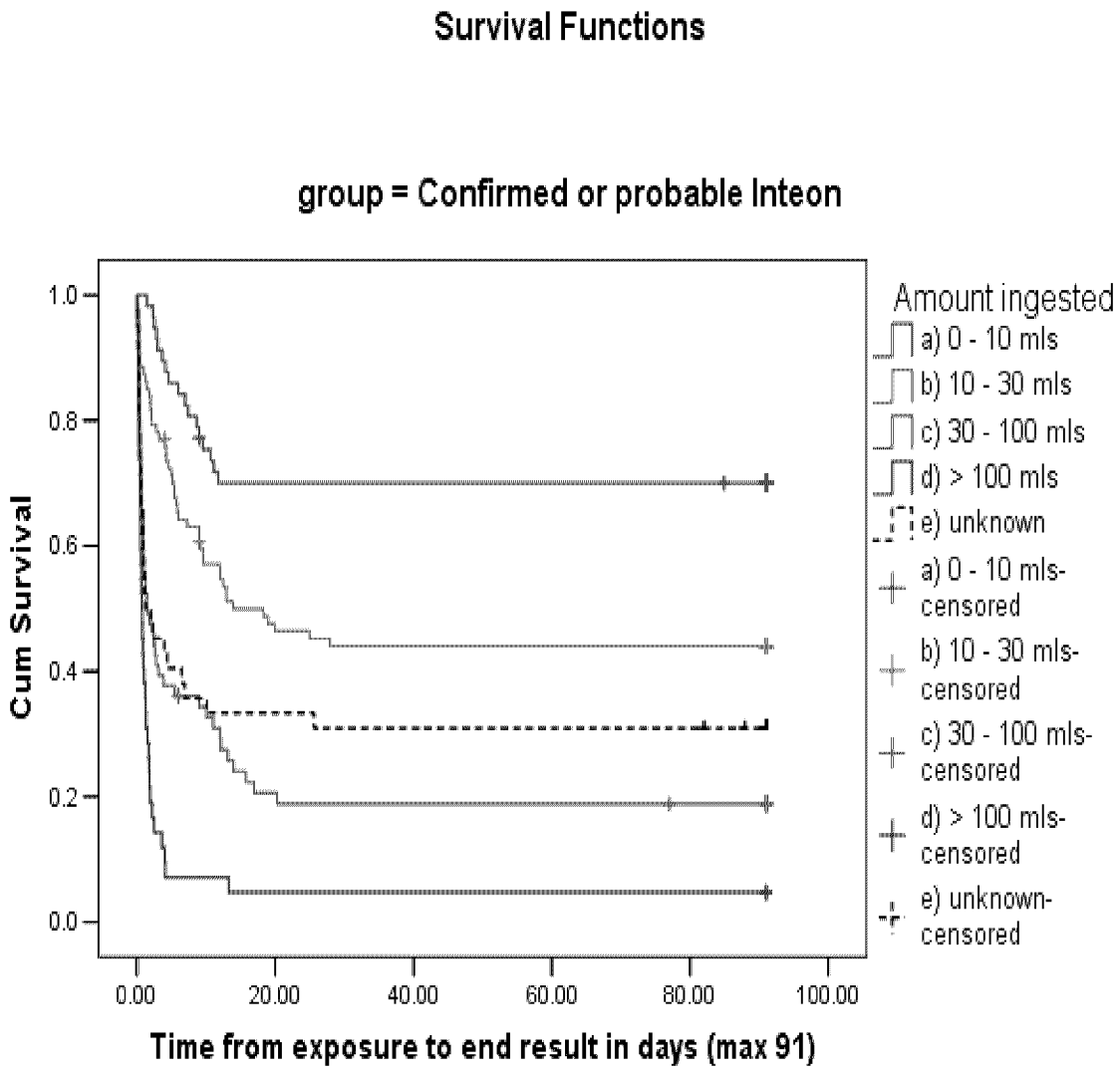
Overall Comparisons

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox	9.187	1	.002

Test of equality of survival distributions for the different levels group Old/new product status.

Survival by group





Median survival time

Cox PH regression – Log Dose
Stratification by Centre

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
group	-.366	.129	8.018	1	.005	.694	.538	.893
age50	.911	.183	24.757	1	.000	2.487	1.737	3.561
sex	.334	.160	4.384	1	.036	1.397	1.022	1.910
weight	.019	.009	4.778	1	.029	1.019	1.002	1.036
absorb	.137	.180	.576	1	.448	1.146	.806	1.631
rx4hrs	.068	.132	.266	1	.606	1.070	.827	1.385
lavage	.143	.148	.937	1	.333	1.154	.863	1.543
lndose	.649	.053	50.613	1	.000	1.913	1.725	2.122

Potency estimate = Exp(-0.366/0.649) = 0.569 i.e. an individual would need to ingest 1.76 times more Inteon than standard product to have the same effect.

Sensitivity Analysis

Cox PH Comparison of Confirmed Inteon (201) and all Old cases (382) - Stratification by Centre (3 groupings)

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
groups2	-.426	.127	11.232	1	.001	.653	.509	.838
age50	.857	.182	22.145	1	.000	2.357	1.649	3.368
sex	.286	.155	3.424	1	.064	1.331	.983	1.803
weightm	.016	.008	3.736	1	.053	1.016	1.000	1.033
absorb2	.115	.179	.413	1	.521	1.122	.790	1.594
rx4hrs	.394	.127	9.597	1	.002	1.483	1.156	1.904
lavagey	.020	.147	.019	1	.890	1.021	.766	1.361
lndose	.595	.050	139.892	1	.000	1.813	1.643	2.001

Potency estimate = Exp(-0.426/0.595) = 0.488 i.e. an individual would need to ingest 2.05 times more Inteon than standard product to have the same effect.

Summary

- The overall survival rate is increased from 25.6% to 35.3% which is considered to be clinically significant
- All statistical analyses indicate that this was a real difference between the two products
- The correlation between amount ingested and survival was strong; in all ingestion sub-groups, INTEON® showed increased survival
- 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.

Next steps

- A fully homogenous INTEON® formulation has been submitted for registration in Sri Lanka
- It is proposed that monitoring will continue. (Protocol to be submitted to Ethics Committees)
- It is anticipated that the fully homogenous INTEON® formulation will lead to a further reduction in toxicity

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